CHEMICAL REVIEWS

REVIEW

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Synthesis of Heterocycles Mediated by Benzotriazole. 2. Bicyclic Systems

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CONTENTS

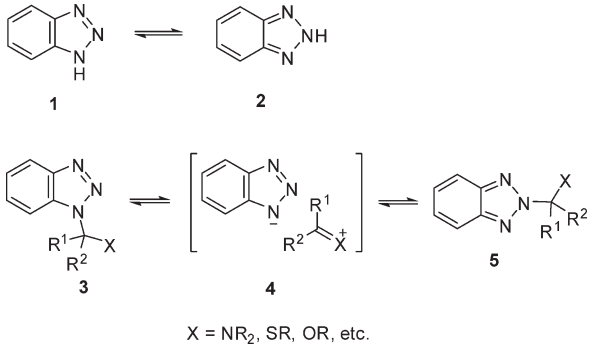
Received: January 19, 2011
Published: September 06, 2011

1. INTRODUCTION

In part 1 of this treatment,[1] we described application of benzotriazole methodology to the synthesis of monocyclic heterocycles as well as preparative methods for basic benzotriazole derivatives used in this synthesis. In part 2, we are dealing with more complicated bicyclic systems. Addition of a fused ring dramatically increases the number of permutations (regioisomers), producing a series of molecules with the same formula but different physicochemical properties. However, such molecules are still small enough to be easily prepared and become convenient building blocks in molecular design. It is not surprising therefore that most of the applications of benzotriazole methodology fall into this category. To show all of its involvements in preparation of final heterocyclic products, we discuss here not only benzotriazole playing a key role in the cyclization process but also its assistance in preparation of important intermediates for cyclization and modification of existing substituents on heterocyclic rings.

Basic chemistry of benzotriazole is discussed in part 1 of this review.[1] However, to make the present discussion clear, we want to stress that short-term "benzotriazole" means 1*H*-benzotriazole (**1**) and its tautomeric form 2*H*-benzotriazole (**2**), as both forms are in rapid prototropic equilibrium in solutions.[2] Similarly, under reaction conditions, many benzotriazol-1-yl derivatives **3** equilibrate with their benzotriazol-2-yl isomers **5**, especially when group X is a strong electron donor;[3,4] intermediate ionic form **4** is often the acting agent. Therefore, in many instances, when we use a simplified expression benzotriazol-1-yl compound **3**, we mean also its isomer **5** or a mixture of both (Scheme 1).

Scheme 1



2. (5,5)-C_7X RING SYSTEMS (X = N OR S)

Of three different locations possible for a nitrogen atom in a (5,5)-fused ring system, so far only synthesis of the core structure of pyrrolizine **6** has been based on benzotriazolyl intermediates. The divalent heteroatoms, oxygen and sulfur, are represented here by cyclopenta[*c*]thiophene system **7** (Figure 1).

2.1. Pyrrolizine

Among three different locations of a nitrogen atom in a ring system consisting of two fused five-membered rings, the bridging position is most explored. A simple route to such compounds, pyrrolo[1,2-*a*]pyrroles (or pyrrolizines), based on derivatives of benzotriazole starts from 1-propargylbenzotriazole (**8**). Thus, epoxides **9**, obtained by treatment of lithiated **8** with α-bromoketones, are subjected to a reaction with ethanolamine to provide 1-(2-hydroxyethyl)pyrroles **10** in 40−70% yields, which are further converted into tosylates **11** is 60−98% yields. In an intramolecular S_N2 reaction of lithiated **11**, the second ring is closed with elimination of a tosylate anion to furnish 6-substituted 1-(benzotriazol-1-yl)-2,3-dihydro-1*H*-pyrrolizines **12** in

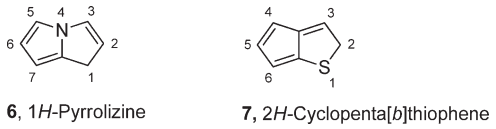
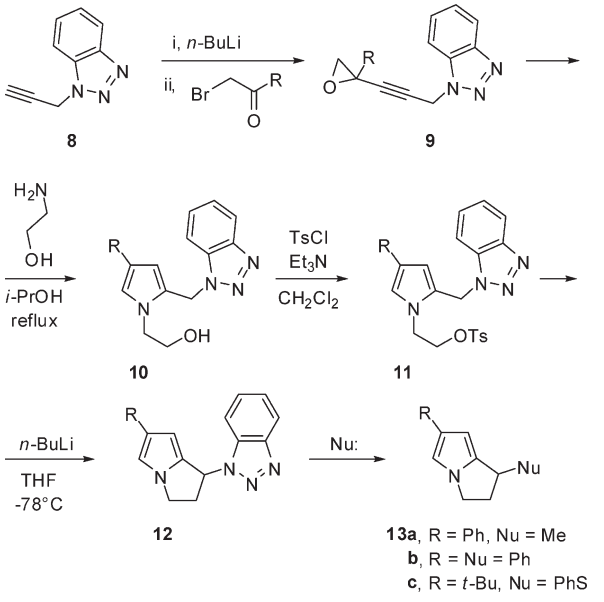


Figure 1. Atom numbering in (5,5)-C_7X ring systems (X = N or S).

Scheme 2



dx.doi.org/10.1021/cr200031r |*Chem. Rev.* 2011, 111, 7063–7120

75−90% yields. In refluxing toluene, Grignard reagents replace readily the benzotriazolyl moiety in **12** (R = Ph) to provide 1,6-disubstituted 2,3-dihydro-1*H*-pyrrolizines **13a** (90% yield) and **13b** (85% yield). Similarly, a reaction of **12** (R = *t*-Bu) with sodium thiophenoxide carried out in refluxing DMF gives pyrrolizine **13c** in 60% yield (Scheme 2).[5]

It is expected that benzotriazolyl derivative **12** dissociates partially in solution to iminium cation **14** and a benzotriazolide anion, especially at elevated temperatures. In most nucleophilic substitution reactions, nucleophiles attack C-1 in **14** to provide products **13**; however, in a reaction with sodium cyanide, **12** is converted to C-5 substituted derivative **15** in 65% yield. This unusual regioselectivity can be explained by the small size of the cyanide anion (no steric repulsion from the bulky *t*-butyl group at C-6) or thermodynamic effects (the cyanide anion adds originally to C-1, but the product dissociates back to **14**). In another approach to derivatization of **12**, it is lithiated and treated with an electrophile, ethyl benzoate, to give 1,1-disubstituted product **16** in 80% yield. Reduction with $LiAlH_4$ converts **16** to an alcohol that undergoes spontaneous dehydration to benzylidene derivative **17**, isolated in 40% yield. Treatment with the sodium salt of diethyl malonate does not cause substitution of the benzotriazolyl moiety in **12** but its elimination to give 6-(*t*-butyl)-3*H*-pyrrolizine **18** in 56% yield (Scheme 3).[5]

1-Acylbenzotriazole **20**, obtained from *N*-Cbz protected L-Proline (**19**), benzotriazole (**1**), and thionyl chloride, reacts with ethyl(triphenylphosphoranylidene)acetate to give (2*S*)-1-benzyloxycarbonyl-2-(ethoxycarbonyltriphenylphosphoranyl ideneacetyl)pyrrolidine (**21**) in 66% yield. Deprotection of the pyrrolidine nitrogen in **21** is followed by closure of the second ring to form pyrrolizine-1,3-dione **23**. A similar reaction of **20** with (triphenylphosphoranylidene)acetonitrile gives (2*S*)-1-benzyloxycarbonyl-2-(cyanotriphenylphosphoranylideneacetyl)-pyrrolidine (**22**) in 64% yield that is deprotected and cyclized in 33% HBr in acetic acid to 3*H*-1-ammonio-2-triphenylphosphonio-5,6,7,7a-tetrahydropyrrolizin-3-one dibromide (**24**) in 66% yield (Scheme 4).[6]

2.2. Cyclopenta[*b*]thiophene

In acidic solutions, 1-(hydroxymethyl)benzotriazole (**25**) generates iminium ion **26** that can be trapped by nucleophiles. Thus, prolonged heating of **25** and 2-methylthiophene in refluxing glacial acetic acid provides 2-(benzotriazol-1-yl)-5-methylthiophene (**27**) in 50% yield.[7] Treatment of lithiated **27** with electrophiles leads to derivatives **28**. Complexation of the benzotriazolyl N-3 atom in **27** and **28** with zinc bromide promotes dissociation of these molecules with formation of cations **29** (sulfur analogues of iminium ions **14**) that can be readily trapped by styrenes to give benzylic cations **30**. The subsequent intramolecular electrophilic attack on C-3 of thiophene closes the second ring to furnish mixtures of cyclopenta-[*b*]thiophene systems **31** and **32** (**b** and **c**) in 83−85% yields. Symmetrically substituted product **31a**, from a reaction of **27** with zinc bromide and 1,1-diphenylethylene, is obtained in 52% yield. For nonsymmetrical products, *trans*-stereoisomers **31b** and **31c** are predominant (**31**/**32** ≈ 2:1) (Scheme 5).[8]

3. (5,5)-C_6NX RING SYSTEMS (X = N OR O)

Among dozens of possible (5,5)-bicyclic systems with two heteroatoms, those with a bridgehead nitrogen atom are the most common and the most frequently targeted using benzotriazole methodology. Figure 2 shows core structures of investigated molecules with ring formula C_6N_2 (**33**−**35**) and C_6NO (**36** and **37**).

3.1. Pyrrolo[1,2-*a*]imidazole

Condensation of succinaldehyde, generated in situ by acidic hydrolysis of 2,5-dimethoxytetrahydrofuran with benzotriazole and *N*-phenylethylenediamine gives 1-phenyl-5-(benzotriazol-1-yl)hexahydro-1*H*-pyrrolo[1,2-*a*]imidazole (**38**) in 82% yield. In reactions with Grignard reagents, the benzotriazolyl moiety in **38** is readily replaced with alkyl, alkenyl, alkinyl, or aryl groups to provide derivatives **39** in 86−93% yields. Treatment of **38** with 1-phenyl-1-(trimethylsilyloxy)ethylene results in phenacyl derivative **40** in 87% yield. Diethyl phosphonate **41** is obtained in 74% yield in a reaction of **38** with triethyl phosphite. NMR data of the products, especially nuclear Overhauser effect (NOE), indicate that only one diastereomer forms with cis orientation of its H-5 and H-8a atoms (Scheme 6).[9]

Condensation of **1** with succinaldehyde and commercially available amino amides **42** provides optically active 1,3,5-trisubstituted hexahydro-1*H*-pyrrolo[1,2-*a*]imidazol-2-ones **43** in 84−91% yields. Structural studies based on NOE measurements revealed 3*S*,5*R*,7a*R* configuration of the chiral centers in these molecules. Treatment of **43** with sodium borohydride in THF results in products **44**, but the yields are relatively low (42−51%) due to the competing reduction of the carbonyl group and opening of the imidazole ring (Scheme 7).[10]

3.2. Pyrrolo[1,2-*c*]imidazole

The pyrrolo[1,2-c]imidazole system is readily generated in one step by condensation of benzotriazol-1-yl-pyrrol-2-ylmethanone (**45**) with isocyanates and isothiocyanates in the presence of a base. The reaction with isocyanates, run in refluxing tetrahydrofuran (THF) with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base, gives 2-substituted 2,3-dihydropyrrolo-[1,2-*c*]imidazole-1,3-diones **46** in 71−95% yields. The reaction with isothiocyanates requires higher temperatures, and it is run in a pressure vial in the presence of triethylamine to give 2-substituted 3-thioxo-2,3-dihydropyrrolo[1,2-*c*]imidazol-1-ones **47** in 26% (R = Ph) to 77% (R = Et) yields (Scheme 8).[11]

3.3. Pyrrolo[3,4-*c*]pyrrole

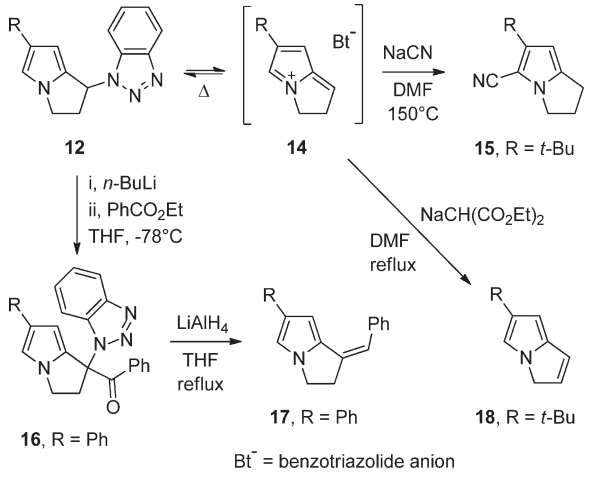
N-Benzylidene(α-benzotriazol-1-ylbenzylamine) (**48**) is readily prepared in 92% yield by condensation of benzaldehyde with ammonia and benzotriazole in an ethanolic solution. Treatment of **48** with *n*-BuLi at −78 °C generates anion **49** that adds to *N*-methylmaleimide to give anion **50**. Spontaneous elimination of a benzotriazolide anion from **50** results in two stereoisomers of 1,2,3,3a,4,6a-hexahydro-2-methyl-1,3-dioxo-4,6-diphenylpyrrolo-[3,4-*c*]pyrrole, **51** and **52**, which are separated by column chromatography. According to the NMR data, the predominant isomer (57% yield) has 3a,4-trans configuration **51**, and the minor isomer (10% yield) has 3a,4-cis configuration **52** (Scheme 9).[12]

3.4. Pyrrolo[2,1-*b*]oxazole

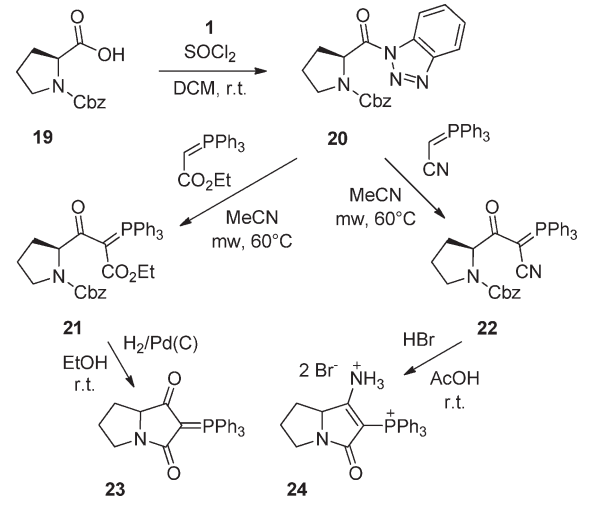
Condensation of succinaldehyde, obtained by hydrolysis of 2,5-dimethoxytetrahydrofuran with 0.1 N HCl, with benzotriazole and (*S*)-phenylglycinol (**53**) in dichloromethane/water, provides crystalline (3*S*,5*R*,7a*R*)-hexahydro-5-(benzotriazol-1-yl) -3-phenylpyrrolo[2,1-*b*]oxazole (**54**) in 80% yield.[13] Treatment of **54** with Grignard reagents causes opening of the oxazoline ring, but use of silanes instead allows substitution of the benzotriazole moiety without destruction of the bicyclic system. Thus, with allylsilanes, derivatives **55** are obtained in 40−45% yields. Ketones

dx.doi.org/10.1021/cr200031r |*Chem. Rev.* 2011, 111, 7063–7120

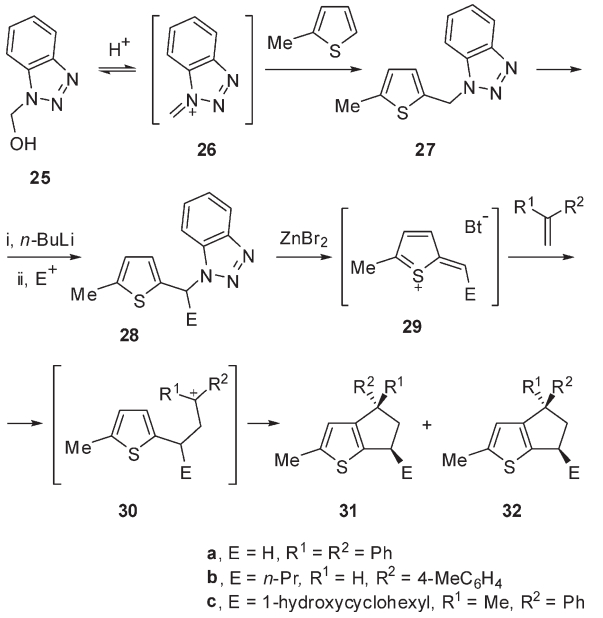
Scheme 3



Scheme 4



Scheme 5



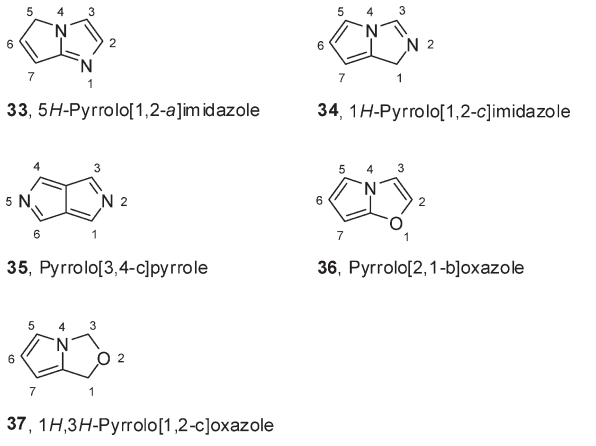


Figure 2. Atom numbering in (5,5)-C_6NX ring systems (X = N or O).

56 are obtained in 35% (R^2 = *t*-Bu) to 54% (R = Ph) yields from reactions of **54** with vinyloxysilanes. In a reaction of **54** with 1-methoxy-1-trimethylsilyloxy-2-methyl-1-propene, partial racemization occurs resulting in ester **57** (64% yield) as a mixture of two diastereomers in a ratio of 2:1. The chiral auxiliary can be readily removed from the obtained bicyclic products by hydrogenation over a palladium catalyst to provide the corresponding chiral 2-substituted pyrrolidines in nearly quantitative yields (Scheme 10).[14]

In analogy to the reaction in Scheme 10, compound **58**, the enantiomer of **54**, is obtained from benzotriazole, succinaldehyde, and (*R*)-phenylglycinol. A reaction of **58** with triethyl phosphite and catalytic amounts of zinc bromide gives diethyl (3*R*,5*S*,7a*S*)-hexahydro-3-phenylpyrrolo[2,1-*b*]oxazol-5-ylphosphonate (**59**) in 77% yield.[15] In a similar manner, **54** is converted to diethyl (3*S*,5*R*,7a*R*)-hexahydro-3-phenylpyrrolo[2,1-*b*]oxazol-5-ylphosphonate.[16] The anion derived from **59**, upon its treatment with *n*-BuLi, reacts with methyl iodide to provide derivative **60a** in 80% yield. Relatively lower yields of alkylated products **60b** (35%) and **60c** (41%) are obtained from similar reactions of **59** with ethyl and propyl iodides, respectively. All these alkylations proceed with retention of the stereochemistry at C-5. Hydrogenation of **60a** over a palladium catalyst provides diethyl (2*S*)-2-methylpyrrolidin-2-ylphosphonate in 83% yield (Scheme 11).[15]

3.5. Pyrrolo[1,2-*c*]oxazole

Condensation of **45** with aldehydes or ketones in the presence of DBU, as a strong and non-nucleophilic base, provides 3-substituted pyrrolo[1,2-*c*]oxazol-1-ones **61** in 47% (R^1 = Ph, R^2 = Me) to 98% (R^1 = *i*-Pr, R^2 = H) yields. The reaction is of a wide scope and works well with both enolizable and nonenolizable aldehydes and ketones (Scheme 12).[11]

4. (5,5)-RING SYSTEMS WITH THREE OR MORE HETEROATOMS

Derivatives of two heterocyclic systems that belong to this category, furo[2,3-*c*]pyrazole (**62**) and imidazolo[1,2-*c*][1,2,4]

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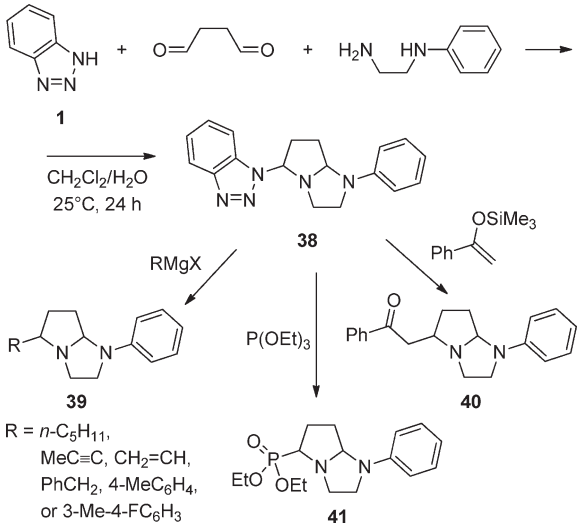
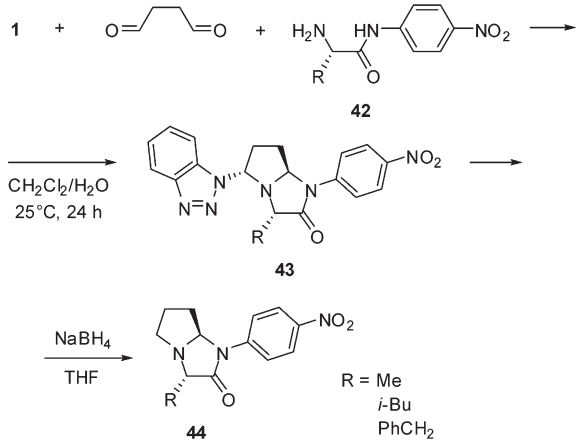
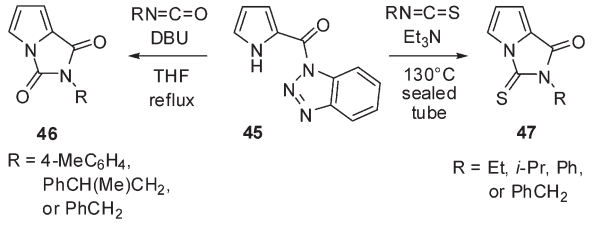
Scheme 6



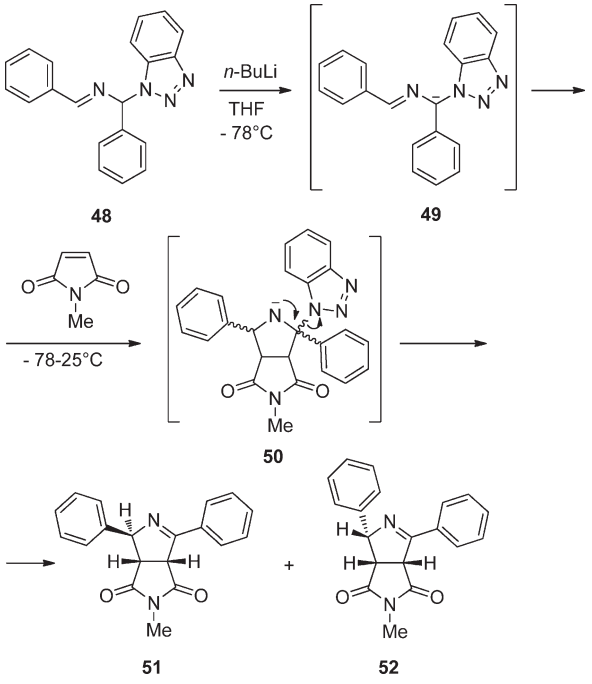
Scheme 7



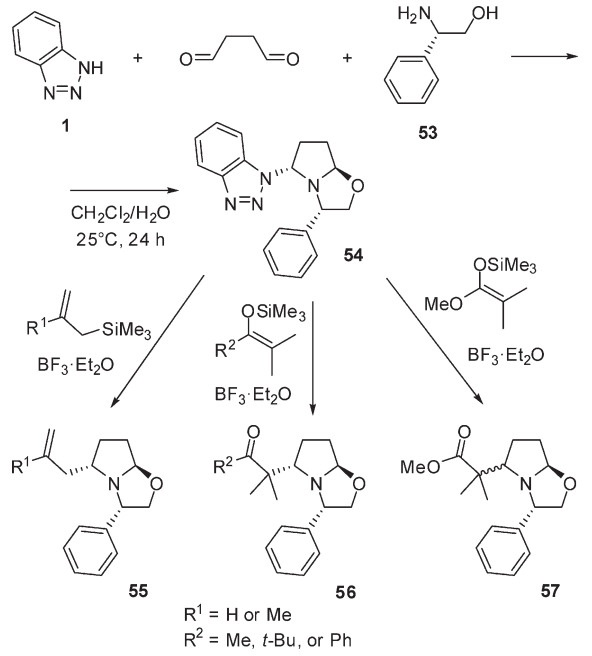
Scheme 8



Scheme 9



Scheme 10



-triazole (**63**), have been obtained using benzotriazole methodology (Figure 3).

4.1. Furo[2,3-*c*]pyrazole

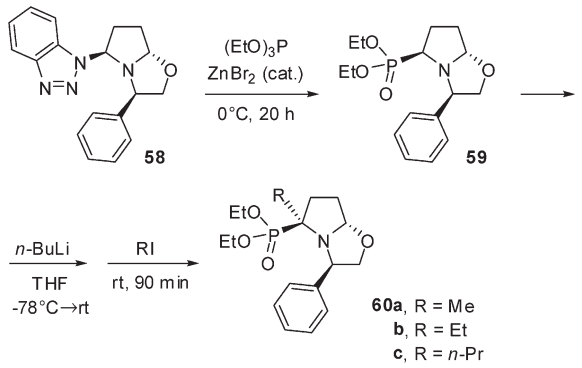
Condensation of 1,2-diphenylhydrazine with formaldehyde and benzotriazole in the presence of a dehydrating agent (molecular sieves 3 Å) provides 1-(benzotriazol-1-ylmethyl)-1,2-diphenylhydrazine **64** in 88% yield. Complexation of the benzotriazolyl moiety in **64** with zinc bromide allows dissociation of the molecule into benzotriazolide−zinc complex and iminium cation **65** that can be trapped by various nucleophiles. When 2,3-dihydrofuran is used as a nucleophile, 1,2-diphenyl-2,3,3a,4,5,6a-hexahydrofuro[2,3-*c*]pyrazole (**66**) is obtained in 84% yield (Scheme 13).[17]

4.2. Imidazolo[1,2-*c*][1,2,4]-triazole

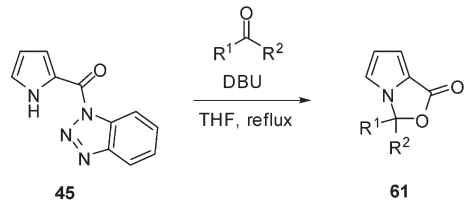
In solutions, 1-(morpholin-4-ylmethyl)benzotriazole (**67**) dissociates partially into the benzotriazolide anion and

dx.doi.org/10.1021/cr200031r |*Chem. Rev.* 2011, 111, 7063–7120

Scheme 11



Scheme 12

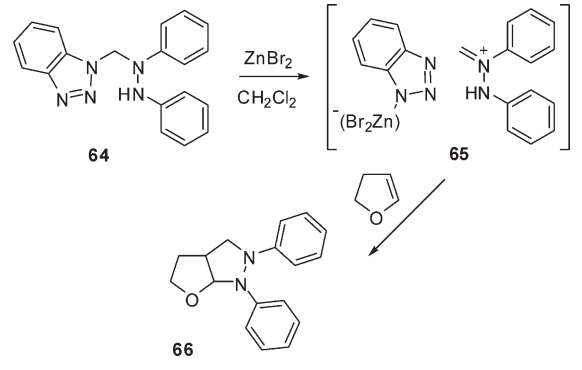


$R^1R^2C{=}O$ = *i*-PrCHO, 4-MeC_6H_4CHO, 2-furyl-CHO, Me_2CO, Ph(Me)CO, $(CH_2)_4CO$, or $(CH_2)_5CO$

62, 1*H*-Furo[2,3-*c*]pyrazole **63**, 1*H*-Imidazolo[1,2-c][1,2,4]-triazole

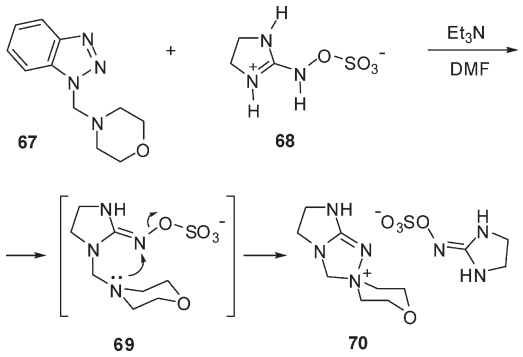
Figure 3. Atom numbering in (5,5)-ring systems with three or more heteroatoms.

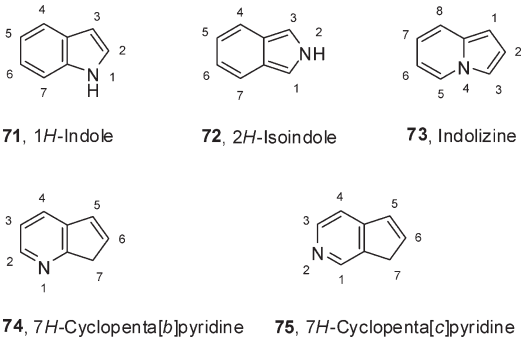
Scheme 13



N-methylenemorpholinium cation. The iminium cation reacts readily with deprotonated 2-hydroxyliminoimidazoline-*O*-sulfonate **68** to produce intermediate **69**. Electron-withdrawing ability of the sulfonate group renders some positive charge to the imino nitrogen atom in **69**. A nucleophilic attack of the piperidine nitrogen on the imino group and elimination of a sulfate anion results in 3,5,6,7-tetrahydroimidazo[2,1-*c*]1,2,4-triazole system

Scheme 14





71, 1*H*-Indole **72**, 2*H*-Isoindole **73**, Indolizine

74, 7*H*-Cyclopenta[*b*]pyridine **75**, 7*H*-Cyclopenta[*c*]pyridine

Figure 4. Atom numbering in (5,6)-C_8N ring systems.

(**70**). A salt of cation **70** with unreacted starting material **68** precipitates from the solution and is isolated in 61% yield. Several analogues of **67** derived from five- and six-membered heterocyclic amines giving similar products with **68** are also described (Scheme 14).[18]

5. (5,6)-C_8N RING SYSTEMS

Considering indene, (5,6)-C_9, as the parent molecule, replacement of one of its carbon atoms with nitrogen gives rise to five distinct (5,6)-C_8N ring systems, **71**−**75** (Figure 4). Among these heterocycles, 1*H*-indole (**71**) and its derivatives are the most abundant in nature and most frequently studied in laboratories, including their synthesis with application of benzotriazole methodology.

5.1. Indole

5.1.1. Substituent at N. 1-(Chloromethyl)benzotriazole (**76**) reacts with **71** in the presence of a base to provide 1-(indol-1-ylmethyl)benzotriazole (**77**) in 84% yield. Strong bases allow proton abstraction from the methylene group in **77**, and the generated anion can be trapped by various electrophiles. Thus, treatment of **77** with LDA followed by benzyl bromide gives benzylated product **78** in 86% yield. With the *n*-butyllithium base and *p*-tolualdehyde electrophile, alcohol **79** is obtained in 68% yield (the predominant diastereomer). Similarly, reactions of lithiated **77** with carboxylic esters result in ketones **80** in 75−95% yields. Sodium borohydride can reduce the carbonyl group in **80** without affecting the benzotriazolyl moiety, giving alcohols **81** in 82−95% yields as mixtures of diastereomers, but zinc with acetic acid removes preferentially

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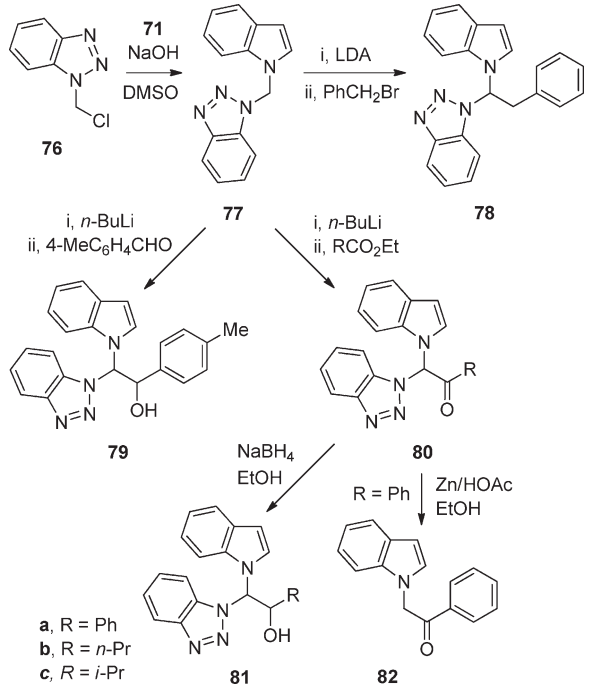
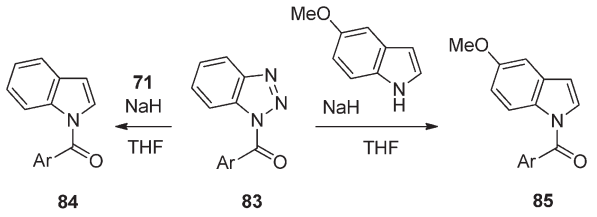
Scheme 15



Scheme 16

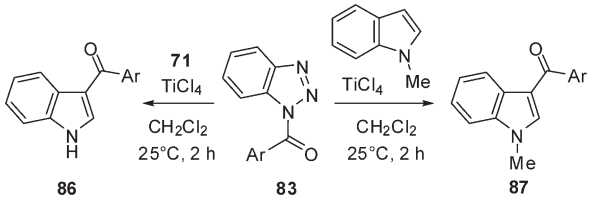


the benzotriazolyl substituent in **80a** to give 1-phenacylindole (**82**) in 43% yield (Scheme 15).[19]

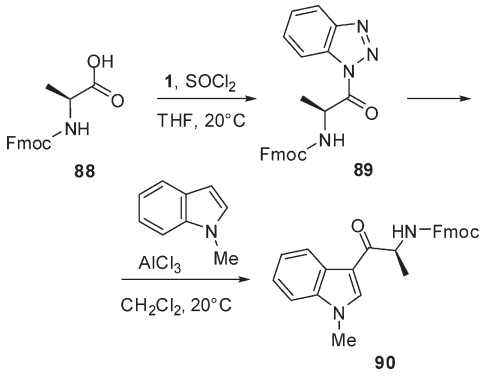
1-Aroylbenzotriazoles **83** are readily available from reactions of the corresponding carboxylic acids with benzotriazole and thionyl chloride. Sodium salts of **71** (generated by addition of NaH) react with **83** to give 1-aroylindoles **84** in 60−91% yields. This work paid special attention to generate **84** with electron-donating methoxy groups, for which no efficient synthetic method was previously available. Even 5-methoxyindole can be effectively *N*-aroylated by this method to give derivatives **85** in 36−87% yields, with the lowest yield for R = 2,6-$(MeO)_2C_6H_3$ (Scheme 16).[20]

5.1.2. Substituent at C-3. Acylation of indole with 1-aroylbenzotriazoles **83** in the presence of a Lewis acid ($TiCl_4$) provides 3-aroylindoles **86** in good yields (64−92%) except Ar = 2-pyrrolyl (15%). The reaction works well with both electron-rich and electron-deficient groups Ar and is regioselective, giving exclusively C-3 substituted indoles, while most other acylation methods give also N-acylated side-products. 1-Methylindole is smoothly acylated by **83** as well to give 1-methyl-3-aroylindoles **87** in 27% (R = 2-indolyl) to 92% (R = 4-MeC_6H_4) yields. Low

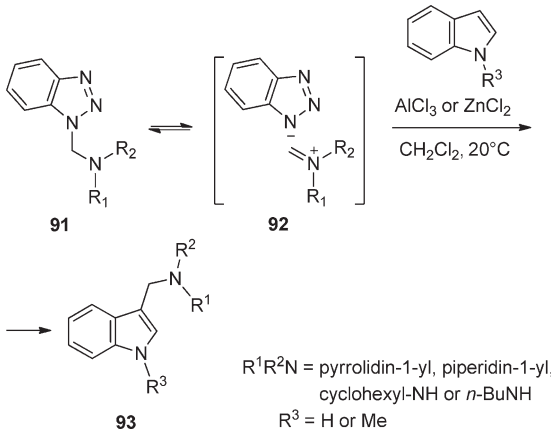
Scheme 17



Scheme 18



Scheme 19

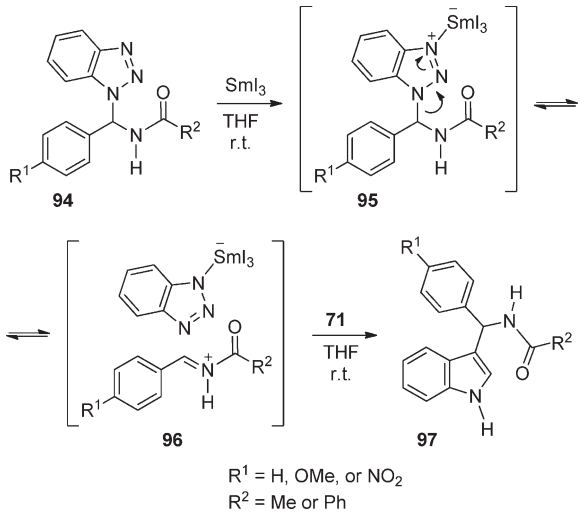


yields of **86** and **87** with R = 2-pyrrolyl and 2-indolyl may result from partial decomposition of the corresponding acylating agents **83** in the presence of $TiCl_4$ (Scheme 17).[21]

N-(9-Fluorenylmethoxycarbonyl)-L-alanine (**88**) reacts with benzotriazole and thionyl chloride to give 1-acylbenzotriazole **89** in 85% yield. Acylation of 1-methylindole with **89** in the presence of $AlCl_3$ provides C-3 substituted indole **90** in 85% yield. The opposite enantiomer of **90** is similarly prepared from Fmoc-protected D-alanine. To obtain derivatives similar to **90** of *N*-unsubstituted indole, *N*-(trimethylsilyl)indole is used as the starting material (Scheme 18).[22]

dx.doi.org/10.1021/cr200031r |*Chem. Rev.* 2011, 111, 7063–7120

Scheme 20



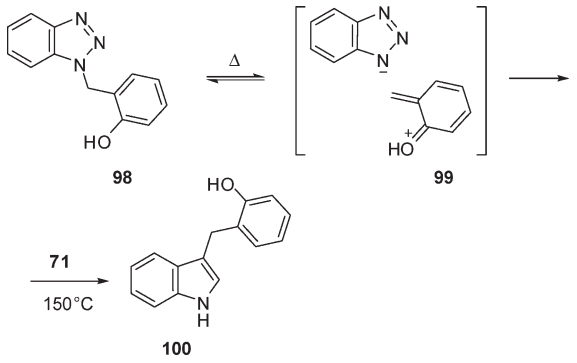
1-(Aminomethyl)benzotriazoles **91**, in mixtures with their benzotriazol-2-yl isomers, are readily prepared by condensation of benzotriazole with formaldehyde and amines. In solutions, especially in the presence of Lewis acids, they dissociate partially to benzotriazolide anions and iminium ions **92** and are convenient aminomethylating agents for various nucleophiles. In their reactions with indole and 1-methylindole catalyzed by Lewis acids, 3-aminomethylated indoles **93** are obtained in 84−93% yields. Aluminum chloride is a good catalyst for aminomethylation with **91** derived from secondary amines, while a milder Lewis acid, $ZnCl_2$, is required for derivatives of primary amines to avoid their decomposition (Scheme 19).[23]

α-Amidoalkylation of indole with *N*-(α-benzotriazol-1-ylbenzyl)amides **94** in the presence of samarium triiodide as a catalyst provides C-3 substituted derivatives **97** in 73−87% yields. 2-Methyl- and 2-phenylindoles react similarly with **94**, giving the corresponding analogues of **97** in good yields, while nitro groups at C-4 and C-5 inhibit the reaction. The process is believed to involve complexation of N-3 of benzotriazole with SmI_3 (**95**), enabling cleavage of the N(1)−C(α) that generates iminium cation **96**. In the final stage, an electrophilic attack of **96** on the C-3 of indole leads to **97** (Scheme 20). It is interesting that typical Lewis acids ($AlCl_3$, $FeCl_3$, and $ZnCl_2$) failed to catalyze this reaction.[24]

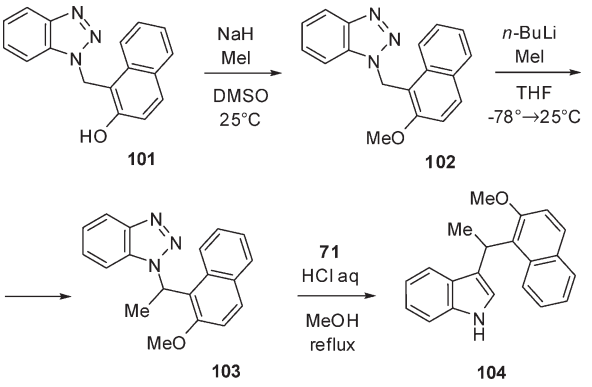
Hydroxybenzylation of indole (**71**) is based on a similar principle. Thus, the reagent, 1-(2-hydroxybenzyl)benzotriazole (**98**), is easily prepared by condensation of 1-(hydroxymethyl) benzotriazole (**25**) with phenol in refluxing acetic acid.[25] At elevated temperature, **98** dissociate partially to benzotriazolide anion and cation **99** that can be trapped by nucleophiles. With indole, the reaction is carried out in a sealed vial at 150 °C for 36 h to give 3-(2-hydroxybenzyl)indole (**100**) in 58% yield (Scheme 21).[26]

It appears that the reaction from Scheme 21 is not limited to phenols; the *ortho*-methoxy group provides also sufficient activation of the benzylic carbon atom. Additionally, the benzylic methylene group can be alkylated to give more complex molecules. In an example given in Scheme 22, starting material **101** is obtained by condensation of 1-(hydroxymethyl)benzotriazole with 2-naphthol. Treatment of **101** with NaH and methyl iodide

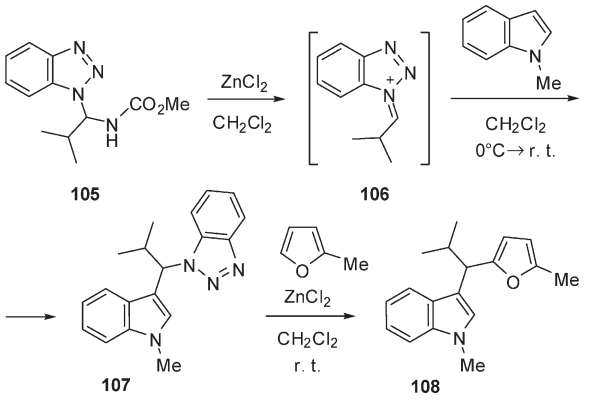
Scheme 21



Scheme 22



Scheme 23

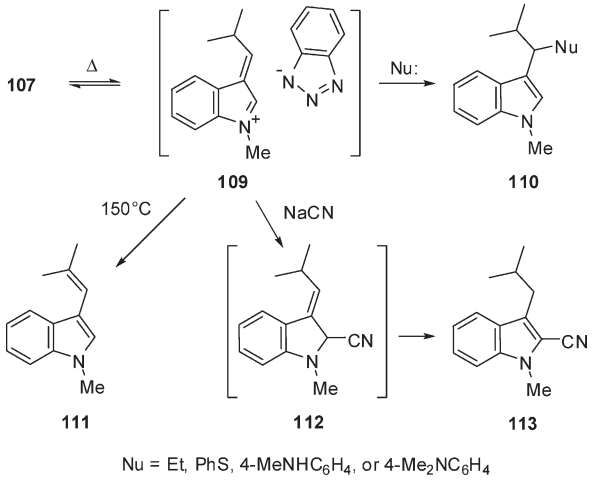


methylates the hydroxy group to give ether **102** in 50% yield. Subsequent lithiation and methylation allows substitution of one of the benzylic protons with a methyl group, resulting in derivative **103** (98% yield). Under relatively mild conditions, refluxing in methanol and catalysis with aqueous HCl, the benzotriazolyl moiety in **103** is replaced by indol-3-yl to provide product **104** in 43% yield.[27]

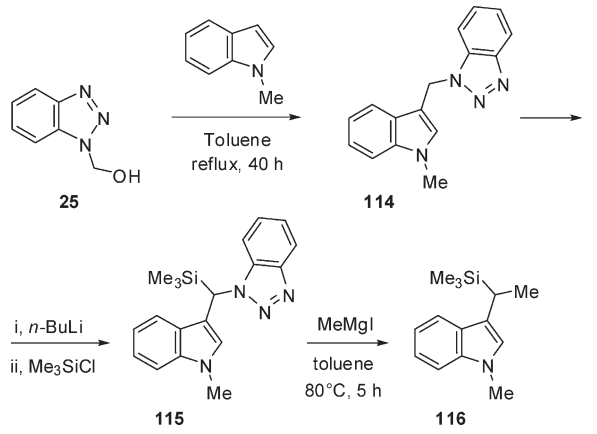
Heating a mixture of benzotriazole with isobutyraldehyde, methyl carbamate, and a catalytic amount of *p*-toluenesulfonic acid (*p*-TSA) in refluxing toluene under a Dean−Stark trap

dx.doi.org/10.1021/cr200031r |*Chem. Rev.* 2011, 111, 7063–7120

Scheme 24



Scheme 25



results in *N*-substituted carbamate **105** (84% yield).[28,29] Iminium cation **106** generated from **105** in the presence of zinc chloride is trapped by 1-methylindole to give 3-substituted indole **107** in 40% yield. Treatment of **107** with electron-rich heterocycles in the presence of zinc chloride allows substitution of the benzotriazolyl moiety; e.g., derivative **108** is obtained in 84% yield when 2-methylfuran is used, and its thienyl analogue is obtained in 90% yield from a reaction of **107** with 2-methylthiophene (Scheme 23).[29]

At elevated temperature or in the presence of benzotriazole complexing agents (e.g., zinc chloride in the reaction shown in Scheme 23), **107** can dissociate into benzotriazolide anion and iminium cation **109** that is easily trapped by various nucleophiles. The net result of the reaction of **107** with most nucleophiles is substitution of the benzotriazole moiety. Thus, in a reaction of **107** with ethylmagnesium bromide in refluxing ethyl ether, derivative **110** (Nu = Et) is obtained in 47% yield. The reaction of **107** with sodium thiophenoxide requires reflux in *n*-butanol and gives **110** (Nu = PhS) in 73% yield. The reactions of **107** with *N*-methylaniline and *N*,*N*-dimethylaniline are run at 130 °C by heating neat mixtures of the reagents in sealed vials for 2 days to give the corresponding **110** in 53% and 74% yields, respectively.

Scheme 26

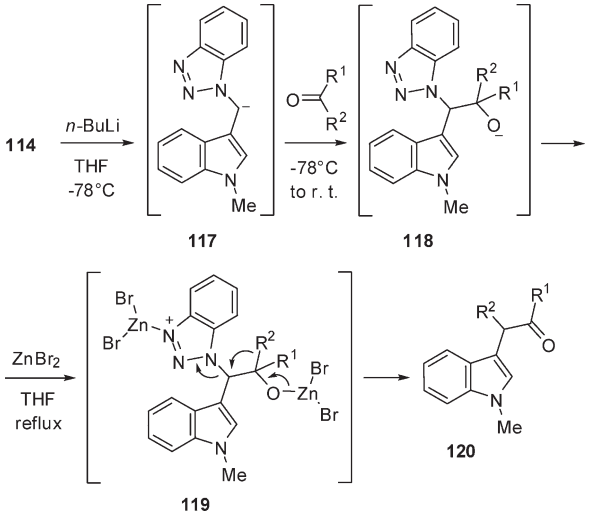
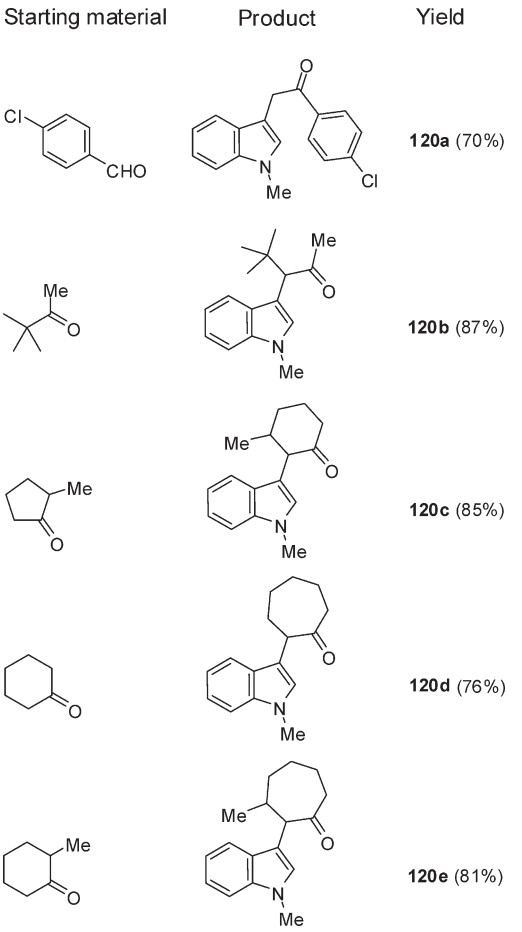


Table 1. (1-Methylindol-1-yl)methylene Insertions into Molecules of Aldehydes and Ketones



However, cyanide anion prefers addition to C-2 of **109** to give intermediate **112** that tautomerizes to more stable form **113**, isolated in 60% yield. When heating of **107** in dimethylformamide

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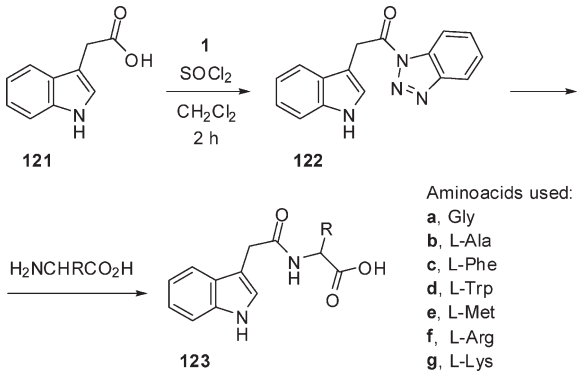
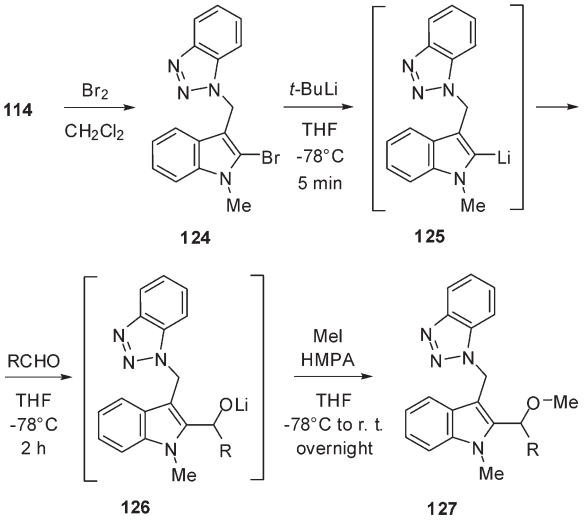
Scheme 27



Scheme 28



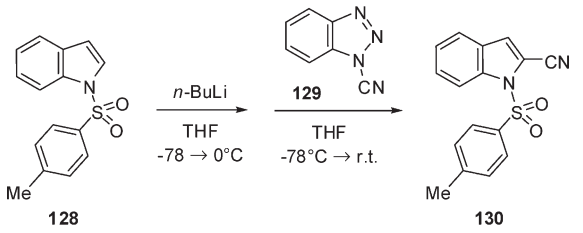
R = 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, or 1-methylindol-3-yl

(DMF) is performed without any nucleophile, elimination product **111** is obtained in 50% yield (Scheme 24).[30]

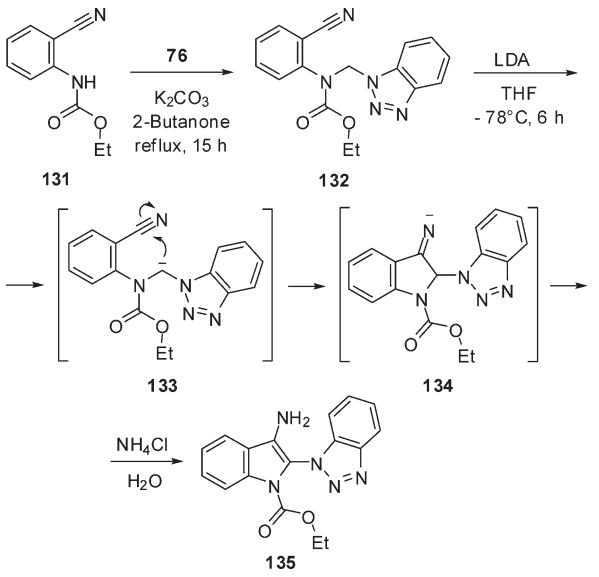
In another approach, 3-(benzotriazol-1-ylmethyl)-1-methylindole (**114**) is obtained in 40% yield by prolonged heating of 1-methylindole with 1-(hydroxymethyl)benzotriazole (**25**) in refluxing toluene. Treatment of **114** with *n*-BuLi generates an anion, which is trapped by chlorotrimethylsilane to give derivative **115** in 93% yield. Substitution of the benzotriazolyl moiety in **115** by a methyl group from methylmagnesium iodide furnishes 1-methyl-3-(1-trimethylsilyl)ethylindole (**116**) in 90% yield (Scheme 25).[30]

Anion **117** obtained from **114** by proton extraction with *n*-BuLi can be trapped by carbonyl compounds to give alkoxy anions **118**. In situ treatment with three molar equivalents of zinc bromide converts **118** into ketones **120**. This insertion of (1-methylindol-3-yl)methylene group into the carbonyl compound molecule starts from activation of the benzotriazolyl moiety for leaving by complexation of its N-3 atom with zinc bromide (**119**). The subsequent 1,2-shift of the R^2 group furnishes ketone **120** (Scheme 26). The characteristic feature of this reaction is its high regioselectivity—only in the case of product **120e** its

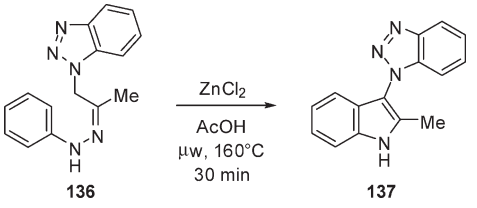
Scheme 29



Scheme 30



Scheme 31



regioisomer, 2-(1-methylindol-3-yl)-6-methylcycloheptanone, is obtained in 3% yield as a side-product. As the examples given indicate (Table 1), shift of the hydride anion is preferred over the 4-chlorophenyl group (**120a**); and of two different aliphatic groups (**120b**, **c**, and **e**), the one with the carbon-α bearing more substituents moves. This order of reactivity is similar to that observed in other pinacol-type rearrangements.[7,31]

Benzotriazole methodology is also efficient for modification of the existing indole substituents. Thus, in the example of Scheme 27, indole-3-acetic acid (**121**) is treated with benzotriazole and thionyl chloride to give 1-(1*H*-benzotriazol-1-yl)-2-(1*H*-indol-3-yl)-1-ethanone **122** in 86% yield. Coupling of **122** with unprotected amino acids results in derivatives **123** in 40% (**123a**) to 66% (**123c**) yields.[32]

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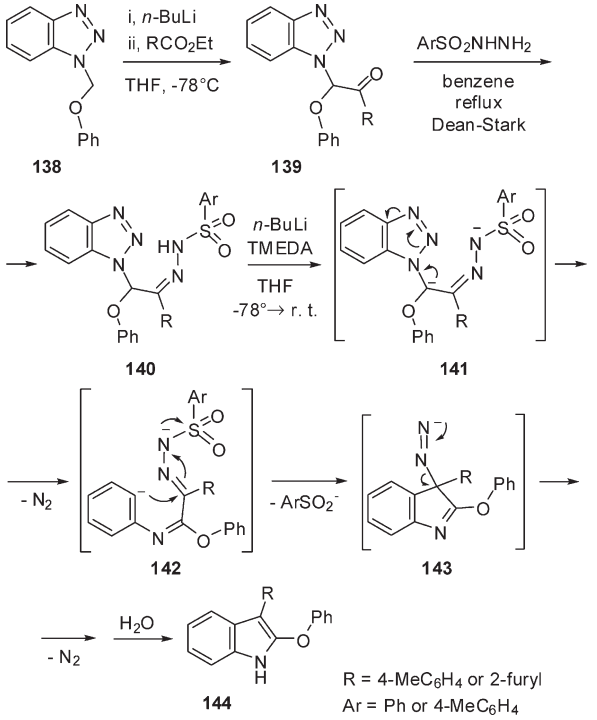
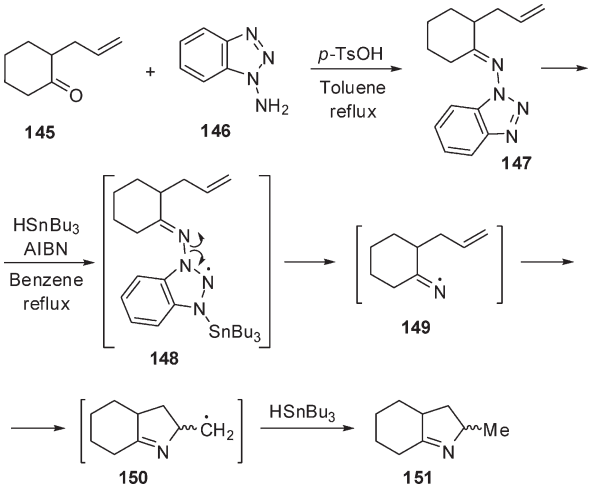
Scheme 32



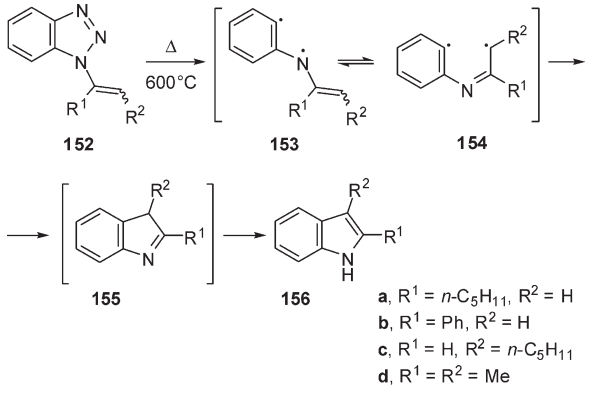
138 139 140 141 142 143 144

Scheme 33



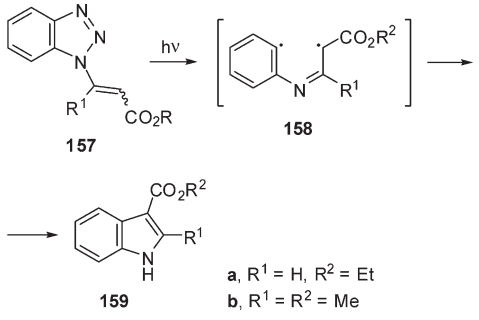
145 146 147 148 149 150 151

Scheme 34



152 153 154 155 156

Scheme 35



157 158 159

5.1.3. Substituent at C-2. To lithiate 3-(benzotriazol-1-ylmethyl)-1-methylindole (**114**) at C-2, it is first brominated to give 2-bromo derivative **124** (80% yield). Using *t*-butyllithium, **124** is smoothly converted to 2-lithio derivative **125** that is subsequently treated with heteroaryl aldehydes to give addition products **126**. The following in situ treatment with iodomethane in hexamethylphosphoramide (HMPA) furnishes 2-(1-methoxy-1-arylmethyl)indoles **127** in 81−88% yields. If the methylation step is omitted, direct workup of the reaction mixture containing **126** gives the corresponding alcohols instead of ethers **127**, as is illustrated by preparation of 3-(benzotriazol-1-ylmethyl)-2-(1-hydroxy-1-thien-3-ylmethyl)-1-methylindole in 91% yield (Scheme 28).[33]

Electron-withdrawing substituents at the nitrogen atom allow direct lithiation of indole at C-2 and further reactions with electrophiles to provide 2-substituted indoles. Thus, 1-tosylindole (**128**)[34] is lithiated with *n*-BuLi and treated with 1-cyanobenzotriazole (**129**) to give 1-(4-toluenesulfonyl)-1*H*-indole-2-carbonitrile (**130**) in 43% yield (Scheme 29).[35]

5.1.4. Ring Formation. *N*-Benzotriazol-1-ylmethyl derivative **132** is obtained in 86% yield by reaction of ethyl 2-cyanophenylcarbamate (**131**) with 1-(chloromethyl)benzotriazole (**76**) and potassium carbonate. Treatment of **132** with lithium diisopropylamide (LDA) generates anion **133** that then attacks the CN group to close the heterocyclic ring. During workup, anion **134** is neutralized, and the resulting imine tautomerizes to 3-aminoindole **135**, isolated in 70% yield (Scheme 30).[36]

In a Fischer type synthesis, phenylhydrazone **136**, derived from 1-(benzotriazol-1-yl)acetone, is smoothly converted to 3-(benzotriazol-1-yl)-2-methylindole (**137**) in 88% yield upon treatment with zinc chloride and acetic acid in a microwave oven (Scheme 31).[37]

Opening the benzotriazole heterocyclic ring with elimination of a molecule of nitrogen followed by cyclization through bond formation between the C-β (of the N-1 substituent) and C-3a atoms allows conversion of 1-substituted benzotriazoles into the corresponding indoles. Thus, 1-(phenoxymethyl)benzotriazole **138**, readily available from a reaction of 1-(chloromethyl) benzotriazole with sodium phenoxide,[38] is treated with *n*-BuLi followed by esters of aryl carboxylic acids to give 1-aryl-2-(benzotriazol-1-yl)-2-phenoxyethanones **139** (92−95% yields) that are subsequently converted into their arylsulfonyl hydrazones

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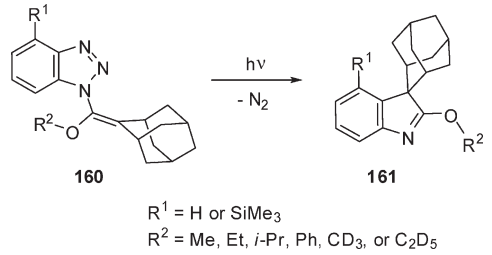
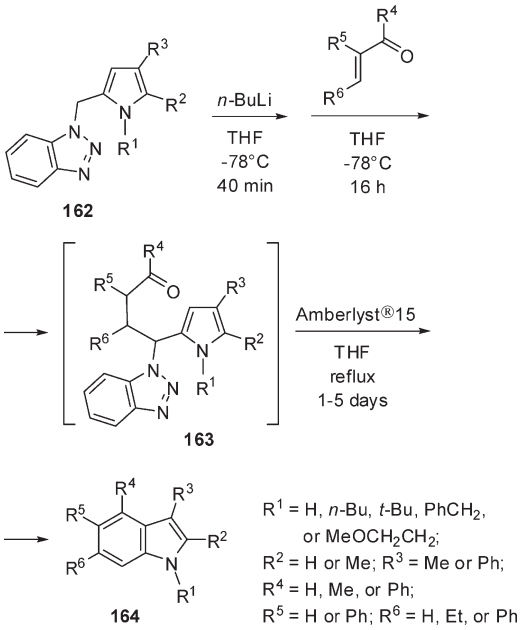
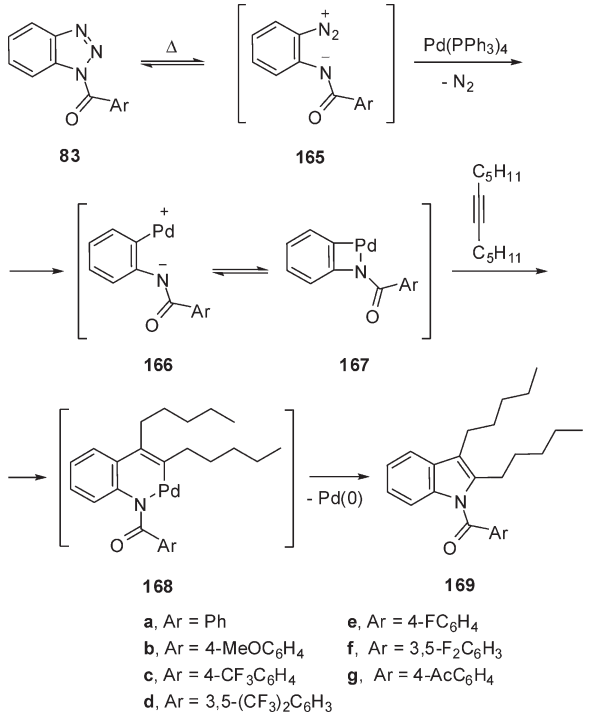
Scheme 36



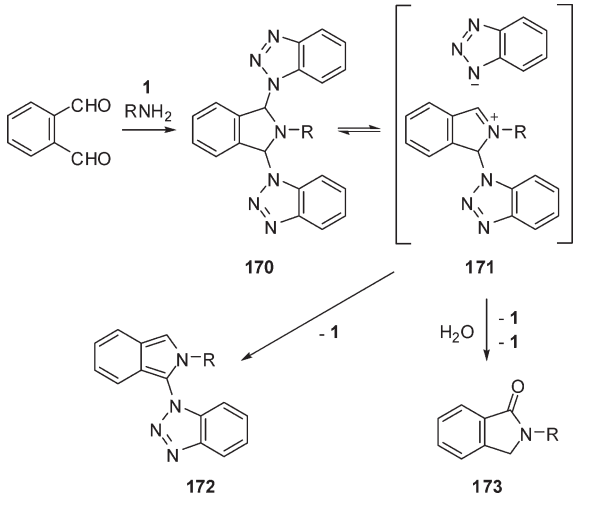
Scheme 37



Scheme 38



Scheme 39



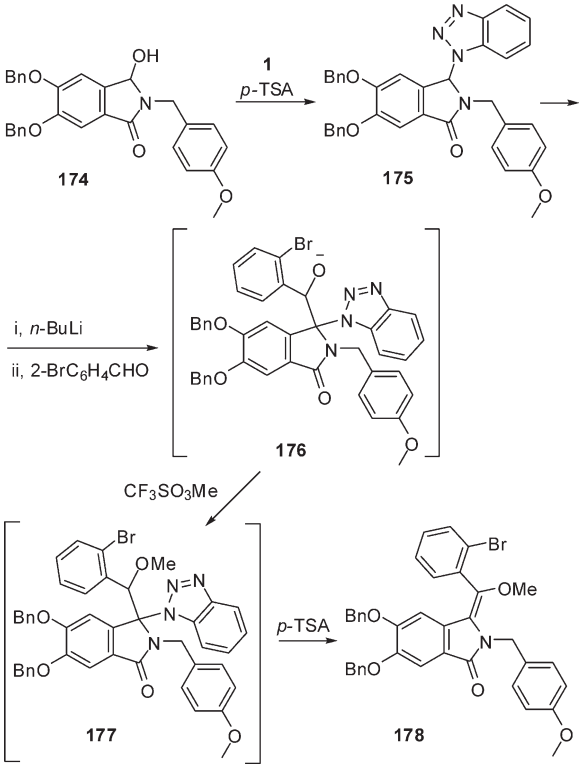
140 in 56−89% yields.[39] Electron shifts in dianion **141**, resulting from treatment of **140** with three molar equivalents of *n*-BuLi and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), opens the benzotriazole ring and causes extrusion of a molecule of nitrogen to produce new dianion **142**. A nucleophilic attack of the just-generated aryl anion on the C═N bond in **142** forms a new five-membered ring accompanied by elimination of arenesulfinate anion, leading to anion **143**. Elimination of nitrogen from **143** generates an indolide anion that catches a proton during workup to give indole **144**. 3-Aryl-2-phenoxyindoles **144** are isolated in 38−83% yields (Scheme 32).[40]

N-(Benzotriazol-1-yl)imine **147**, obtained in a reaction of 2-allylcyclohexanone (**145**) with 1-aminobenzotriazole (**146**), is treated with tributyltin hydride and a catalytic amount of 2,2′-azobisisobutyronitrile (AIBN) to give 2-methylhexahydroindole **151** in 73% yield, as a diastereomeric mixture (ratio 3:2). According to the proposed mechanism, addition of a tributylstannyl radical to N-3 of benzotriazole generates radical **148** that by scission of an N−N bond is converted to iminyl radical **149**. Cyclization of **149** results in a new radical (**150**). Reaction of **150** with tributyltin hydride gives final product **151** and a tributylstannyl radical that propagates the chain reaction (Scheme 33).[41]

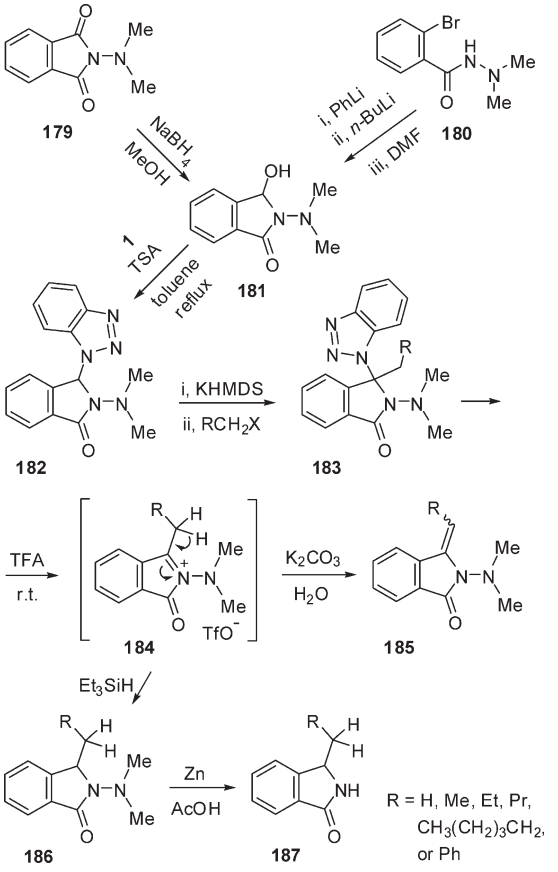
Besides the ionic pathway (Scheme 32), extrusion of nitrogen from the benzotriazole system can also be achieved in a radical mode by applying high temperature. Thus, flash pyrolysis of 1-(alken-1-yl)benzotriazoles **152** leads to diradicals **153**. Electron pairing in the diradicals, forms **154**, results in molecules of 3*H*-indoles **155** that spontaneously tautomerize to more stable 1*H*-indoles **156**. Despite the extreme conditions in this process, yields of products **156** are relatively good: 56% for **a**, 67% for **b**, 42% for **c**, and 34% for **d** (Scheme 34).[42] Flash vacuum pyrolysis of (*E*)- and (*Z*)-ethyl 3-(benzotriazol-1-yl)-3-phenylpropenoates at 450 °C gives quantitatively ethyl 2-phenylindole-3-carboxylate.[43] Pyrolysis of α-(benzotriazol-1-yl)alkyl ketones also produces indoles, in a complex rearrangement scheme, but the yields are low (9−34%) and the main product is aniline.[44]

dx.doi.org/10.1021/cr200031r |*Chem. Rev.* 2011, 111, 7063–7120

Scheme 40



Scheme 41



Another method for generation of diradicals from benzotriazole derivatives by extrusion of nitrogen relies on photochemistry. In the examples of such approach, 3-(benzotriazol-1-yl)acrylates **157**, as mixtures of *E* and *Z* isomers, are obtained in 97% (**a**) and 44% (**b**) yields by addition of benzotriazole to the corresponding propiolates. Photolysis of **157** with a UV lamp (353.7 nm) converts them into esters of 3-indolecarboxylic acids **159** in 74% and 72% yields, **a** and **b**, respectively. The reaction is believed to proceed via diradical **158** (Scheme 35).[45]

Photolysis of adamantanylidene derivatives **160** gives spiro-3*H*-indoles **161** in 31−44% yields (Scheme 36).[46] These examples indicate that the photochemical conversion of benzotriazole to indole derivatives is quite insensitive to steric hindrance at the reacting centers.

In a total synthesis of indoles, the heterocyclic ring is made first, and the benzene ring is then constructed from acyclic elements. Thus, pyrrole derivatives **162** are prepared in 32−62% yields in reactions of lithiated 1-propargylbenzotriazole with α-bromoketones and amines. Addition of lithiated **162** to α,*β*-unsaturated aldehydes or ketones generates ketones **163** that can be isolated but are usually directly converted to indoles **164** (51−76% yields) via elimination of benzotriazole in cyclization reactions promoted by heating with strongly acidic Amberlyst 15 resin (Scheme 37).[47]

Palladium-catalyzed extrusion of nitrogen from 1-acylbenzotriazoles provides another route for conversion of benzotriazoles to indoles. Thus, heating at 130 °C a mixture of 1-aroylbenzotriazole **83**, 6-dodecyne, and 10 mol % of $Pd(PPh_3)_4$ results in formation of 1-aroylindoles in 39% (**169d**) to 69% (**169c**) yields. The proposed mechanism starts from thermally initiated opening of the triazole ring in **83** with formation of iminobenzenediazonium species **165**. In the following steps, oxidative addition of **165** to palladium and the subsequent elimination of nitrogen leads to forms **166** and **167** that insert the alkyne to form intermediate **168**. Finally, reductive elimination of Pd(0) from **168** results in indole **169** (Scheme 38).[48]

5.2. Isoindole

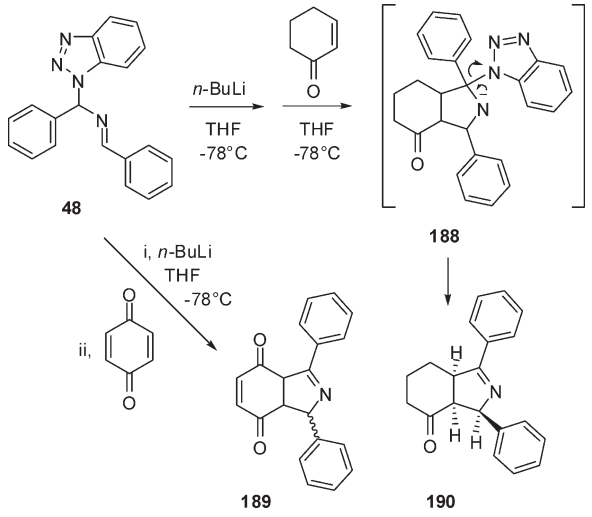
Under mild conditions, condensation of phthalaldehyde with excess benzotriazole (**1**) and amines provides 2-substituted 1,3-(benzotriazol-1-yl)-isoindolines **170**, which can be isolated in good yields when arylamines are used.[49,50] Depending on the reaction conditions, especially presence or absence of water and pH of the reaction mixture, products **170**, which exist in equilibrium with their ionic forms **171**, eliminate benzotriazole to give 2-substituted 1-(benzotriazol-1-yl)-2*H*-isoindoles **172**[51,52] or undergo hydrolysis to isoindolinones **173** (Scheme 39).[49,50,53]

Acid-catalyzed condensation of 3-hydroxyisoindolin-1-one **174** with benzotriazole provides its 3-(benzotriazol-1-yl) derivative **175** in 86% yield. Addition of lithiated **175** to the carbonyl group of 2-bromobenzaldehyde results in alkoxide anion **176** that is subsequently converted to methyl ether **177** by treatment with methyl triflate. Final addition of *p*-TSA to the reaction mixture causes protonation of the benzotriazolyl moiety, resulting in its elimination to give 3-(α-methoxy-3-bromobenzylidene)isoindolin-1-one **178** (69% yield), which is an intermediate in the first total synthesis of 9-methoxyacepharanone A, an important alkaloid (Scheme 40).[54]

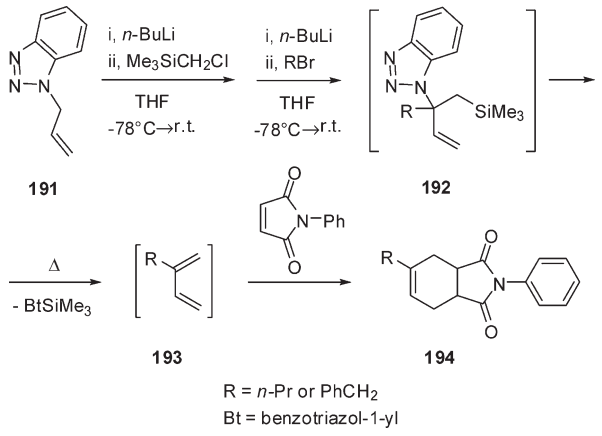
Reduction of *N*-(dimethylamino)phthalimide **179** with sodium borohydride gives 2-dimethylamino-3-hydroxyisoindolinone (**191**)

dx.doi.org/10.1021/cr200031r |*Chem. Rev.* 2011, 111, 7063–7120

Scheme 42

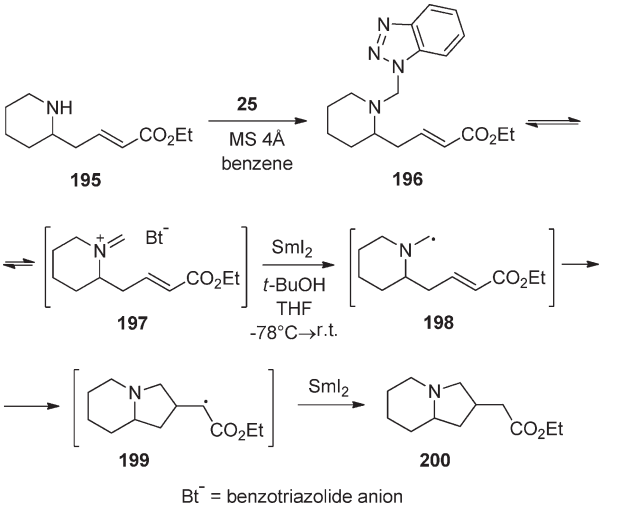


Scheme 43

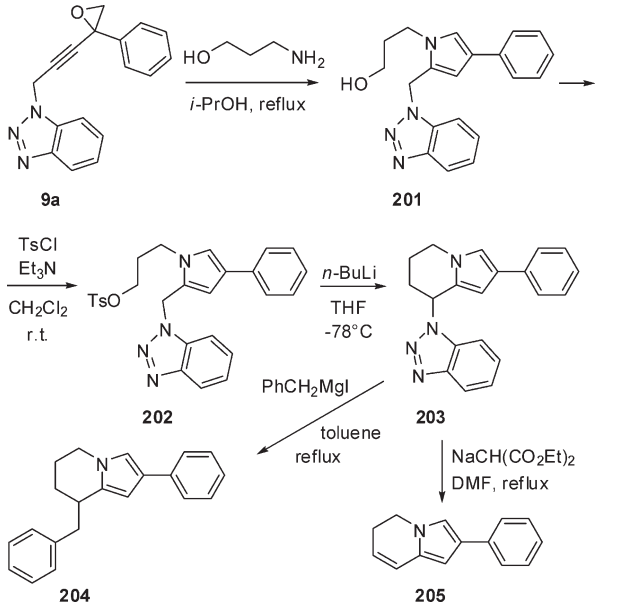


in 82% yield.[55] Alternatively, **181** is prepared in a reaction of double-lithiated hydrazone **180** with DMF.[56] Condensation of **181** with benzotriazole in the presence of a catalytic amount of *p*-toluenesulfonic acid provides 3-(benzotriazol-1-yl)isoindolinone **182** in 91% yield.[56] Use of (*S*)-2-(methoxymethyl)pyrrolidin-1-yl as a chiral substituent instead of a simple dimethylamino group in **181** allows stereoselective introduction of the benzotriazol-1-yl substituent to give an (*S*)-2-(methoxymethyl)pyrrolidin-1-yl analogue of **182** as a mixture of 3*S* and 3*R* diastereomers in a ratio of 85:15.[57] Treatment of **182** with potassium hexamethyldisilazide (KHMDS) followed by alkyl iodides or benzyl bromide generates alkylated products **183** that eliminate benzotriazole when exposed to trifluoroacetic acid (TFA) to give salts **184**. Basic workup (aqueous K_2CO_3) removes a proton from the methylene group, converting salts **184** into neutral molecules, 2-dimethylamino-3-methylene-2,3-dihydro-1*H*-isoindol-1-one, or their 3-alkylmethylene- or 3-phenylmethylene- analogues, **185**, that are isolated in 88−94% yields.[56] Reduction of **184** with triethylsilane provides 3-substituted 2,3-dihydro-1*H*-isoindol-1-ones **186** in 87−94% yields. The N−N bond in **186** is conveniently cleaved with zinc in acetic acid to give 2-isoindolidones **187** in 69−82% yields (Scheme 41).[55]

Scheme 44



Scheme 45

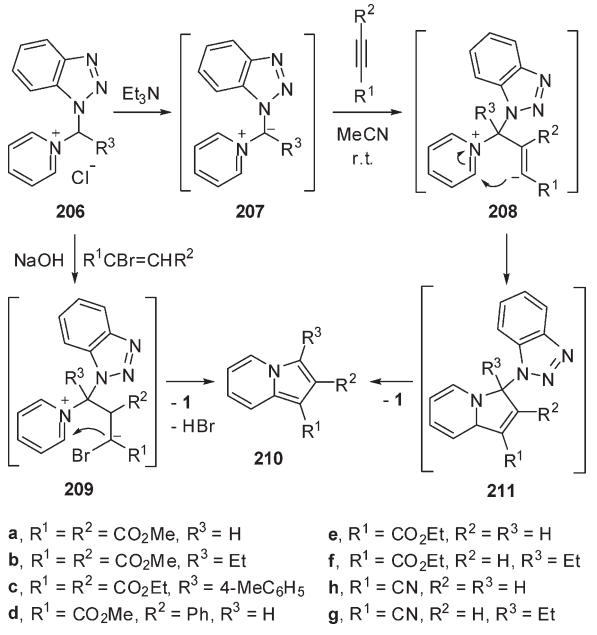


The anion generated from **48** on its treatment with *n*-BuLi adds to 2-cyclohexen-1-one to give isoindolidin-7-one anion **188** that spontaneously eliminates benzotriazolide anion to form regio- and diastereoselectively hexahydro-1,3-diphenyl-1*H*-isoindol-7-one **190** in 65% yield. The stereochemistry of **190** is given by NMR and X-ray crystallographic studies. A similar addition of **48** to quinone gives a mixture of products from which derivative **189**, with stereochemistry not established, is isolated in 18% yield (Scheme 42).[12]

The isoindole ring system also can be achieved by building of a six-membered ring on a pyrrole scaffold. Diels−Alder additions of dienes to maleimide provide an easy access to such molecules, and dienes are readily available with an aid of benzotriazole methodology. Thus, double alkylation of the methylene group in 1-allylbenzotriazole (**191**),[58] with chloromethytrimethylsilane

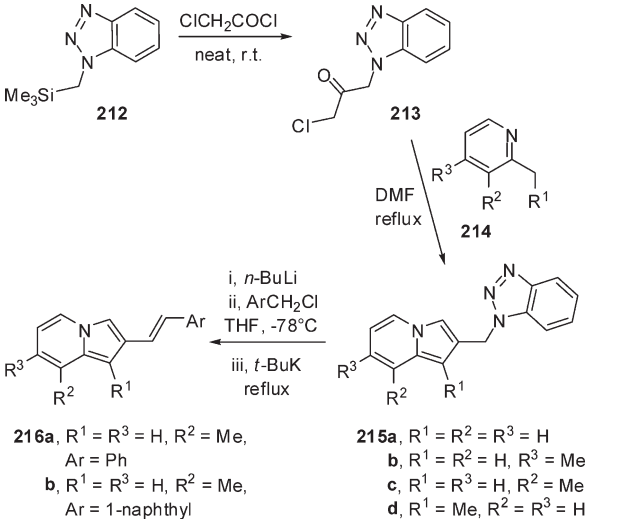
dx.doi.org/10.1021/cr200031r |*Chem. Rev.* 2011, 111, 7063–7120

Scheme 46



a, $R^1 = R^2 = CO_2Me$, $R^3 = H$
b, $R^1 = R^2 = CO_2Me$, $R^3 = Et$
c, $R^1 = R^2 = CO_2Et$, $R^3 = 4\text{-}MeC_6H_5$
d, $R^1 = CO_2Me$, $R^2 = Ph$, $R^3 = H$
e, $R^1 = CO_2Et$, $R^2 = R^3 = H$
f, $R^1 = CO_2Et$, $R^2 = H$, $R^3 = Et$
h, $R^1 = CN$, $R^2 = R^3 = H$
g, $R^1 = CN$, $R^2 = H$, $R^3 = Et$

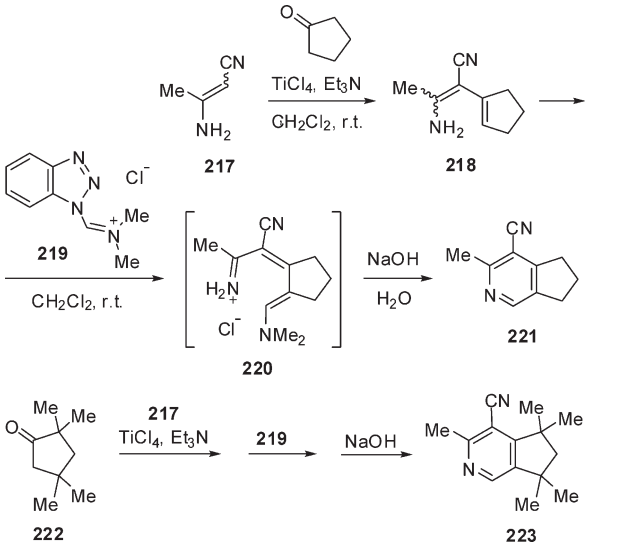
Scheme 47



216a, $R^1 = R^3 = H$, $R^2 = Me$, Ar = Ph
b, $R^1 = R^3 = H$, $R^2 = Me$, Ar = 1-naphthyl

215a, $R^1 = R^2 = R^3 = H$
b, $R^1 = R^2 = H$, $R^3 = Me$
c, $R^1 = R^3 = H$, $R^2 = Me$
d, $R^1 = Me$, $R^2 = R^3 = H$

Scheme 48



and RBr, generates thermally unstable derivatives **192** that readily eliminate 1-(trimethylsilyl)benzotriazole to afford dienes **193**, which are trapped in situ by *N*-phenylmaleimide to give 5-substituted 2-phenyl-2,3,3a,4,7,7a-hexahydro-1*H*-isoindole-1,3-diones **194** in 65% (R = *n*-Pr) and 54% (R = $PhCH_2$) yields (Scheme 43).[59]

5.3. Indolizine

Ester **195** is prepared by Wittig reaction of *N*-Boc protected piperidin-2-ylacetaldehyde[60] with (carbethoxymethylene)triphenylphosphorane and removal of the protecting group by TFA. Condensation of **195** with 1-(hydroxymethyl)benzotriazole (**25**) provides derivative **196** that is subsequently subjected to a reaction with samarium(II) iodide to give ethyl (indolizidin-2-yl)acetate (**200**) in 58% yield as a mixture of two diastereomers, which are separated by column chromatography. The reaction is assumed to proceed via reduction of iminium cation **197**[4,61] to radical **198** that by intramolecular addition to the double bond forms a five-membered ring and generates new radical **199**. Final reduction with another molecule of SmI_2 converts **199** to neutral indolizidine **200** (Scheme 44).[62]

The reaction of alkynyloxirane **9a** with 3-aminopropanol gives 1-(3-hydroxypropyl)pyrrole **201** in 60% yield. Upon treatment with *n*-BuLi, tosyl derivative **202** undergoes cyclocondensation with formation of a six-membered ring to give 8-(benzotriazol-1-yl)-2-phenyl-5,6,7,8-tetrahydroindolizine **203** in 90% yield. The benzotriazolyl moiety in **203** can be substituted with nucleophiles, as is illustrated by its reaction with benzylmagnesium iodide providing indolizine **204** in 80% yield; however, elimination of benzotriazole is preferred when sodium diethylmalonate is used as a nucleophile giving 2-phenyl-5,6-dihydroindolizine **205** in 68% yield (Scheme 45).[5]

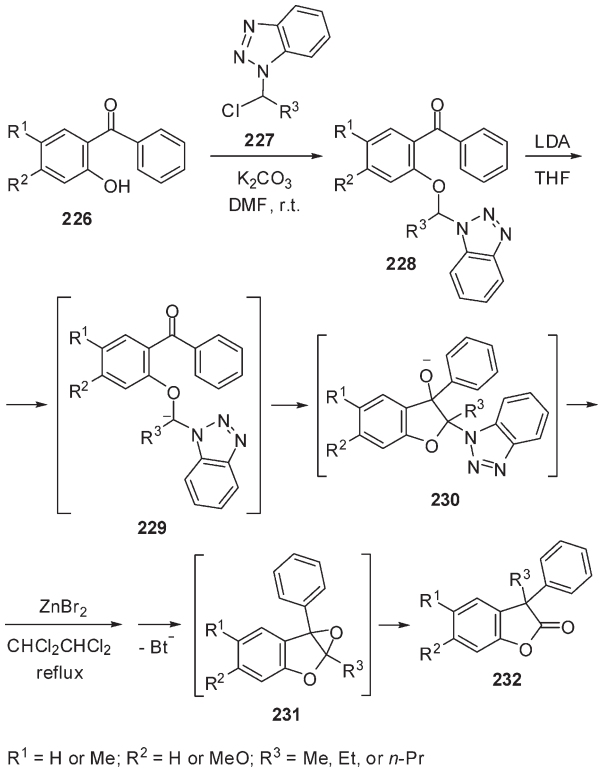
Condensation of benzotriazole with aldehydes and pyridine in the presence of thionyl chloride generates salts **206** in 71−73% yields. Treatment with triethylamine converts **206** into ylides **207** that can be effectively trapped with dienophiles. Thus, additions of **207** to the triple bond of 2-butynedioic acid esters result in zwitterions **208** that cyclize to 3,8a-dihydroinolizines **211**. Elimination of benzotriazole (**1**) from **211** restores aromaticity of the system, producing indolizines **210a**−**c** in 66−69% yields. Methyl 3-phenyl-2-propynoate reacts similarly to give indolizine **210d** in 59% yield. In an alternative approach, salts **206** are treated with ethyl 3-bromoacrylate or 3-bromoacrylonitrile in the presence of NaOH. In that case, initially obtained zwitterions **209** undergo cyclization followed by elimination of benzotriazole and HBr to give indolizines **210e**−**g** in 71−74% yields (Scheme 46).[63]

1-(Trimethylsilylmethyl)benzotriazole (**212**)[64] reacts with chloroacetyl chloride to give 1-(benzotriazol-1-yl)-3-chloroacetone (**213**), a versatile 1,2- or 1,3-dielectrophile, in 84% yield. Condensation of **213** with 2-alkylpyridines **214** in refluxing DMF provides 2-(benzotriazol-1-ylmethyl)indolizines **215** in 54−66%

dx.doi.org/10.1021/cr200031r |*Chem. Rev.* 2011, 111, 7063–7120

Figure 5. Atom numbering in benzofuran and benzothiophene.

Scheme 49



yields. Removal of benzotriazole moiety from indolizines **215** is demonstrated by lithiation of **215c** and treatment with benzyl or naphth-1-ylmethyl chloride followed by heating with *t*-BuOK to give 2-(2-arylethenyl)indolizines **216a** (75% yield) and **216b** (70% yield) (Scheme 47).[65]

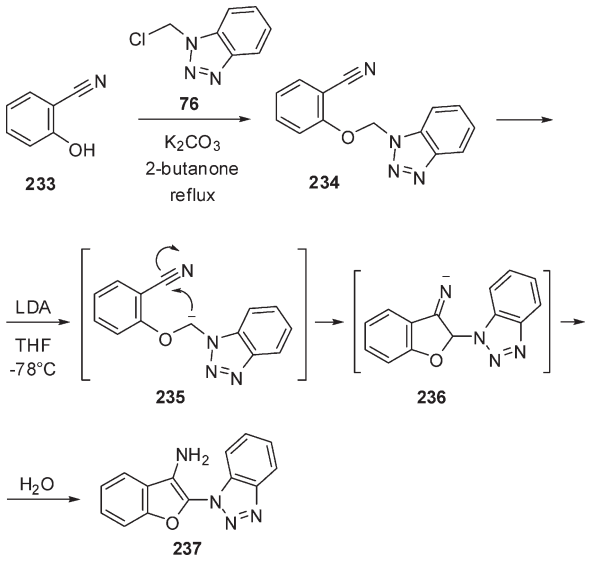
5.4. Cyclopenta[*c*]pyridine

In the presence of the $TiCl_4/Et_3N$ catalyst, cyclopentanone reacts with 3-aminocrotononitrile (**217**) to give 3-amino-2-(1-cyclopenten-1-yl)-2-butenenitrile (**218**) in 69% yield. Condensation of **218** with iminium chloride **219**, a Vilsmeier type reagent readily available from reaction of 1-(trimethylsilyl)benzotriazole with DMF and $SOCl_2$,[66] provides 3-methyl-6,7-dihydro-5*H*-cyclopenta[*c*]pyridine-4-carbonitrile (**221**) in 68% yield. The structure of intermediate **220** is confirmed by NMR spectra of the reaction mixture before addition of NaOH that causes its cyclization. An analogous reaction sequence converts 2,2,4,4-tetramethylcyclopentanone (**222**) into cyclopenta[*c*]pyridine derivative **223** in 60% yield (Scheme 48).[67]

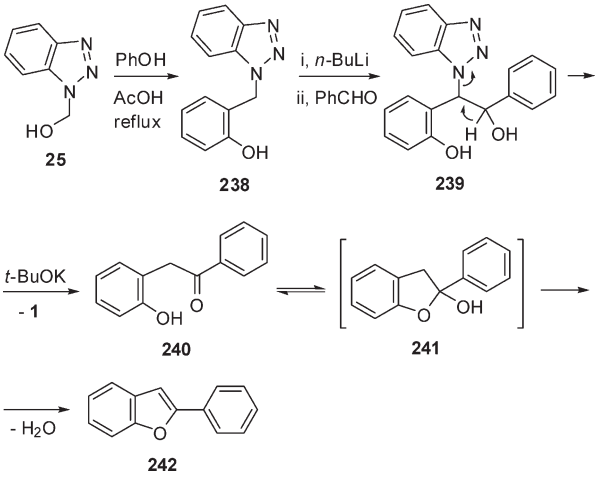
6. (5,6)-C_8O AND -C_8S RING SYSTEMS

Derivatives of benzofuran (**224**) and benzothiophene (**225**) that have been synthesized using benzotriazole methodology are discussed in this section (Figure 5).

Scheme 50



Scheme 51



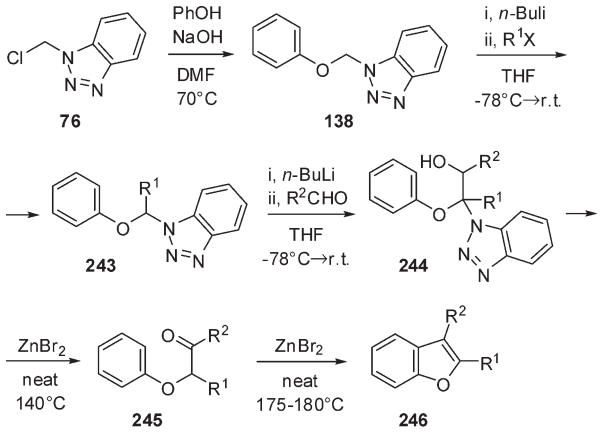
6.1. Benzofuran

Most of the synthetic methods for benzofuran systems rely on addition of a two-carbon unit to a phenol molecule. The synthetic pathway may start from formation of the C(3)−C(3a) bond and be finalized by formation of the O−C(2) bond; or it can be done in the opposite order, with the O−C(2) bond coming first. Application of benzotriazole methodology to this process allows easy access to the two-carbon unit, which can be constructed in intermediate steps on the synthetic pathway.

In an example of the first approach, C(3)−C(3a) bond before O−C(2), phenols are benzoylated to give 2-hydroxybenzophenones **226** that react with 1-(1-chloroalkyl)benzotriazoles **227**[68] under basic conditions (K_2CO_3) to provide 1-(benzotriazol-1-yl)-alkyl 2-benzoylphenyl ethers **228** in 56−77% yields. Treatment of **228** with LDA generates anions **229** that in an intramolecular nucleophilic attack on the carbonyl group form a heterocyclic ring of 2,3-dihydrobenzofurans **230**. To prove structure of intermediates **230**, one of them ($R^1 = R^2 = H$, $R^3 = Me$)

dx.doi.org/10.1021/cr200031r |*Chem. Rev.* 2011, 111, 7063–7120

Scheme 52



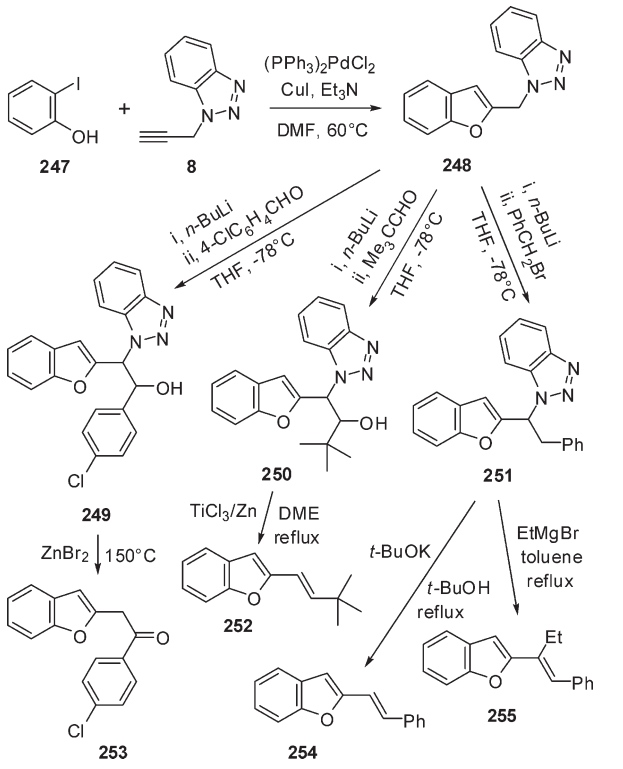
was neutralized, separated, and analyzed by NMR. In all other cases, reaction mixtures containing **230** were treated with zinc bromide and heated at reflux in 1,1,2,2-tetrachloroethane to give 2,3-dihydrobenzofuran-2-ones **232** in 41−70% yields (Scheme 49). The reaction mechanism probably involves formation of oxirane intermediates **231** and their rearrangement.[69]

A similar approach is used for the synthesis of 3-amino-2-(benzotriazol-1-yl)furan **237** (Scheme 50). Thus, alkylation of salicylonitrile (**233**) with 1-(chloromethyl)benzotriazole (**76**) provides ether **234** in 96% yield. Treatment of **234** with LDA generates anion **235** that attacks the cyano group to give cyclic imine anion **236**. Hydrolysis and tautomerization of **236** during aqueous workup results in **237** (59% yield).[36]

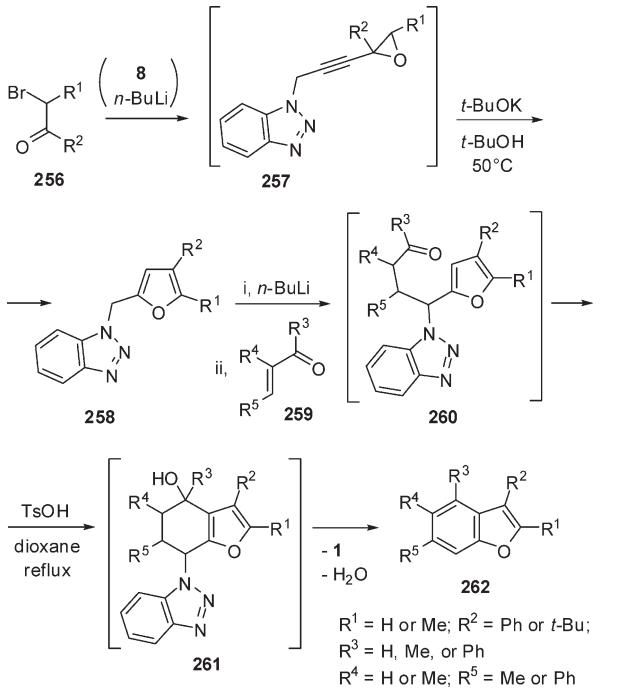
Another approach to conversion of phenols into benzofurans with aid of benzotriazole methodology is outlined in Scheme 51. Thus, condensation of 1-(hydroxymethyl)benzotriazole (**25**) with phenol in refluxing acetic acid produces 2-(benzotriazol-1-ylmethyl)phenol (**238**) in 55% yield.[25] Addition of lithiated **238** to the carbonyl group of benzaldehyde generates alcohol **239** that eliminates benzotriazole (**1**) upon treatment with *t*-BuOK to give 2-phenacylphenol (**240**) in 40% yield. Derivative **240** is a convenient precursor of 2-phenylfuran (**242**); even during storage at room temperature, it spontaneously eliminates water, probably via intermediate **241**, to give **242**.[70]

For the benzofuran synthesis shown in Scheme 52, the reaction sequence starts from formation of the O−C(2) bond, then the C(2)−C(3) bond is added, and finally the heterocyclic ring is closed by the C(3)−C(3a) bond. In this pathway, (benzotriazol-1-yl)methyl phenyl ether (**138**) is obtained in 96% yield by nucleophilic substitution of the chloride in **76** by phenoxide anion. Lithiation of the methylene group in **138** allows its alkylation to give ethers **243** in 88−95% yields. Repeated lithiation followed by treatment with aldehydes converts **243** into β-hydroxyalkyl ethers **244**. Of the four examples given, only **244d** was isolated, purified, and characterized as a mixture of two diastereomers; others were directly treated with $ZnBr_2$, after evaporation of THF, to be converted to β-ketoalkyl ethers **245** in 62−84% yields. At higher temperature (175−180 °C), the heterocyclic ring is closed in an electrophilic attack

Scheme 53



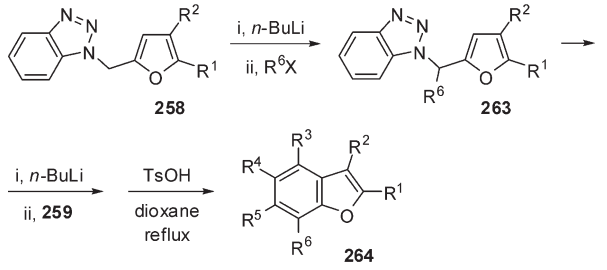
Scheme 54



of the carbonyl group activated by $ZnBr_2$ on the *ortho*-carbon atom to furnish benzofurans in 59% (**246c**) to 80% (**246a**) yields. Starting this reaction sequence from phenols bearing alkyl groups on the aromatic ring allows preparation of **246** with substituents on C-4 to C-7.[71]

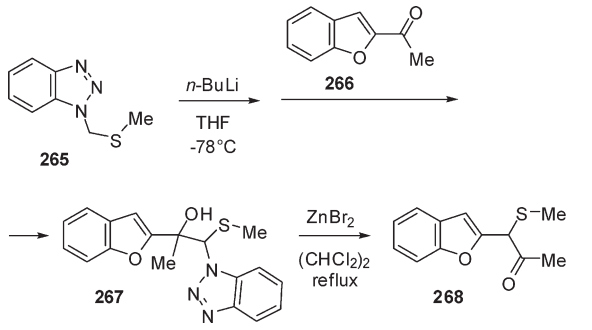
dx.doi.org/10.1021/cr200031r |*Chem. Rev.* 2011, 111, 7063–7120

Scheme 55

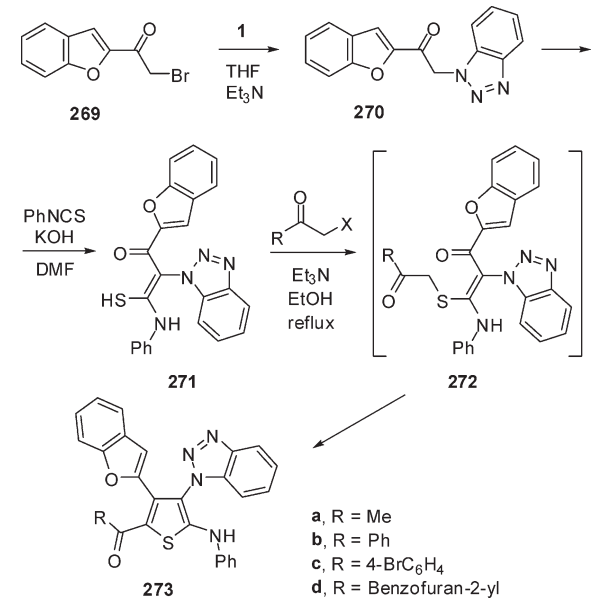


a, $R^1 = R^4 = H$, $R^2 = t$-Bu, $R^3 = R^5 = Ph$, $R^6 = PhCH_2$
b, $R^1 = Me$, $R^2 = R^3 = R^5 = Ph$, $R^4 = H$, $R^6 = n$-Bu
c, $R^1 = R^3 = H$, $R^2 = t$-Bu, $R^4 = Me$, $R^5 = Ph$, $R^6 = PhCH_2$

Scheme 56



Scheme 57



a, R = Me
b, R = Ph
c, R = 4-BrC_6H_4
d, R = Benzofuran-2-yl

The two-carbon element for construction of the furan ring can be delivered in the form of a propargyl group, as in the reaction depicted in Scheme 53. Thus, cycloaddition of 1-propargylbenzotriazole (**8**) with 2-iodophenol (**247**), promoted by a palladium/copper catalyst, directly provides 2-(benzotriazol-1-ylmethyl)furan (**248**) in 70% yield. The activation of the methylene group in **248** by the benzotriazolyl substituent allows lithiation of the methylene and reactions with electrophiles. In the examples given, lithiated **248** reacts with aldehydes to give alcohols **249** and **250** in 65 and 72%, respectively, and with benzyl bromide to give 2-[(1-benzotriazol-1-yl)-2-phenylethyl]benzofuran (**251**) in 74% yield. Several methods are employed for removal of the benzotriazolyl moiety from benzofuran derivatives **249**−**251**: (i) heating with zinc bromide converts **249** into ketone **253** in 64% yield; (ii) in a reaction with low-valent titanium ($TiCl_3$ + Zn), **250** is converted into alkene **252** in 68% yield; (iii) treatment of **251** with potassium *tert*-butoxide allows elimination of benzotriazole to give 2-(2-phenylethenyl)benzofuran (**254**) in 87% yield; (iv) ethylmagnesium bromide in refluxing toluene converts **251** into 2-(1-ethyl-2-phenylethenyl)benzofuran (**255**) in 52% yield. The dehydrogenation mechanism of reaction **251** → **255** is not clear.[72]

In all the examples of benzofuran synthesis discussed so far (Schemes 49−53), the heterocyclic ring is built on a phenol scaffold, but benzofurans can also be build by construction of the benzene ring on furan derivatives. Thus, the reaction sequence shown in Scheme 54 starts from the synthesis of 2-(benzotriazol-1-ylmethyl)furans **258** (yields 60−74%) by treatment of lithiated **8** with α-bromoketones (**256**). The reaction proceeds via oxirane **257** that upon treatment with potassium *tert*-butoxide undergoes deprotonation of the methylene group followed by ring-opening and rearrangement to **258**, involving a cumulene intermediate.[73] Addition of lithiated **258** to α,β-unsaturated aldehydes and ketones **259** results in products **260** that are subsequently converted to benzofurans **262** (yields 46−66%) by heating with an acid. This reaction is expected to involve formation of saturated cyclization product **261** that eliminates benzotriazole and water to give **262**.[72]

To introduce a substituent to C-7 of the benzofuran system, the lithiated methylene group in intermediates **258** is first alkylated to give derivatives **263** in 50−66% yields. The subsequent lithiation, addition to **259**, and cyclization by TsOH in refluxing dioxane furnishes benzofurans **264** in 48−50% yields (Scheme 55).[72]

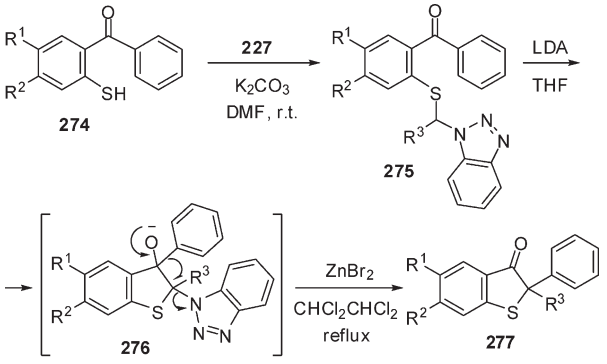
Benzotriazole methodology can also be used as a convenient tool for modification of functional groups attached to benzofuran. Thus, in the first such example (Scheme 56), an anion derived from thioether **265** adds to the carbonyl group of 2-acetylbenzofuran (**266**) to give alcohol **267** in 75% yield. Treatment of **267** with zinc bromide at elevated temperature cleaves the benzotriazolyl−N1−Cα bond, and the generated carbocation rearranges to 1-thiomethoxy-1-(benzofuran-2-yl)acetone (**268**), isolated in 40% yield.[74]

In another example of benzotriazole aid to benzofuran derivatization (Scheme 57), 2-(bromoacetyl)benzofuran (**269**) is treated with benzotriazole (**1**) to give ketone **270** in 74% yield that is subsequently treated with phenyl isothiocyanate to give enaminone **271** (69% yield). Condensation of **271** with halomethyl ketones produces intermediates **272** that in the presence of KOH cyclize to thiophenes **273** with 63−72% yields.[75]

6.2. Benzothiophene

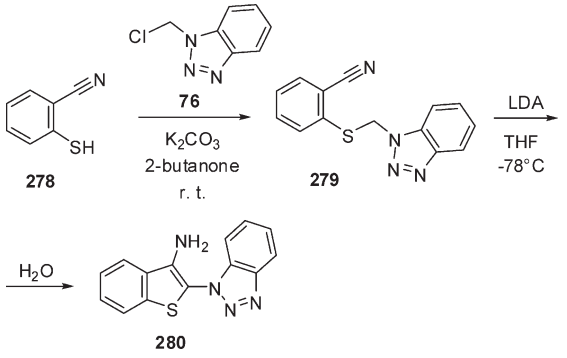
Generally speaking, chemistry and synthetic methods for benzothiophene and benzofuran are similar; however, in some instances, due to subtle electronic differences between oxygen and sulfur, replacement of the oxygen with sulfur atom in the

Scheme 58



R^1 = H or Me, R^2 = H or MeO, R^3 = Me, Et, or *n*-Pr

Scheme 59

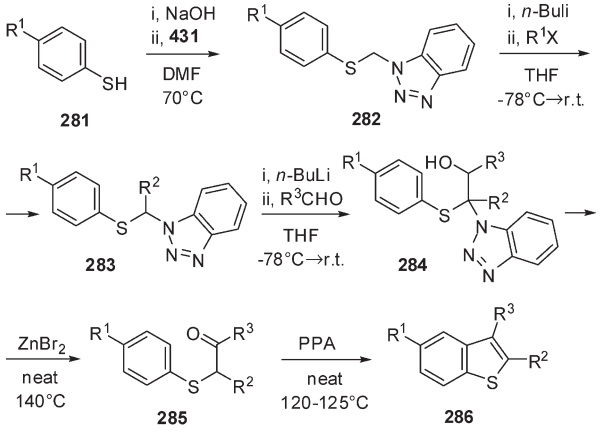


starting material leads to a completely different product. Thus, following the example of Scheme 49, 2-sulfanylbenzophenones **274**, sulfur analogues of phenols **226**, are *S*-alkylated with 1-(1-chloroalkyl)benzotriazoles **227** in the presence of anhydrous potassium carbonate to give derivatives **275** in 43% ($R^1 = R^3 =$ Me, R^2 = H) to 98% (R^1 = H, R^2 = MeO, R^3 = Me) yields. Intramolecular addition of lithiated **275** to the carbonyl group closes the heterocyclic ring to form anion **276**. At this point, the analogy with benzofurans ends: the subsequent treatment with zinc bromide converts **276** into 2,3-dihydrobenzothiophen-3-ones **277** in 37% (R^1 = H, R^2 = MeO, R^3 = Et) to 75% ($R^1 = R^2 =$ H, R^3 = Et) yields, while 2,3-dihydrobenzofuran-2-ones are obtained from **230**, oxygen analogues of **276**. A simple migration of the phenyl group from C-3 to C-2 accompanies departure of the benzotriazolyl moiety in **276** (Scheme 58), whereas **230** undergoes more complex transformations involving an oxirane ring.[69]

Analogously to the synthesis of 3-amino-2-(benzotriazol-1-yl) furan (**237**), thiosalicylonitrile (**278**) is alkylated with 1--(chloromethyl)benzotriazole (**76**), and the obtained thioether **279** is treated with LDA to give 3-amino-2-(benzotriazol-1-yl)thiophene (**280**) in 78% yield (Scheme 59).[36]

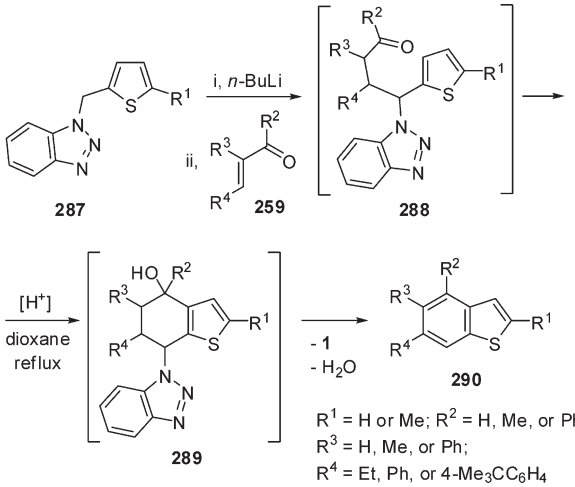
Similarly to the corresponding synthesis of benzofurans (Scheme 52), benzothiophene systems can be easily built on thiophenol templates using benzotriazole methodology. In this approach, thiophenols **281** are benzotriazolomethylated using 1-(chloromethyl)benzotriazole (**76**) to produce thioethers **282**

Scheme 60



a, R^1 = Cl, R^2 = $PhCH_2$, R^3 = $PhCH_2CH_2$
b, R^1 = Me, R^2 = Me, R^3 = 4-MeC_6H_4

Scheme 61



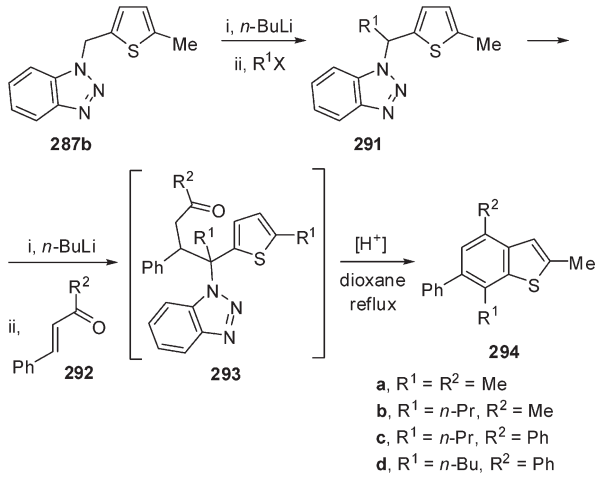
R^1 = H or Me; R^2 = H, Me, or Ph;
R^3 = H, Me, or Ph;
R^4 = Et, Ph, or 4-$Me_3CC_6H_4$

in practically quantitative yields. In a one-pot procedure, alkylation of lithiated **282** provides thioethers **283** that are lithiated once more and treated with aldehydes to give β-hydroxythioethers **284**. Elimination of benzotriazole by heating with zinc bromide converts alcohols **284** into ketones **285** (81% yield for **285b**, 3 steps). Finally, cyclization using polyphosphoric acid (PPA) furnishes benzothiophenes **286** in 78−79% yields (Scheme 60).[71]

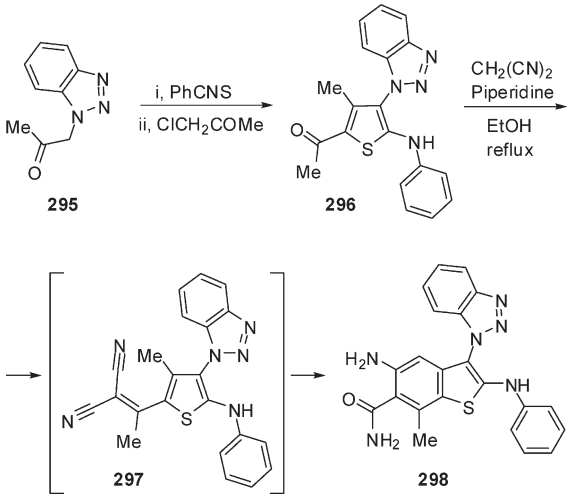
In analogy to benzofurans (Scheme 54), benzothiophenes can also be obtained by addition of a benzene ring to thiophene. Thus, starting 2-(benzotriazol-1-ylmethyl)thiophenes **287** are readily prepared by condensation of thiophenes with 1-(hydroxymethyl)benzotriazole (**25**) in refluxing acetic acid.[7] Addition of lithiated **287** to α,β-unsaturated aldehydes and ketones **259** provides derivatives **288**, which upon treatment with Amberlyst-15 acidic resin in refluxing dioxane cyclize to 4,5,6,7-tetrahydrobenzothiophenes **289** that spontaneously undergo aromatization by elimination of benzotriazole and water to give benzothiophenes **290** in 45% (R^1 = Me, $R^2 = R^4$ = Ph, R^3 = H)

dx.doi.org/10.1021/cr200031r |*Chem. Rev.* 2011, 111, 7063–7120

Scheme 62



Scheme 63



to 90% ($R^1 = R^3 = H$, $R^2 = R^4 = Ph$) yields (Scheme 61).[8] To introduce a substituent to C-7, the methylene group in **287b** is first alkylated to give 2-(1-benzotriazol-1-ylalkyl)-5-methylthiophenes **291**, which are then subjected to regular addition to alkenones **292** to give ketones **293** that by treatment with an acid are converted to 2,4,6,7-tetrasubstituted benzothiophenes in 36% (**294c**) to 81% (**294a**) yields (Scheme 62).[8]

In another example of such an approach (Scheme 63), condensation of (benzotriazol-1-yl)acetone (**295**) with phenyl isothiocyanate and chloroacetone provides thiophene **296** in 83% yield. The acetyl and methyl groups of **296** are used for construction of the benzene ring in a reaction with malononitrile, via intermediate **297**. One of the cyano groups of **297** is used for cyclocondensation with the methyl group, while the other is hydrolyzed to the amido group to give final benzothiophene **298** in 66% yield.[76]

7. (5,6)-C_7N_2 RING SYSTEMS

There are 20 possible (5,6)-bicyclic ring systems with skeleton formula C_7N_2: one with both nitrogens on the bridge, three with one nitrogen on the bridge and one in the five-membered ring,

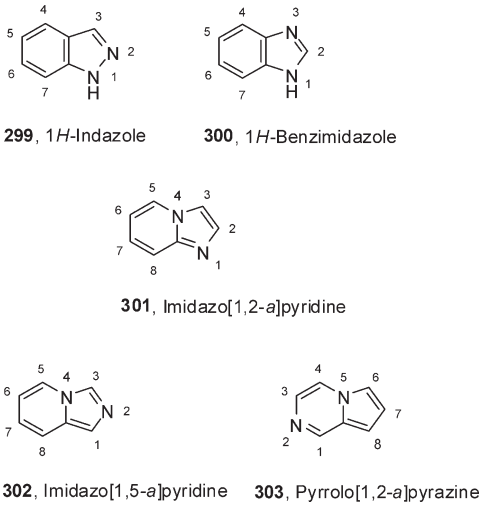
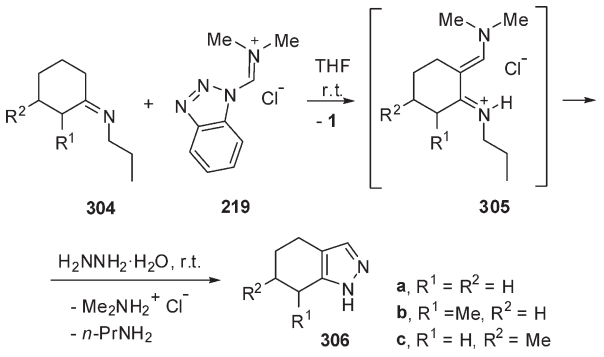


Figure 6. Atom numbering in (5,6)-C_7N_2 ring systems.

Scheme 64



four with one nitrogen on the bridge and one in the six-membered ring, two with both nitrogens exclusively in the five-membered ring, four with both nitrogens exclusively in the six-membered ring, and six with one nitrogen in the five-membered ring and one in the six-membered ring without sharing them between rings. The benzotriazole assisted synthesis has been applied only to the five most common of these systems, which are presented in Figure 6. To avoid confusion, atom numbering is given for each of these heterocycles.

7.1. Indazole

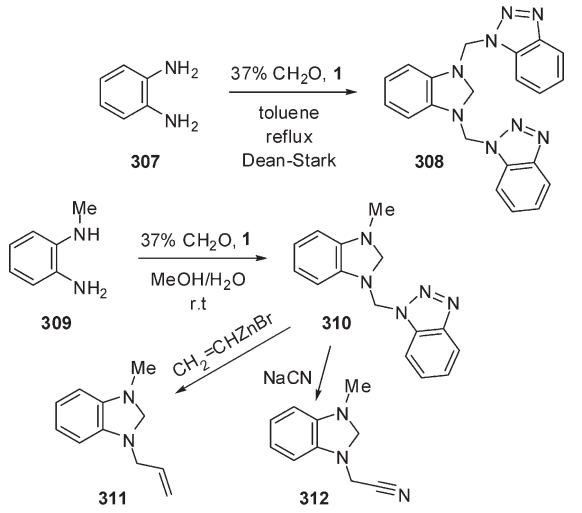
Imine **304a**, prepared by condensation of cyclohexanone with propylamine in the presence of $TiCl_4$ and triethylamine, reacts with benzotriazoloformiminium chloride **219** to give salt **305a**. Compound **305a** can be considered as a protected form of 2-formylcyclohexanone—its condensation with hydrazine provides 4,5,6,7-tetrahydroindazole (**306a**) in 66% yield. Similar reactions carried out on imines (**304b** and **304c**), derived from 2- and 3-methylcyclohexanones, produce the corresponding 4,5,6,7-tetrahydroindazoles, but the yields are low: 20% for **306b** and 19% for **306c** (contaminated with its 4-methyl isomer) (Scheme 64).[77]

7.2. Benzimidazole

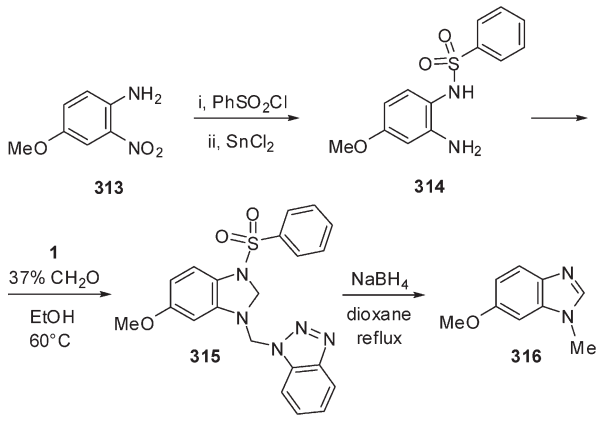
7.2.1. Benzimidazolines. Benzimidazolines, a common name for 2,3-dihydrobenzimidazoles, having *N*-(benzotriazol-1-ylmethyl)

dx.doi.org/10.1021/cr200031r |*Chem. Rev.* 2011, 111, 7063–7120

Scheme 65



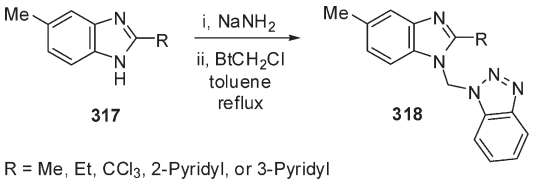
Scheme 66



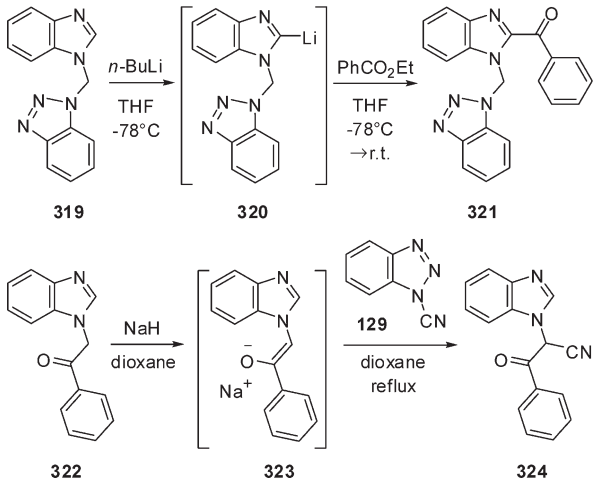
substituents are readily prepared by condensation of 1,2-phenylenediamines with formaldehyde and benzotriazole. Thus, refluxing a solution of **307**, 37% aqueous formaldehyde, and benzotriazole in toluene results in a glassy material of three isomeric products, Bt(1)−Bt(1), Bt(1)−Bt(2), and Bt(2)−Bt(2), from which Bt(1)−Bt(1) isomer **308** is separated in 22% yield by recrystallization from ethanol/dioxane.[78] In methanol−water, *N*-methylphenylenediamine (**309**) reacts with two molecules of formaldehyde and one of benzotriazole to give 1-(benzotriazol-1-ylmethyl)-3-methyl-2,3-dihydrobenzimidazole (**310**) and its benzotriazol-2-yl isomer in a ratio of 6:1 and total yield of 85%. The benzotriazolyl substituent in **310** can be replaced with soft nucleophiles: with vinylzinc bromide, benzimidazoline **311** is obtained in 83% yield; and with sodium cyanide, derivative **312** is produced in 94% yield. However, products **311** and **312** decompose slowly when exposed to air (Scheme 65).[79]

The amino group in 4-methoxy-2-nitroaniline (**313**) is protected with a benzenesulfonyl substituent, and the nitro group is reduced to provide sulfonamide **314** in 79% yield. Condensation with formaldehyde and benzotriazole converts **314** into 3-benzenesulfonyl-1-(benzotriazol-1-ylmethyl)-6-methoxy-2,3-dihydrobenzimidazole (**315**) and its benzotriazol-2-yl isomer in

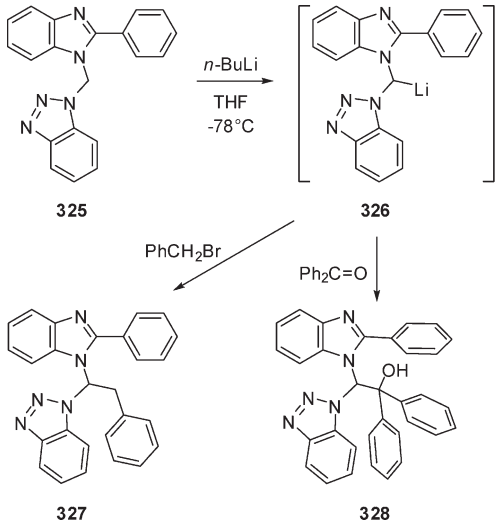
Scheme 67



Scheme 68



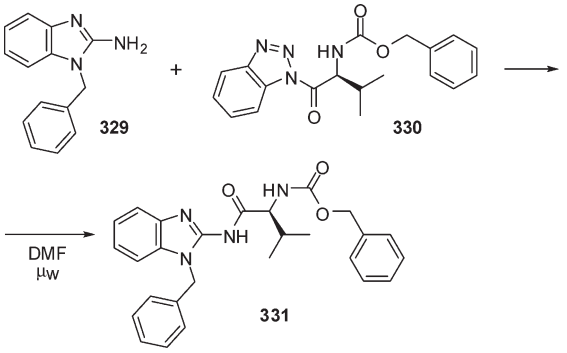
Scheme 69



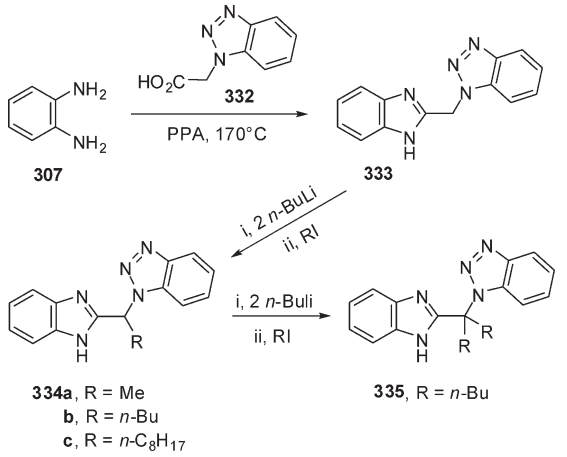
high yield. Treatment of **315** with sodium borohydride in refluxing dioxane causes elimination of benzenesulfinic acid and reduction of the benzotriazolylmethyl group to produce 6-methoxy-1-methylbenzimidazole (**316**) in 75% yield. This is an example of using a benzotriazole auxiliary in regioselective synthesis of disubstituted benzimidazoles—simple methylation of 5-methoxybenzimidazole results in a mixture of two isomers that are difficult to separate (Scheme 66).[80]

dx.doi.org/10.1021/cr200031r |*Chem. Rev.* 2011, 111, 7063–7120

Scheme 70



Scheme 71

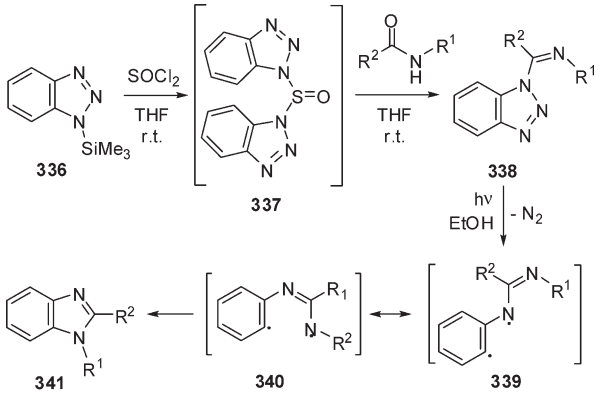


7.2.2. Substituents at N-1. Anions generated from 2-substituted 5-methylbenzimidazoles **317** by sodium amide are treated with 1-(chloromethyl)benzotriazole in refluxing toluene to give 1-(benzotriazol-1-ylmethyl)benzimidazoles **318** in 70−72% yields (Scheme 67). 6-Methyl regioisomers of **318** have not been isolated. Products **318** exhibit interesting antifungal activity.[81]

1-(Benzotriazol-1-ylmethyl)benzimidazole (**319**) is prepared in 80% yield by reaction of benzimidazole with sodium ethoxide and 1-(chloromethyl)benzotriazole in ethanol. Because of higher acidity of the hydrogen at C-2 than in the methylene group, treatment of **319** with *n*-butyllithium generates intermediate **320** that is trapped in a reaction with ethyl benzoate to give 1,2-disubstituted benzimidazole **321** in 78% yield.[19] However, the more acidic methylene group in 1-phenacylbenzimidazole (**322**) allows generation of anion **323** without affecting the hydrogen at C-2. Using 1-cyanobenzotriazole (**129**) as electrophile, anion **323** is trapped to give nitrile **324** in 82% yield (Scheme 68).[82]

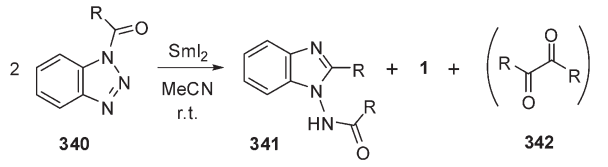
In 1-(benzotriazol-1-ylmethyl)benzimidazoles with a substituent at C-2, like derivative **325**, the lithiation takes place on the methylene group, allowing substitution of its hydrogens with electrophiles. Treatment of lithiated intermediate **326** with benzyl bromide provides benzylated derivative **327** in 83% yield, whereas in the reaction with benzophenone, alcohol **328** is obtained in 79% yield (Scheme 69).[19]

Scheme 72



R1 = Ph, 4-MeC6H4, 4-i-PrC6H4, 4-ClC6H4, 4-BrC6H4, or 2-AcC6H4
R2 = Me or Ph

Scheme 73



R = Me, Et, n-C4H9, n-C6H13, n-C8H17, n-C9H19, c-C6H11, Ph, 2-ClC6H4, 3-ClC6H4, 4-ClC6H4, or 4-MeC6H4

7.2.3. Substituents at C-2. Treatment of 2-amino-1-benzylbenzimidazole (**329**) with 1-acylbenzotriazole **330**, obtained in a reaction of benzotriazole and thionyl chloride with *N*-protected L-valine, provides derivative **331** in 98% yield (Scheme 70).[83]

(Benzotriazol-1-yl)acetic acid (**332**) is obtained in 90% yield from a reaction of benzotriazole with chloroacetic acid in refluxing toluene. Condensation of **332** with *ortho*-phenylenediamine (**307**) in polyphosphoric acid at 170 °C provides 2-(benzotriazol-1-ylmethyl)benzimidazole (**333**) in 70% yield. The X-ray crystal structure of **333**, as hemihydrate, has been analyzed.[84] The dianion generated from **333** by 2 equiv of *n*-BuLi is selectively C-alkylated with *n*-alkyl iodides to give 2-(1-benzotriazol-1-ylalkyl)benzimidazoles **334a**−**c** in 68, 57, and 62% yields, respectively. Repeated lithiation and treatment with *n*-butyl iodide converts **334b** into dialkylated product **335** in 40% yield (Scheme 71).[85] Some derivatives of **333** have found application as antiviral agents.[86,87]

7.2.4. Ring Conversion of Benzotriazoles into Benzimidazoles. 1-Imidoylbenzotriazoles **338** are readily prepared in reactions of amides with 1,1′-sulfinyldibenzotriazole (**337**) that is generated in situ from 1-(trimethylsilyl)benzotriazole (**336**) and thionyl chloride.[88] Irradiation of **338** with UV light (from a medium-pressure Hg lamp) causes their conversion into benzimidazoles **341** in 23% (R^1 = 4-MeC_6H_4, R^2 = Me) to 87% (R^1 = R^2 = Ph) yields. The reaction is believed to proceed via extrusion of nitrogen from the benzotriazole ring to give diradical **339**, mesomeric with diradical **340**, which undergoes coupling to imidazole **341** (Scheme 72).[89]

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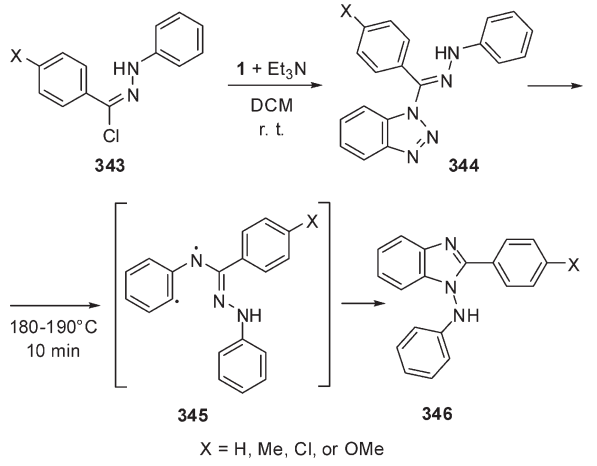
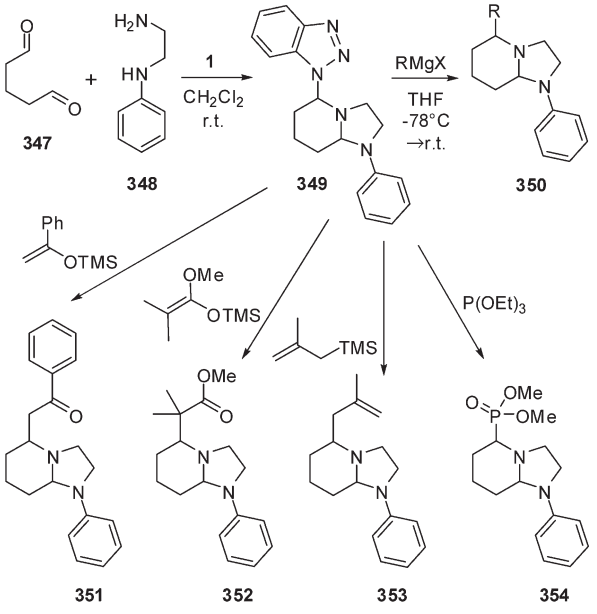
Scheme 74



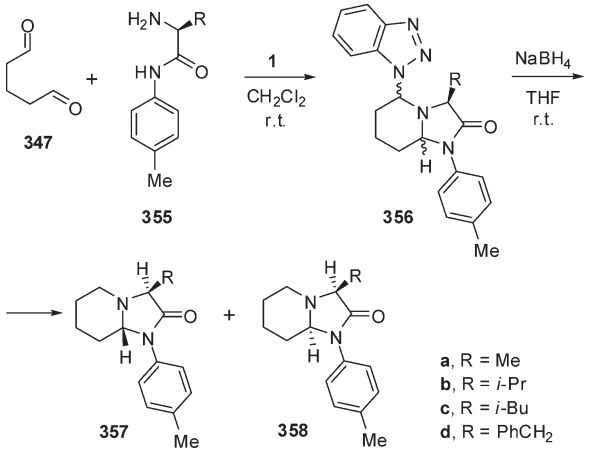
Scheme 75



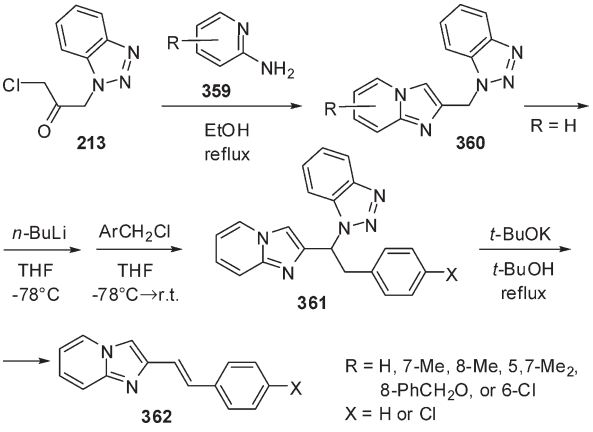
Opening of the heterocyclic ring in benzotriazole derivatives and subsequent ring-closing to a benzimidazole system can also be done without loss of nitrogen. Thus, reduction of 1-acylbenzotriazoles **340** with samarium(II) iodide (2 molar equiv) leads to 1-acylamido-2-alkyl(or aryl)benzimidazoles **341** in 43% (R = 4-ClC_6H_4) to 82% (R = *c*-C_6H_{11}) yields. In some of these reactions, α-diketones **342** are isolated as side-products; however, in the case of R = 4-$MeOC_6H_4$, the corresponding α-diketone is the only product, isolated in 72% yield. Acetonitrile must play a vital role in these reactions, as only α-diketones **342** are obtained from reduction of **340** with SmI_2 in THF. The mechanism of conversion of **340** to **341**, involving a couple of SETs, is not clear (Scheme 73).[90]

1-Benzoylbenzotriazole phenylhydrazones **344** are readily prepared in 45−63% yields by substitution of the chlorine atom in *N*-phenylbenzohydrazonyl chlorides **343** with benzotriazole. Brief heating at 180−190 °C causes extrusion of nitrogen from the benzotriazole ring with formation of diradicals **345** that immediately cyclize to 2-aryl-1-(phenylamino)benzimidazoles **346**, which are separated in 70−78% yields (Scheme 74).[91]

Scheme 76



Scheme 77

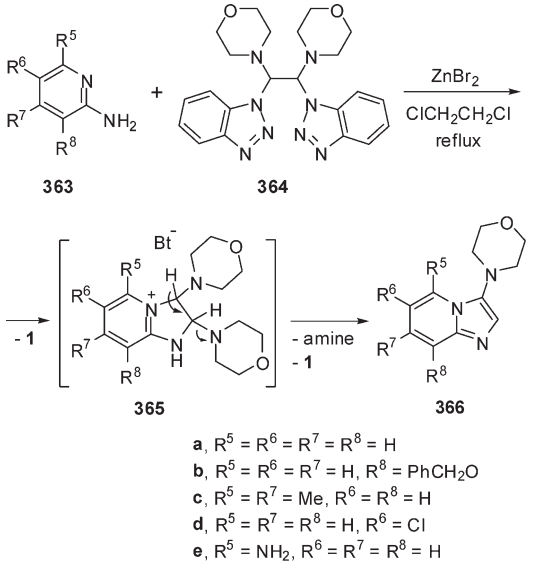


7.3. Imidazo[1,2-*a*]pyridine

7.3.1. Octahydro Derivatives. Condensation of glutaraldehyde (**347**, 50% aqueous solution) with *N*-phenyl-1,2-ethylenediamine (**348**) in dichloromethane provides a mixture of 1-phenyl-5-(benzotriazol-1-yl)octahydroimidazo[1,2-*a*]pyridine (**349**) and its benzotriazol-2-yl isomer (ratio 7:3) in quantitative yield. Because there is no difference in reactivity of these isomers, the crude product mixture is used in the subsequent reactions without separation. Thus, organomagnesium reagents convert **349** (and its Bt-2 isomer) into 1-phenyloctahydroimidazo[1,2-*a*]pyridines **350**, substituted at C-5 with an alkyl, aryl, or alkynyl group, in 79−91% yields. In the presence of $BF_3 \cdot OEt_2$, **349** reacts with alken-1-ylsilyl ethers and 2-methylallylsilane to give ketone **351** (71% yield), ester **352** (69% yield), and alkene **353** (66% yield), respectively. Nucleophilic substitution of the benzotriazolyl moiety in **349** with triethyl phosphite results in phosphonate **354** in 71% yield (Scheme 75).[9]

dx.doi.org/10.1021/cr200031r |*Chem. Rev.* 2011, 111, 7063–7120

Scheme 78



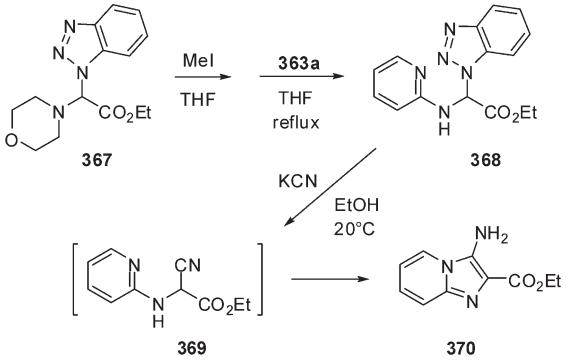
Condensation of **347** with benzotriazole and amides **355** derived from chiral amino acids provides 1,3,5-trisubstituted octahydroimidazo[1,2-*a*]pyridin-2-ones **356** as complex mixtures of stereo- and benzotriazol-1-yl/2-yl isomers. Removal of the benzotriazolyl moieties from **356** by treatment with sodium borohydride provides optically active trans 1,3-disubstituted octahydroimidazo[1,2-*a*]pyridin-2-ones **357** in 42% (**c**) to 58% (**b**) yields and small amounts (0−11%) of their cis isomers **358** (Scheme 76).[10]

7.3.2. Aromatic Systems. Most of the synthetic methods for imidazo[1,2-*a*]pyridines rely on addition of a two-carbon unit to 2-aminopyridine. Thus, in the first approach, cyclocondensation of 1-(benzotriazol-1-yl)-3-chloroacetone (**213**) with 2-aminopyridines **359** gives 2-(benzotriazol-1-ylmethyl)imidazo[1,2-*a*]pyridines **360** in 43% (R = 5,7-Me_2) to 76% (R = 8-$PhCH_2O$) yields. To demonstrate removal of the benzotriazolyl moiety from a molecule, the methylene group in one of **360** (with R = H) is benzylated to give derivatives **361** that without separation are subsequently treated with *t*-BuOK in refluxing *t*-butanol to furnish 2-(*E*-2-arylethylene)imidazo[1,2-*a*]pyridines **362** in 71−74% yields (Scheme 77).[65]

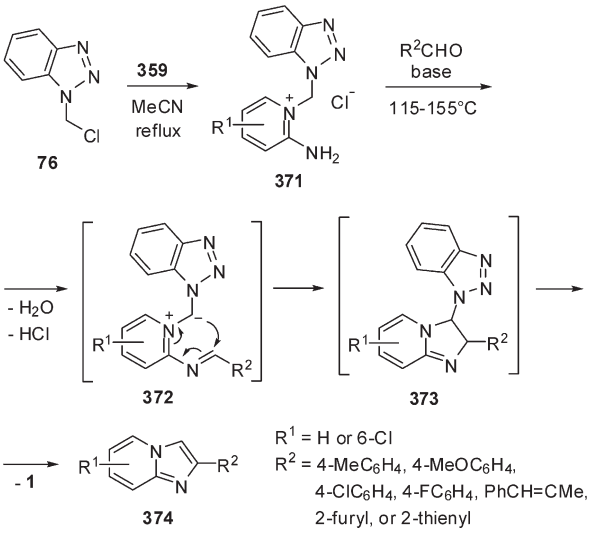
Derivative **364**, readily prepared by condensation of glyoxal with benzotriazole and morpholine,[92] is a convenient two-carbon 1,2-dielectrophile. In its reaction with 2-aminopyridines **363** catalyzed by zinc bromide, 3-(morpholin-4-yl)imidazo[1,2-*a*]pyridines are obtained in 64% (**366e**) to 92% (**366d**) yields. NMR studies, including NOE effects, support the molecular structures of the products and indicate that the morpholinyl group at C-2 in intermediate **365** is eliminated selectively. Piperidine and pyrrolidine analogues of **364** react similarly with 2-aminopyridines, providing the corresponding 3-aminoimidazo-[1,2-*a*]pyridines in high yields (Scheme 78).[93] Similarly, analogues of **364** obtained by condensation of benzotriazole and various amines with glyoxal are used for efficient preparation of 1,6,7-trisubstituted imidazo[1,2-*a*]pyridines that are designed for treatment of noninsulin-dependent diabetes mellitus.[94]

Condensation of ethyl glyoxylate with benzotriazole and morpholine provides 2-aminoester **367** in quantitative yield.[95]

Scheme 79



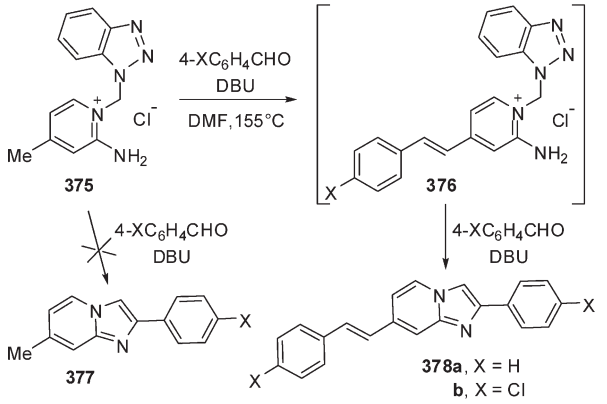
Scheme 80



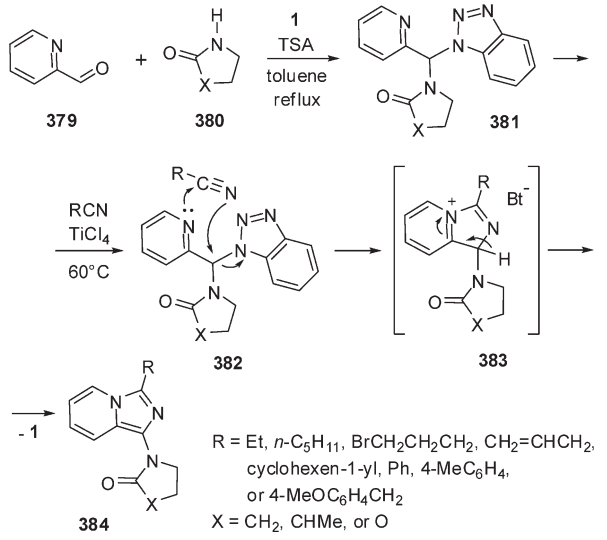
Quaternization of the morpholinyl nitrogen in **367** with methyl iodide allows easy substitution of the morpholinyl moiety with 2-aminopyridine (**363a**), resulting in derivative **368** (70% yield). Treatment with potassium cyanide in ethanol gives 2-aminonitrile **369** that spontaneously cyclizes to 3-amino-2-(ethoxycarbonyl)imidazo[1,2-*a*]pyridine (**370**), isolated in 80% yield (Scheme 79).[96]

For building of imidazo[1,2-*a*]pyridines on the 2-aminopyridine foundation, the two-carbon unit may also be added as two one-carbon fragments. In an example of such a strategy shown in Scheme 80, pyridines **359** are first *N*-benzotriazolomethylated with 1-(chloromethyl)benzotriazole (**76**) to give pyridinium salts **371** in 67−71% yield. Treatment with aldehydes in the presence of a base converts **371** into 2-substituted imidazo[1,2-*a*]pyridines **374** in 61−78% yields. One of the possible reaction pathways involves condensation of an aldehyde with the amino group in **371** and removal of a proton from the methylene group, resulting in azomethine ylide **372**. In the following step, addition of the ylide carbon to the C=N group results in formation of the C(2)−C(3) bond in 2,3-dihydroimidazo[1,2-*a*]pyridine **373**. Promoted by the base, **373** readily eliminates benzotriazole to give final product **374**. Alternatively, the reaction pathway may

Scheme 81



Scheme 82



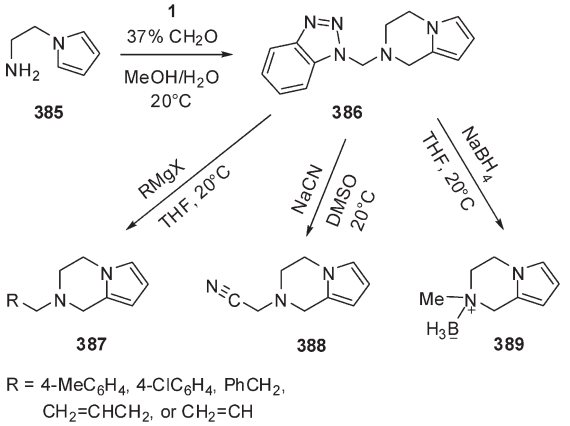
start from addition of the methylene in **371** to the carbonyl group of an aldehyde and ends by formation of the N(1)−C(2) bond. For derivatives of unsubstituted 2-aminopyridines (R^1 = H), treatment with DBU in DMF at 115 °C converts **371** into **374**; but for the less reactive compounds with R^1 = 6-Cl, a stronger base (potassium carbonate) and higher temperature (155 °C) are required.[97]

When 2-amino-4-methylpyridinium salt **375** is used in the reaction with aryl aldehydes in equimolar amounts, derivatives **378** are obtained in low yields instead of the expected products **377**. Increasing the ratio of an aldehyde to **375** to 2:1 increases the yield of **378a** and **b** to 66% and 71%, respectively. Because no other products are isolated in these attempts, the observations suggest that the methyl group in **375** is more reactive than the amino and methylene groups leading to intermediates **376** that subsequently react with another molecule of an aldehyde to give final products **378** (Scheme 81).[97]

7.4. Imidazo[1,5-*a*]pyridine

N-[α-(Benzotriazol-1-yl)(pyridin-2-yl)methyl]amides **381**, prepared by condensation of 2-pyridinecarbaldehyde (**379**) with

Scheme 83



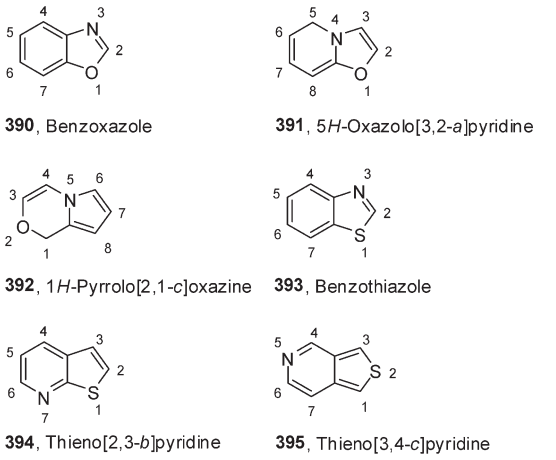


Figure 7. Atom numbering in bicyclic systems of section 8.

cyclic amides **380** and benzotriazole, undergo cyclocondensation with nitriles in the presence of titanium tetrachloride to give 1-amidoimidazo[1,5-*a*]pyridines **384** in 81−91% yields. In the first step (**382**), titanium tetrachloride is expected to coordinate N-3 of the benzotriazolyl moiety to assist in its leaving and the nitrile CN group to make it more electrophilic. The intermediate bicyclic cation **383** readily eliminates the α-proton (formally benzotriazole) to achieve full aromaticity for the system (Scheme 82).[98]

7.5. Pyrrolo[1,2-*a*]pyrazine

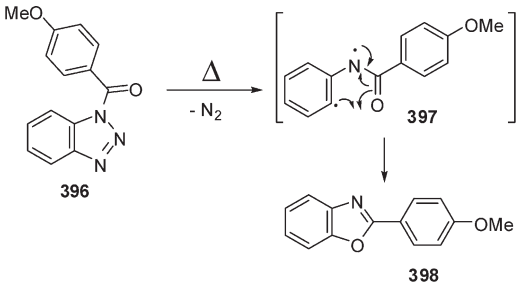
Cyclocondensation of 1-(2-aminoethyl)pyrrole (**385**) with 2 mol of formaldehyde and 1 mol of benzotriazole provides 2-(benzotriazol-1-ylmethyl)-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine (**386**) in 74% yield. In reactions with organomagnesium reagents, the benzotriazolyl moiety in **386** is readily replaced by aryl, benzyl, allyl, or vinyl groups to give 2-substituted 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines (**387**) in 75−92% yields. Nitrile **388** is obtained in 80% yield by treatment of **386** with sodium cyanide in dimethyl sulfoxide (DMSO). Reduction of **386** with sodium borohydride results in stable complex **389**, separated by column chromatography in 65% yield (Scheme 83).[99]

8. (5,6)-C_7NO AND -C_7NS RING SYSTEMS

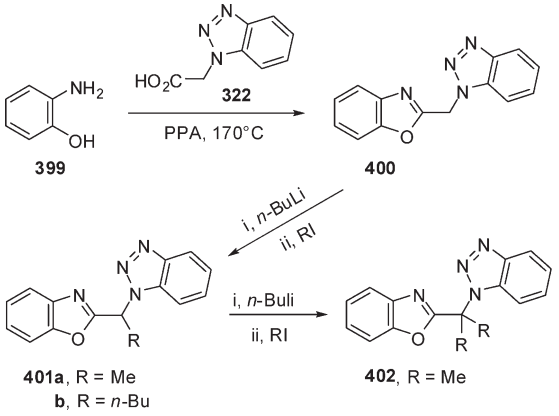
Of the many dozen possible (5,6)-bicyclic systems with C_7NO and C_7NS ring formulas, derivatives of only the six structures

dx.doi.org/10.1021/cr200031r |*Chem. Rev.* 2011, 111, 7063–7120

Scheme 84



Scheme 85



shown in Figure 7 have been investigated in connection with benzotriazole chemistry.

8.1. Benzoxazole

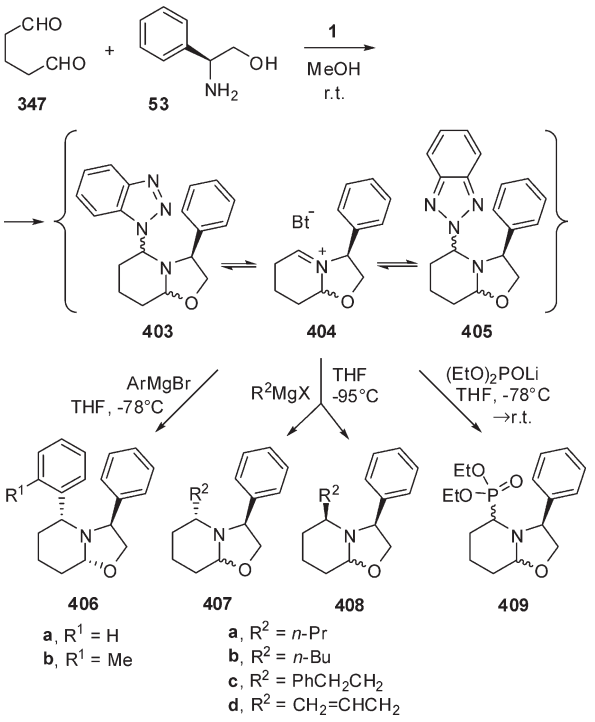
Static pyrolysis of 1-(4-anisoyl)benzotriazole (**396**) in a degassed Pyrex tube at 330 °C for 15 min gives 2-(4-anisyl)benzoxazole (**398**) in 21% yield. The transformation is explained by extrusion of nitrogen from the benzotriazole ring with formation of diradical **397** that subsequently cyclizes to benzoxazole **398**. Other 1-aryloylbenzotriazoles undergo similar pyrolysis giving the corresponding 2-substituted benzoxazoles, but the yields are even lower due to several competing pathways in rearrangement of diradical **397** (Scheme 84).[100]

Cyclocondensation of 2-aminophenol (**399**) with (benzotriazol-1-y)acetic acid (**322**) promoted by PPA provides 2-(benzotriazol-1-yl)benzoxazole (**400**) in 50% yield. Lithiation of the methylene group in **400** (in THF at −100 °C) followed by treatment with alkyl iodides gives 2-(1-benzotriazol-1-ylalkyl)-benzoxazoles **401a** and **401b** in 92% and 80% yields, respectively. In a one-pot approach, repeated treatment of **401a** with *n*-BuLi and methyl iodide leads to 2-[2-(benzotriazol-1-yl)prop-2-yl]-benzimidazole (**402**) in 30% yield (Scheme 85).[85]

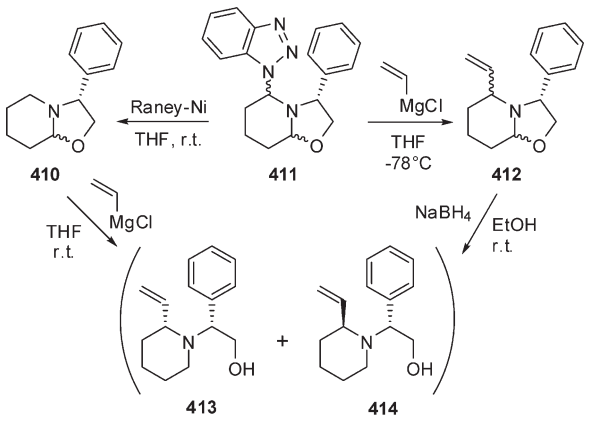
8.2. Oxazolo[3,2-*a*]pyridine

Cyclocondensation of glutaraldehyde (**347**) with (*S*)-2-phenylglycinol (**53**) and benzotriazole provides a complex mixture of diastereomers of 5-(benzotriazol-1-yl)- (**403**) and 5-(benzotriazol-2-yl)-3-phenylperhydrooxazolo[3,2-*a*]pyridines (**405**) in almost quantitative yield. Because regioisomers **403** and **405** equilibrate through planar ionic form **404**, outcomes of their

Scheme 86



Scheme 87



reactions with nucleophiles are the same, and the crude mixture can be used in subsequent reactions without separation. Thus, in reactions of **403**−**405** with arylmagnesium bromides, 3,5-disubstituted (3*S*,5*R*,8a*R*)-perhydrooxazolo[3,2-*a*]pyridines **406** are obtained in 85% (**a**) and 82% (**b**) yields; the stereochemistry of **406a** is established by NMR studies and crystallographic X-ray analysis. However, reactions of **403**−**405** with alkylmagnesium reagents generate separable mixtures of stereoisomers **407** and **408**, both of which consist of two diastereomers. For example, use of *n*-propylmagnesium bromide provides two (3*S*,5*S*)-3-phenyl-5-propylperhydrooxazolo[3,2-*a*]pyridines **407a** (yield 57%, diastereomers at C-8a, ratio 9:4) and two (3*S*,5*R*)-3-phenyl-5-propylperhydrooxazolo[3,2-*a*]pyridines **408a** (yield 8%, diastereomers at C-8a, ratio 14:9). Reaction of **403**−**405**

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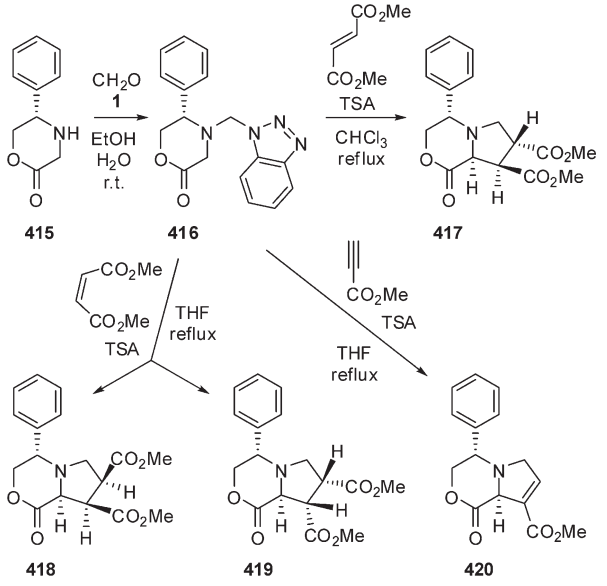
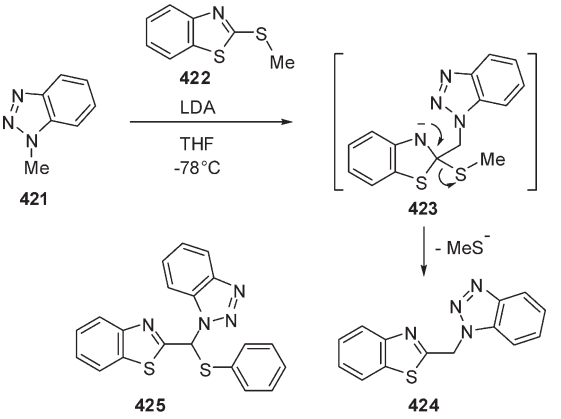
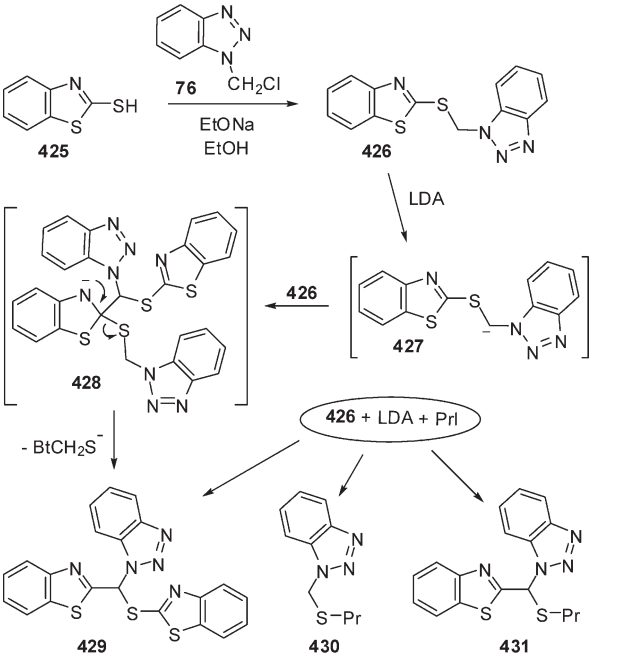
Scheme 88



Scheme 89



Scheme 90



with lithium diethyl phosphite produces a mixture of unspecified diastereomers of phosphonate **409** in a ratio of 93:7 and a total yield of 81% (Scheme 86).[101]

In analogy to the reaction presented in Scheme 86, cyclocondensation of (*R*)-2-phenylglycinol with **347** and benzotriazole yields a complex mixture of stereoisomers of 5-(benzotriazol-1-yl)-3-phenylperhydrooxazolo[3,2-*a*]pyridines (**411**) and their benzotriazol-2-yl regioisomers. Reduction of this mixture with Raney nickel gives (3*R*)-3-phenylperhydrooxazolo[3,2-*a*]pyridine (**410**) in 57% yield as a mixture of two diastereomers in a ratio of 9:1. Treatment of **410** with 4 mol equiv of vinylmagnesium chloride at room temperature causes opening of the oxazole ring leading to a diastereomeric mixture of piperidines **413** and **414** in a ratio of 80:20. However, when the operations are carried out in the opposite order, first treatment of **411** with the Grignard reagent (1 mol equiv at −78 °C) and then reduction of the obtained product **412** with sodium borohydride, a mixture of **413** and **414** is obtained in 11:89 ratio and 54% yield (Scheme 87). The products are separated and used in the synthesis of marine sponge alkaloids.[102]

8.3. Pyrrolo[2,1-*c*][1,4]oxazine

Condensation of formaldehyde and benzotriazole with (5*S*)-5-phenylmorpholin-2-one (**415**) provides (5*S*)-1-(benzotriazol-1ylmethyl-5-phenylmorpholin-2-one (**416**) in 78% yield. Catalyzed by *p*-toluenesulfonic acid (TSA), cycloaddition of an iminium cation generated from **416** to dimethyl fumarate gives dimethyl (4*S*,7*R*,-8*R*,8a*S*)-4-phenylperhydropyrrolo[2,1-*c*][1,4]oxazin-2-one-7,8-dicarboxylate (**417**) in 50% yield. A similar reaction of **416** with dimethyl maleate results in a mixture of endo (**418**, 20% yield) and exo (**419**, 9% yield) stereoisomers. In a reaction with methyl propiolate, methyl (4*S*,8a*S*)-4-phenyl-3,4,6,8a-tetrahydro-1*H*-pyrrolo-[2,1-*c*][1,4]oxazin-2-one-8-carboxylate (**420**) is obtained in 31% yield (Scheme 88).[103]

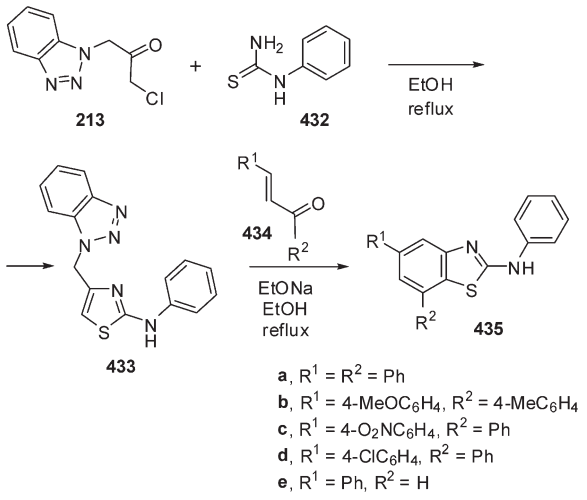
8.4. Benzothiazole

In a reaction of lithiated 1-methylbenzotriazole (**421**) with 2-(methylsulfanyl)benzothiazole (**422**), 2-(benzotriazol-1-ylmethyl) benzothiazole (**424**) is obtained in 85% yield. The reaction must proceed through a nucleophilic attack of an anion derived from **421** on the C-2 atom of thiazole and elimination of a methylsulfanyl anion from intermediate **423**. A similar reaction of lithiated (benzotriazol-1-yl)methyl phenyl sulfide[104] with **422** gives 2-substituted benzothiazole **425** in 92% yield (Scheme 89).[105]

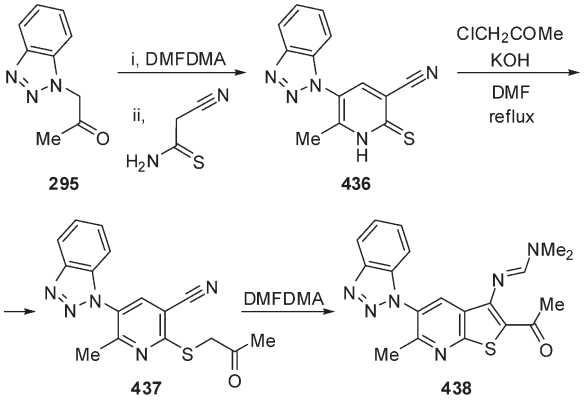
2-Mercaptobenzothiazole (**425**) reacts with 1-(chloromethyl) benzotriazole (**76**) and sodium ethoxide in ethanol to give benzothiazol-2-yl (benzotriazol-1-yl)methyl sulfide (**426**) in practically quantitative yield. Anion **427**, generated from **426** by LDA, adds to another molecule of **426** to give anion **428** that spontaneously eliminates (benzotriazol-1-ylmethyl)sulfanyl anion ($BtCH_2S^-$) to furnish sulfide **429**. When the reaction is quenched by addition of *n*-propyl iodide, apart from **429**, products **430** and **431** are also isolated, in ∼25% yield each. Formation of **430** can be simply explained by alkylation of

dx.doi.org/10.1021/cr200031r |*Chem. Rev.* 2011, 111, 7063–7120

Scheme 91



Scheme 92



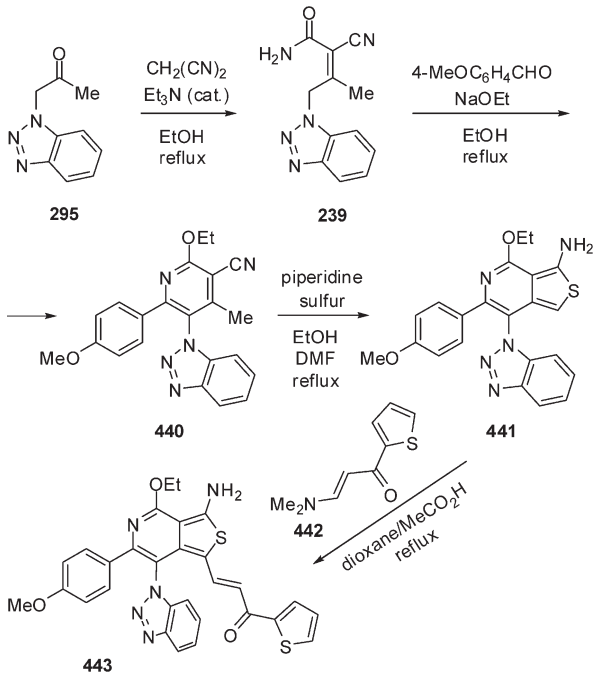
$BtCH_2S^-$ with *n*-propyl iodide. The anion generated from **430** by remaining LDA adds to **426**, and the intermediate obtained (analogous to **428**) eliminates $BtCH_2S^-$ to give sulfide **431** (Scheme 90).[105]

Cyclocondensation of 1-(benzotriazol-1-yl)-3-chloroacetone (**213**) with *N*-phenylthiourea (**432**) gives 2-phenylamino-4-(benzotriazol-1-ylmethyl)thiazole (**433**) in 82% yield. In the presence of sodium ethoxide in refluxing ethanol, **433** reacts with chalcones **434**, producing 2,5,7-trisubstituted benzothiazoles **435** in 59% (**c**) to 74% (**a**) yields. Cinnamaldehyde also reacts with **433**, giving benzothiazole **435e** in 25% yield. The relatively low yield of **435e** is attributed to low stability of starting cinnamaldehyde under basic conditions. The probable mechanism of this reaction involves Michael addition of the activated methylene group in **433** to the C═C bond of chalcone followed by cyclization and aromatization through elimination of benzotriazole and water (Scheme 91).[65]

8.5. Thieno[2,3-*b*]pyridine

Cyclocondensation of (benzotriazol-1-yl)acetone (**295**) with dimethylformamide dimethyl acetal (DMFDMA) and cyanothioacetamide provides 1-thiopyridone **436** in 64% yield. Alkylation of the sulfur atom in **436** with chloroacetone gives acetonyl sulfide **437** (80% yield) that heated with DMFDMA undergoes cyclization to thieno[2,3-*b*]pyridine **438** in 65% yield (Scheme 92).[106]

Scheme 93



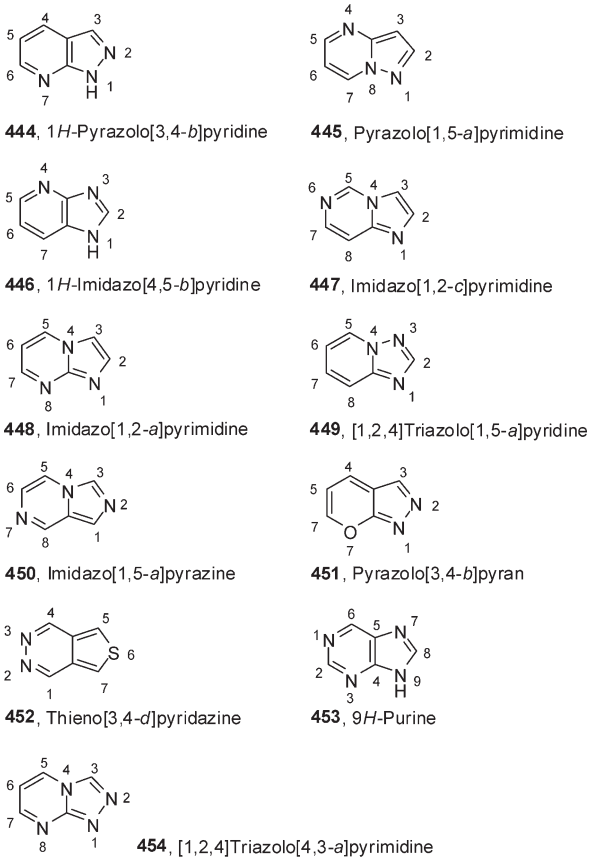
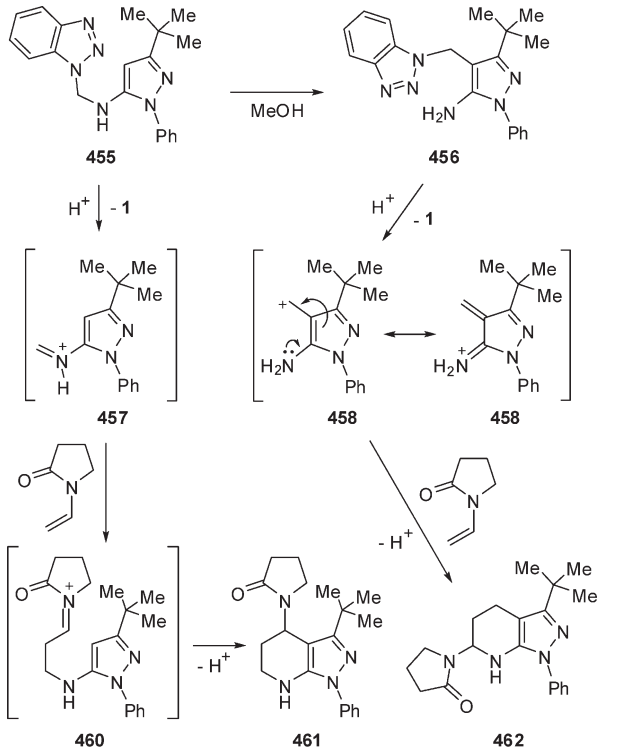


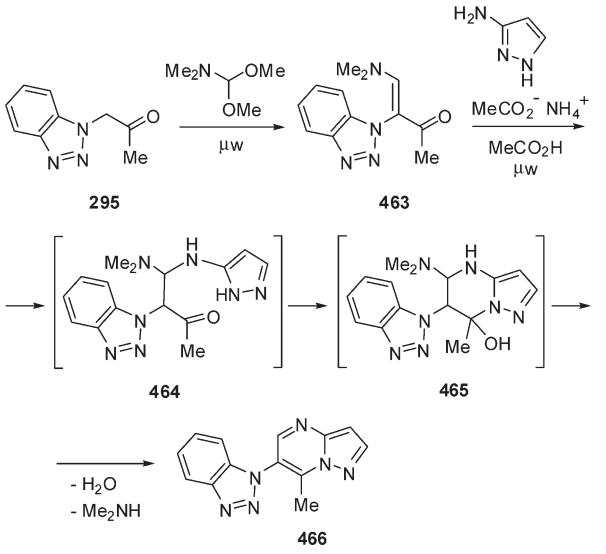
Figure 8. Atom numbering for heterocyclic systems described in this section.

dx.doi.org/10.1021/cr200031r |*Chem. Rev.* 2011, 111, 7063–7120

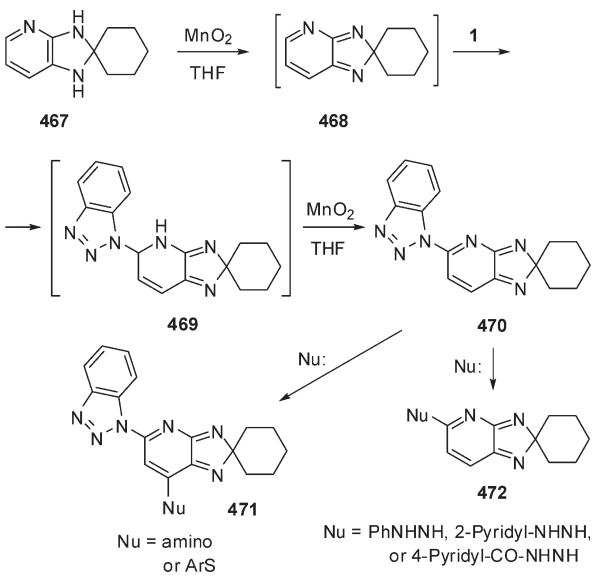
Scheme 94



Scheme 95



Scheme 96



8.6. Thieno[3,4-*c*]pyridine

In the presence of triethylamine catalyst, 1-(benzotriazol-1yl) acetone (**295**) undergoes condensation with malononitrile in refluxing ethanol to give amide **439** in 89% yield. Cyclocondensation of **439** with *p*-anisaldehyde catalyzed by sodium ethoxide provides pyridine **440** in 92% yield. Connection of the Me and CN carbons in **440** with a sulfur atom in a Wilgorodt reaction with elemental sulfur and piperidine gives 3-amino-4-methoxy-6-(4-methoxyphenyl)-7-(benzotriazol-1-yl)thieno[3,4-*c*]pyridine (**441**), isolated in 76% yield. In a reaction of **441** with enaminone **442**, totally substituted thieno[3,4-*c*]pyridine **443** is obtained in 73% yield (Scheme 93).[107]

9. (5,6)-RING SYSTEMS WITH THREE OR MORE HETEROATOMS

Out of hundreds of possible heterocycles that can be assigned to this section, derivatives of only nine core structures shown in Figure 8 have been synthesized with application of benzotriazole intermediates.

9.1. Pyrazolo[3,4-*b*]pyridine

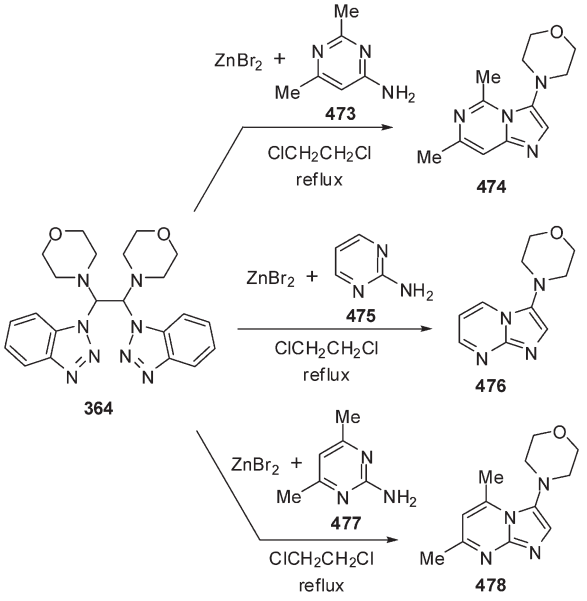
Heating a neat mixture of 5-(benzotriazol-1-ylmethylamino)-3-*t*-butyl-1-phenylpyrazole (**455**), 1-vinyl-2-pyrrolidinone, and a catalytic amount of *p*-toluenesulfonic acid produces 3-*t*-butyl-1-phenyl-4-(pyrrolidin-2-one-1-yl)-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*b*]pyridine (**461**) in 66% yield. The reaction starts from protonation of the benzotriazolyl moiety, making easy cleavage of its bond with the methylene carbon atom. The iminium cation **457** so generated is trapped by 1-vinyl-2-pyrrolidinone to give cation **460** that subsequently closed the pyridine ring in a nucleophilic attack on C-4 of pyrazole. In methanolic solutions, compound **455** rearranges slowly to a thermodynamically more stable product, pyrazole derivative **456**.[108] Subjected to a similar reaction with 1-vinyl-2-pyrrolidinone, **456** gives 3-*t*-butyl-1-phenyl-6-(pyrrolidin-2-one-1-yl)-4,5,6,7-tetrahydro-1*H*-pyrazolo-[3,4-*b*]pyridine (**462**) in 50% yield. In this case, assistance of the amino group at C-5 that stabilizes initial cation **458** in a resonance form **459** is crucial for cleavage of the benzotriazolyl−CH_2 bond and further progress of the reaction (Scheme 94).[109]

9.2. Pyrazolo[1,5-*a*]pyrimidine

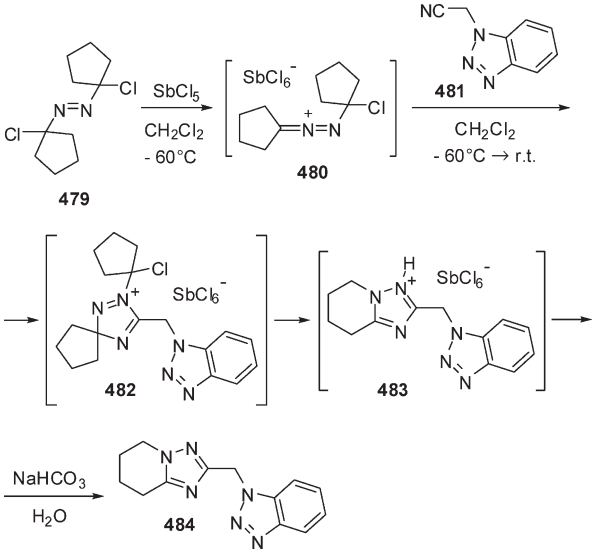
Microwave-assisted condensation of 1-(benzotriazol-1-yl)-acetone (**295**) with *N*,*N*-dimethylformamide dimethyl acetal provides enaminone **463** in 64% yield. Refluxing a solution of **463**, 3-aminopyrazole, and ammonium acetate in acetic acid gives 6-(benzotriazol-1yl)-7-methylpyrazolo[1,5-*a*]pyrimidine (**466**) in 63% yield; however, the yield is increased to 77%,

dx.doi.org/10.1021/cr200031r |*Chem. Rev.* 2011, 111, 7063–7120

Scheme 97



Scheme 98



when microwave heating is used. The reaction mechanism is believed to involve addition of the amine to enaminone **469**, cyclization by addition of the pyrazolyl to carbonyl group in intermediate **464**, and final aromatization by elimination of water and benzotriazole from 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine (**465**) (Scheme 95).[110]

9.3. Imidazo[4,5-b]pyridine

Reaction of 2-spirocyclohexane-2,3-dihydro-1*H*-imidazo[4,5-*b*]-pyridine (**467**)[111] with manganese dioxide and benzotriazole leads to 5-(benzotriazol-1-yl)-2*H*-imidazo[4,5-*b*]pyridine **470**. The reaction is believed to proceed via oxidation of **467** to unstable system **468**. Rapid Michael addition of benzotriazole to **468** results in 4,5-dihydro-2*H*-imidazo[4,5-*b*]pyridine **469** that is subsequently oxidized to **470**. In reactions with hydrazines, the benzotriazolyl moiety in **470** is readily substituted to give 5-hydrazino-2*H*-imidazo[4,5-*b*]pyridines **472**; however, other nucleophiles give products **471** with the benzotriazolyl substituent retained at C-5 (Scheme 96).[112]

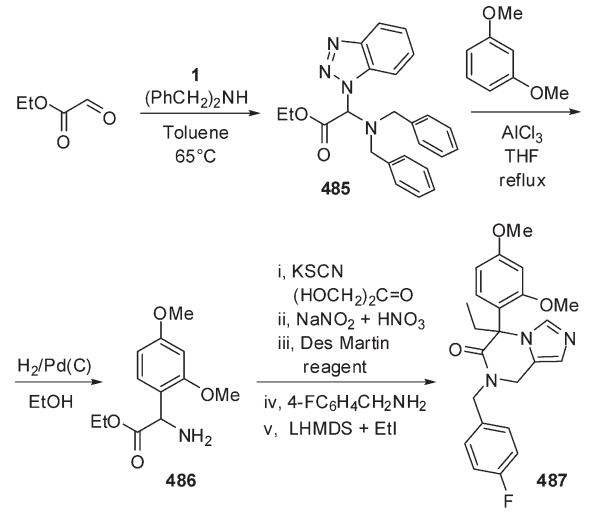
9.4. Imidazopyrimidines

In analogy to its reaction with 2-aminopyridines (Scheme 78), compound **364** reacts with 4-amino-2,6-dimethylpyrimidine (**473**) in the presence of zinc bromide to give 5,7-dimethyl-3-(morpholin-4-yl)imidazo[1,2-*c*]pyrimidine (**474**) in 40% yield. In a similar fashion, 3-(morpholin-4-yl)imidazo[1,2-*a*]pyrimidines **476** (35% yield) and **478** (62% yield) are obtained from reactions of **364** with 2-aminopyrimidines **475** and **477**, respectively. The role of zinc bromide in these reactions is to activate the benzotriazolyl substituents in **364** by coordination of their N-3 atoms, which makes them more prone to elimination with formation of reactive iminium cation species (Scheme 97).[93]

9.5. [1,2,4]Triazolo[1,5-a]pyridine

Dichloride **479**, obtained by chlorination of the bishydrazone derived from cyclopentanone,[113] reacts with antimony(V) chloride and (benzotriazol-1-yl)acetonitrile (**481**) to give 2-(benzotriazol-1-ylmethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-*a*]pyridine

Scheme 99



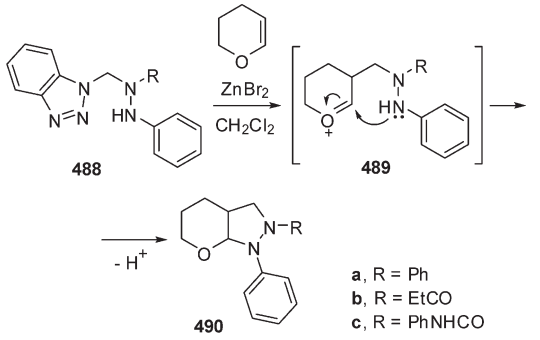
(**484**) in 75% yield. In the first step of this process, **479** is converted by antimony(V) chloride at −60 °C into reactive 1,3-dipolar agent **480** that adds to the CN group of **481** generating spiroadduct **482**. Promoted by antimony(V) chloride at room temperature, the spiro system rearranges and the 1-chlorocyclopentyl substituent is eliminated to give salt **483** that is neutralized during workup to furnish **484** (Scheme 98).[114]

9.6. Imidazo[1,5-a]pyrazine

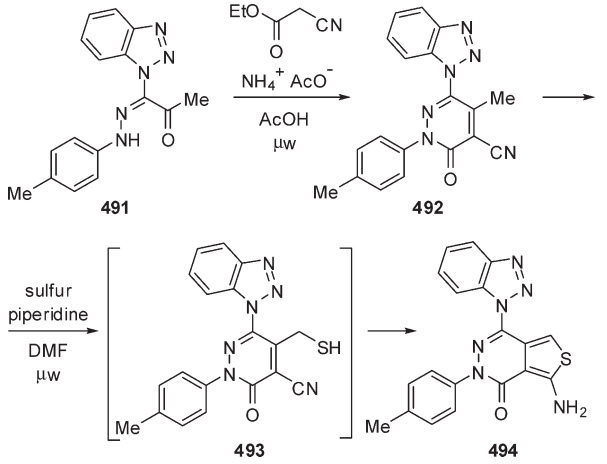
Condensation of benzotriazole and dibenzylamine with ethyl glyoxylate provides amino ester **485**. Substitution of the benzotriazolyl moiety in **485** with (2,4-dimethoxyphenyl) and deprotection of the amino group gives ethyl (2,4-dimethoxyphenyl)glycinate (**486**). In the five following steps, **486** is converted into 5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazine-6-one **487** that exhibits biological activity as aldosterone synthase inhibitor (Scheme 99).[115]

dx.doi.org/10.1021/cr200031r |*Chem. Rev.* 2011, 111, 7063–7120

Scheme 100



Scheme 101



9.7. Pyrazolo[3,4-*b*]pyran

N-(Benzotriazol-1-ylmethyl)hydrazines **488** are prepared as mixtures with their benzotriazol-2-yl isomers by condensation of the corresponding hydrazines with formaldehyde and benzotriazole. In the presence of zinc bromide, the iminium cations generated from **488** (and their benzotriazol-2-yl isomers) are trapped by 3,4-dihydro-2*H*-pyran to give carboxonium cations **489** that subsequently cyclize to 1,2-disubstituted octahydropyrazolo[3,4-*b*]pyrans **490**, isolated in 80% (**a**), 39% (**b**), and 60% (**c**) yields (Scheme 100).[17]

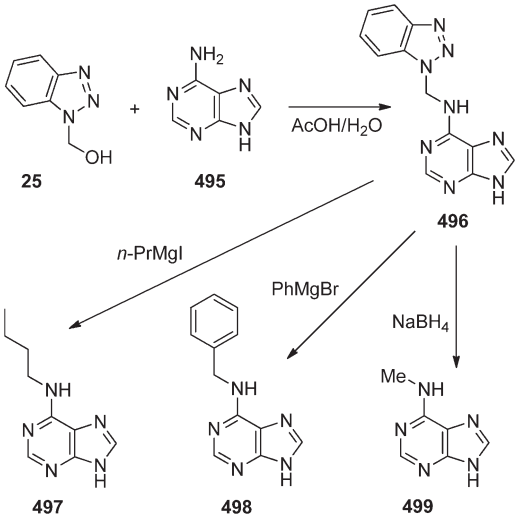
9.8. Thieno[3,4-*d*]pyridazine

Hydrazone **491** is obtained in 86% yield in a reaction of 1-(benzotriazol-1-yl)acetone (**295**) with *p*-tolyldiazonium chloride generated from 1,3-di(*p*-tolyl)triazene in acetic acid. Under microwave conditions, **491** reacts with ethyl cyanoacetate in the presence of ammonium acetate and acetic acid to give pyridazinone **492** in 91% yield. Microwave heating of **492** with elemental sulfur and piperidine provides 7-amino-4-(benzotriazol-1-yl)-2-(4-methylphenyl)thieno[3,4-*d*]pyridazin-(2*H*)-1-one (**494**) in 88% yield. The reaction proceeds by oxidation of the pyridazine methyl in **492** to a mercaptomethyl group, cyclization by addition of the SH to CN group in intermediate **493**, and aromatization by transfer of one proton from C-5 to the amino nitrogen atom (Scheme 101).[116,117]

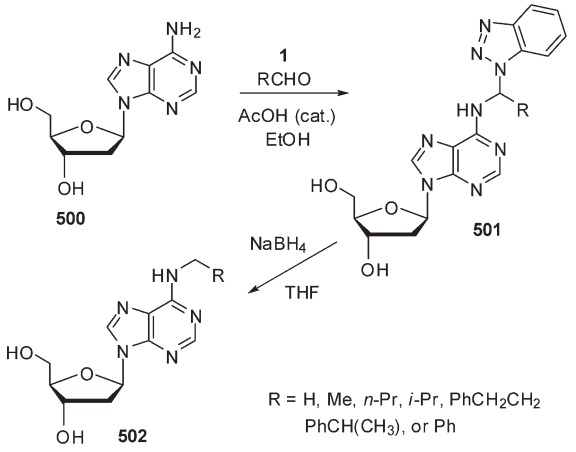
9.9. Purine

Because of its great biological importance, purine is the most frequently investigated (5,6)-ring system. Benzotriazole methodology is efficiently applied here for modification of the functional groups at the purine rings. Thus, condensation of **25** with adenine (**495**) in aqueous acetic acid provides derivative **496** in 95% yield.[118] Treatment of **496** with Grignard reagents generates 6-(butylamino)purine (**497**) and 6-(benzylamino)purine (**498**) in 71% and 80% yields, respectively. Reduction of **496** with sodium borohydride removes the benzotriazolyl moiety to give 6-(methylamino)purine **499** in 75% yield (Scheme 102).[119]

Scheme 102



Scheme 103

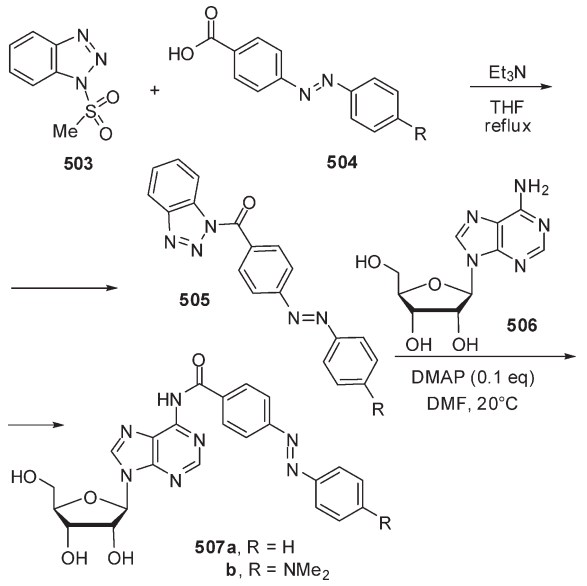


The amino group in 2′-deoxyadenosine can be subjected to similar transformations (Scheme 103). In this case, condensation of adenosine **500** and benzotriazole with aldehydes provides adducts **501** in 65−82% yields. Reduction with sodium borohydride in refluxing THF removes the benzotriazolyl moiety to give 2′-deoxy-N^6-alkyladenosines **502** in 67−88% yields.[120] Naphthalen-1-yl (85% yield) and pyren-1-yl (80% yield) analogues of **501** are preferentially prepared by refluxing solutions of **500**, benzotriazole, and the corresponding aldehydes in toluene with azeotropic removal of water.[121]

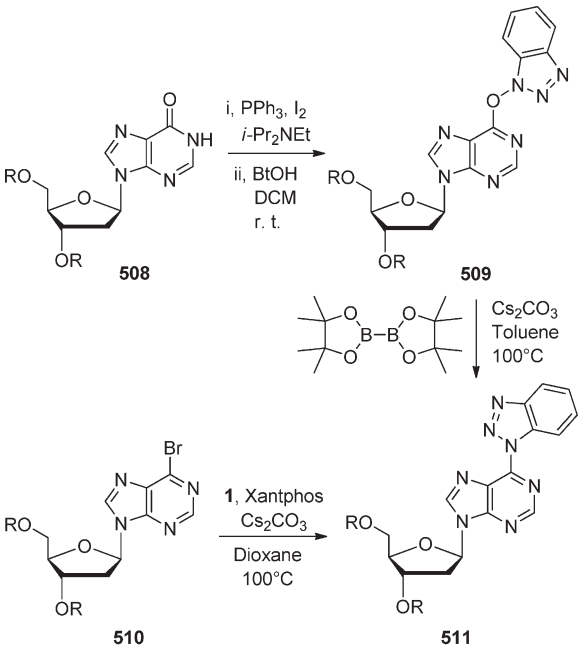
Benzotriazole methodology provides a convenient approach to the synthesis of dye-labeled nucleosides. Thus, 4-(arylazo)benzoic

dx.doi.org/10.1021/cr200031r |*Chem. Rev.* 2011, 111, 7063–7120

Scheme 104



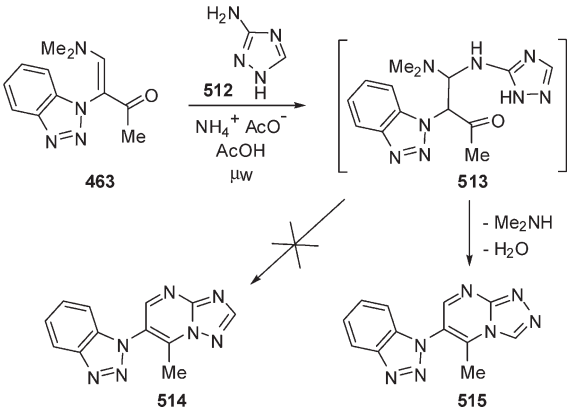
Scheme 105



acids **504** are converted to 1-acylbenzotriazoles **505** with 79−86% yields by treatment with 1-(methylsulfonyl)-1*H*- benzotriazole (**503**). Acylation of adenosine (**506**) with **505** under mild conditions gives N^6-acyladenosines **507a** (68%) and **507b** (53% yield) (Scheme 104).[122]

Two alternative synthetic routes have been developed for direct attachment of a benzotriazol-1-yl substituent to the purine ring.[123] According to the first method, *O*-protected 2′-deoxyinosine **508** is treated with triphenylphosphine and iodine in the presence of *N*,

Scheme 106



N-diisopropylethylamine followed by 1-hydroxybenzotriazole to give O^6-(benzotriazol-1-yl)-2′-deoxyinosine **509** in 93% yield. Deoxygenation of **509** with bispinacolatodiboron results in 6--(benzotriazol-1-yl)-9-(2-deoxy-β-D-ribofuranosyl)purine **511** that is separated in 81% yield. The second method, giving **511** in 78% yield, relies on substitution of the bromine atom in 6-bromo-9-(2-deoxy-β-D-ribofuranosyl)purine **510** with benzotriazole (Scheme 105).

9.10. [1,2,4]Triazolo[4,3-*a*]pyrimidine

Under microwave conditions, in ammonium acetate/acetic acid solution, reaction of enaminone **463** with 3-amino-[1,2,4]-triazole (**512**) provides 6-(benzotriazol-1-yl)-5-methyl-[1,2,4] triazolo[4,3-*a*]pyrimidine (**515**) in 80% yield. The yield of **515** is only 61%, when the reaction is carried out under thermal conditions. The process starts from Michael addition of the amino group of **512** to the C=C bond of enaminone **463** generating intermediate **513**. In the following step, one of the neighboring nitrogen atoms of the triazole ring has to attack the carbonyl group to produce a heterocyclic ring in one of possible alternative structures **514** or **515**. NMR studies, especially NOE, proved that **515** is the only product from this reaction (Scheme 106).[110]

10. (5,7)-RING SYSTEMS

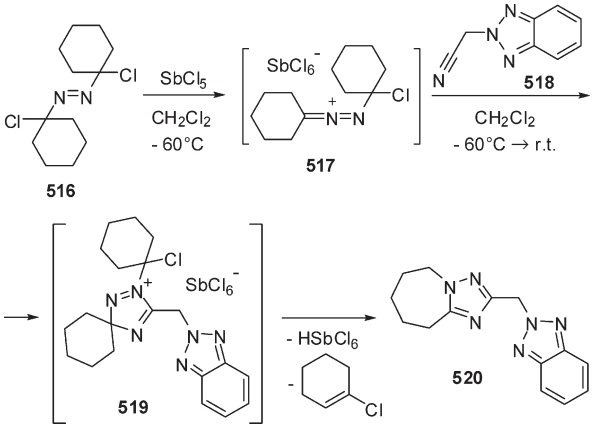
Only one synthesis of a (5,7)-ring system involving a benzotriazolyl substituent has been reported. Thus, in analogy to the corresponding derivative of cyclopentanone (Scheme 98), dichloride **516**, obtained by chlorination of bishydrazone derived from cyclohexanone,[113] reacts with antimony(V) chloride and (benzotriazol-2-yl)acetonitrile (**518**) to give 2-(benzotriazol-2-ylmethyl)-6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[1,5-*a*]azepine (**520**) in 75% yield. In the first step of this process, **516** is converted by antimony(V) chloride at −60 °C into reactive agent **517** that adds to the CN group of **518** generating spiroadduct **519**. Subsequently, at room temperature, the spiro system rearranges and the 1-chlorocyclohexyl substituent is eliminated to give **520** (Scheme 107).[114]

11. (6,6)-C_9N RING SYSTEMS

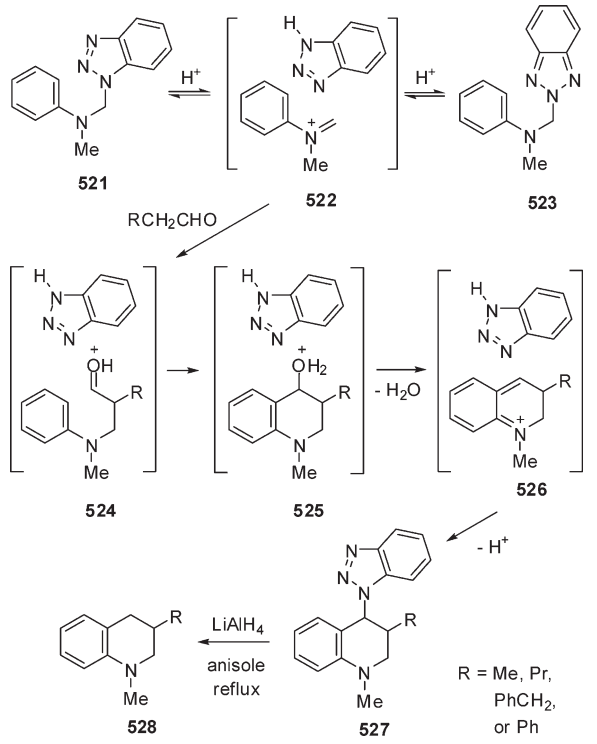
11.1. 1,2,3,4-Tetrahydroquinolines

Application of the benzotriazole methodology to preparation of 1,2,3,4-tetrahydroquinolines is especially prolific, providing a wide range of compounds that might be difficult to obtain by

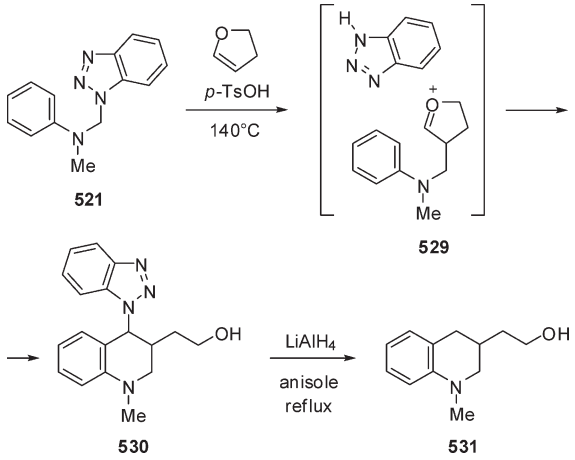
Scheme 107



Scheme 108



Scheme 109



other methods. Comparison of different synthetic approaches for 1,2,3,4-tetrahydroquinolines can be found in a review article.[124]

11.1.1. 1,3-Disubstituted 1,2,3,4-Tetrahydroquinolines. Protonation of 1-(*N*-methyl-*N*-phenylaminomethyl)benzotriazole (**521**) allows its rapid isomerization to 2-(*N*-methyl-*N*-phenylaminomethyl)benzotriazole (**523**).[3,4,61] When an enolizable aldehyde is added to the solution, the intermediate iminium cation (**522**) is trapped to generate oxonium cation **524**. An intramolecular electrophilic attack in **524** closes the heterocyclic ring, leading to protonated 4-hydroxy-1,2,3,4-tetrahydroquinoline **525**. Elimination of a molecule of water from **535** generates iminium cation **526** that adds benzotriazole to form 1,3,4-trisubstituted 1,2,3,4-tetrahydroquinoline **527** as a complex mixture of *cis*/*trans* and benzotriazol-1-yl/-2-yl isomers. Treatment with $LiAlH_4$ in refluxing anisole removes the benzotriazolyl moiety from **527** to give 1,3-disubstituted 1,2,3,4-tetrahydroquinolines **528** in 68−96% yields (Scheme 108).[125] Use of a protective group (e.g., benzyl) instead of the *N*-Me may allow preparation of tetrahydroquinolines monosubstituted at C-3.

Addition of an iminium cation generated from **521** to 1,2-dihydrofuran gives oxonium cation **529**. By the following electrophilic attack on the aniline *ortho*-carbon atom, addition of benzotriazole, and opening of the tetrahydrofuran ring, a complex mixture of stereoisomers of 4-(benzotriazol-1-yl)-3-(2-hydroxyethyl)-1-methyl-1,2,3,4-tetrahydroquinoline (**530**) and its benzotriazol-2-yl analogue is produced. The reaction requires heating of the starting materials and a catalytic amount of *p*-toluenesulfonic acid to 140 °C. By treatment with $LiAlH_4$ in refluxing anisole, the complex mixture of **530** and its isomers is converted into a single product, 1,3-disubstituted tetrahydroquinoline **531**, isolated in 86% yield (Scheme 109). Tetrahydropyran subjected to these reactions, with **521** and then with $LiAlH_4$, gives a homologue of **531** with the 3-hydroxyproyl group at C-3 in 45% yield.[126]

11.1.2. 1,4-Disubstituted 1,2,3,4-Tetrahydroquinolines. By a mechanism analogous to that in Scheme 108, reactions of *N*-[(benzotriazol-1-yl)methyl]anilines **532** with acetaldehyde provide 1-alkyl-4-(benzotriazol-1-yl)-1,2,3,4-tetrahydroquinolines **533** in 64−65% yields. Heating of derivatives **533** with sodium alkoxides allows substitution of the benzotriazolyl moiety with alkoxy groups to give 1-alkyl-4-alkoxy-1,2,3,4-tetrahydroquinolines **534** in 61−83% yields. Grignard reagents convert **533** into 1,4-disubstituted tetrahydroquinolines **535** in 77−92% yields (Scheme 110).[125]

Addition of the iminium cation generated from **532** to ethyl vinyl ether results in oxonium cation **536**. In the following steps, cyclization to tetrahydroquinoline **537** and elimination of a molecule of ethanol leads to cyclic iminium cation **538**. Addition of benzotriazole to **538** furnishes 4-(benzotriazol-1-yl)-1,2,3,4-tetrahydroquinoline **533**, in a mixture with its benzotriazol-2-yl analogue. Treatment of such mixtures with Grignard reagents provides tetrahydroquinolines **535** in 46−79% yields (Scheme 111).[126]

The iminium cations generated from **532** in the presence of catalytic *p*-TsOH adds to 1-vinyl-2-pyrrolidinone at elevated temperatures to give reactive cations **539**. In the subsequent attack on the aromatic ring and elimination of a proton, tetrahydroquinolines

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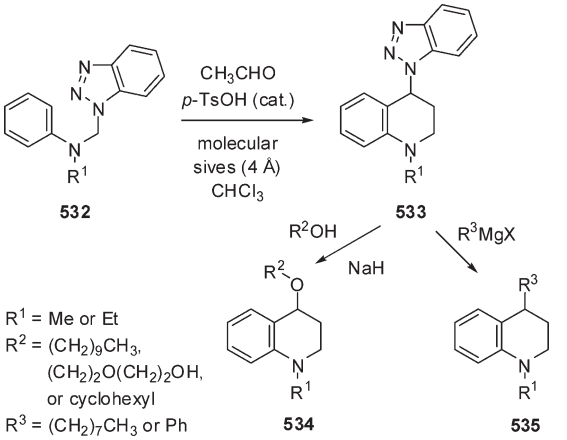
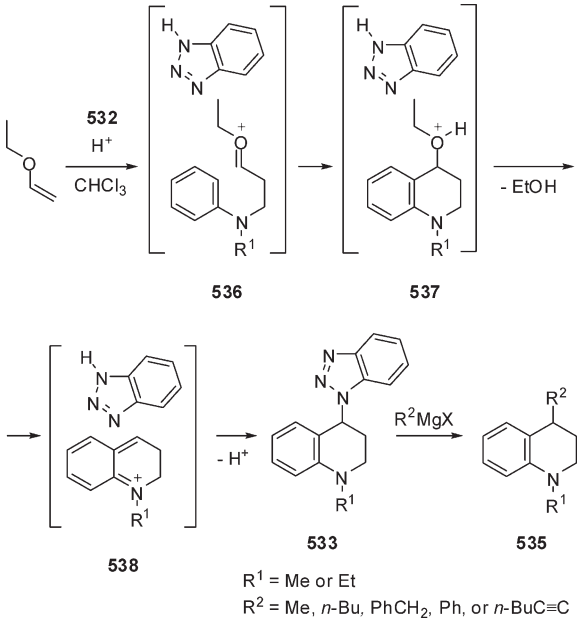
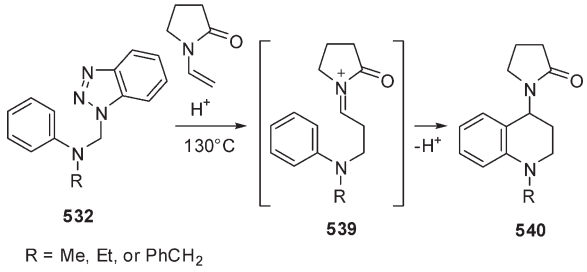
Scheme 110



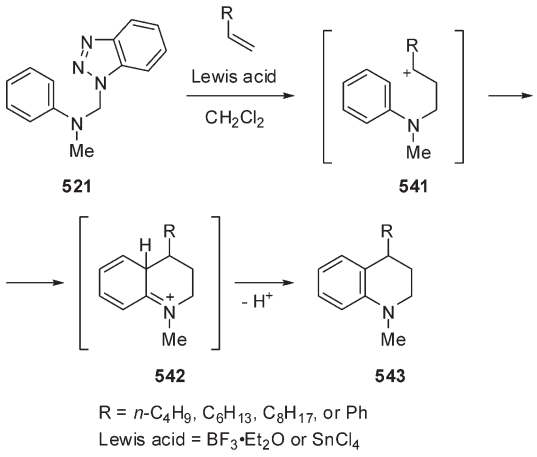
Scheme 111



Scheme 112



Scheme 113



540 are obtained in 80−92% yields (Scheme 112). In this case, elimination of the 2-pyrrolidinone moiety to form heterocyclic iminium cations **538** does not occur, and benzotriazolyl derivatives **533** cannot form. *N*-Methyl-*N*-vinylacetamide reacts similarly with **532** (R = Et) to give 1-ethyl-4-(*N*-methylacetamido)-1,2,3,4-tetrahydroquinoline in 84% yield.[127]

In the presence of Lewis acids, the iminium cation generated from *N*-methyl derivative **521** adds readily to terminal alkenes and styrene to give 1,4-disubstituted 1,2,3,4-tetrahydroquinolines **543** in 84−95% yields (Scheme 113). Following the Markovnikov's rule, the intermediate carbocation **541** could be suggested; however, further studies with cis and trans 1,2-disubstituted alkenes indicate rather a concerted [4 + 2]-cycloaddition with direct formation of iminium cation **542** that subsequently eliminates a proton to regenerate the aromatic ring.[128]

11.1.3. 2,4-Disubstituted 1,2,3,4-Tetrahydroquinolines. Mixtures of benzotriazol-1-yl derivatives **544** with their benzotriazol-2-yl analogues are prepared in practically quantitative yields by condensation of aniline with the corresponding aldehydes and benzotriazole in ethyl ether. When a catalytic amount of *p*-TsOH is added to a neat mixture of **544** and 1-vinyl-2-pyrrolidinone and preheated to 100 °C, a rapid reaction occurs with formation of cis-2,4-disubstituted 1,2,3,4-tetrahydroquinolines **548** and **549**. The reaction is believed to start from the addition of an iminium cation derived from **544** to the vinyl group to form cation **545**. For steric reasons, the following cyclization step can occur only when the group R is directed outward from the reaction center, leading to intermediates **546** and **547** with their cis-oriented substituents at C-2 and C-4. Quantum chemistry calculations rationalize the cis selectivity of the reaction.[129] Under the reaction conditions applied, partial substitution of the 2-pyrrolidinon-1-yl moiety with benzotriazole is observed, leading to lowered yields of enantiomeric mixtures **548** and **549**: 38% for R = Me and 76% for R = Ph (Scheme 114).[127] Milder conditions (toluene, 70 °C) may prevent this side reaction.[129]

This very important reaction of a strong stereochemical control can be easily adapted to synthesis of optically active tetrahydroquinolines. Thus, in a chiral environment, formation of one of the enantiomers may be preferred. In a practical application of this concept, chiral auxiliary **552** is used as a catalyst for cyclocondensation of *N*-(1-benzotriazol-1-ylpropyl)-4-trifluoromethylaniline (**550**) with vinyl carbamate **551** to tetrahydroquinoline **553** with 57% yield and 99% enantioselectivity (Scheme 115).[130]

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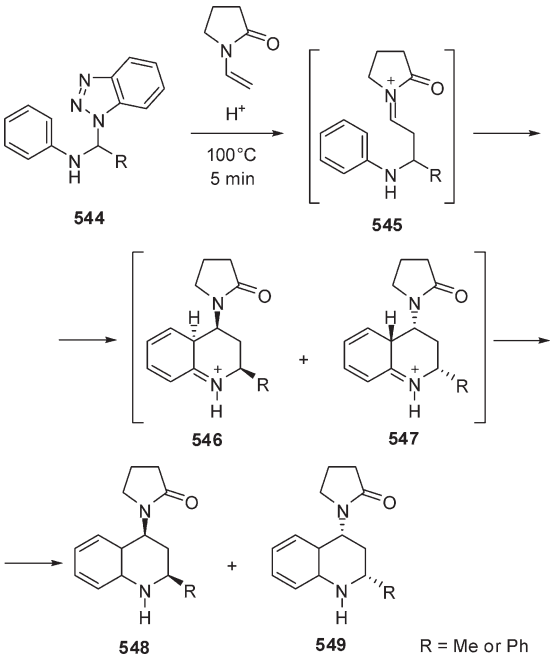
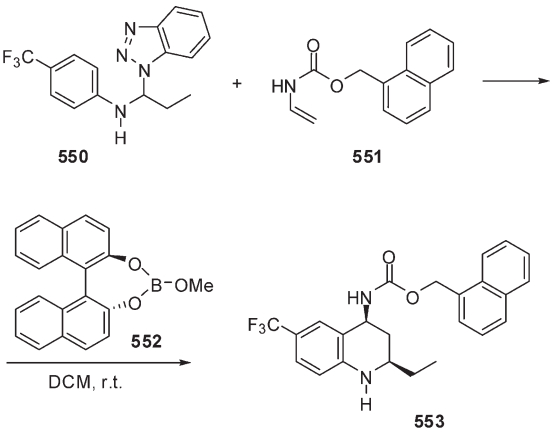
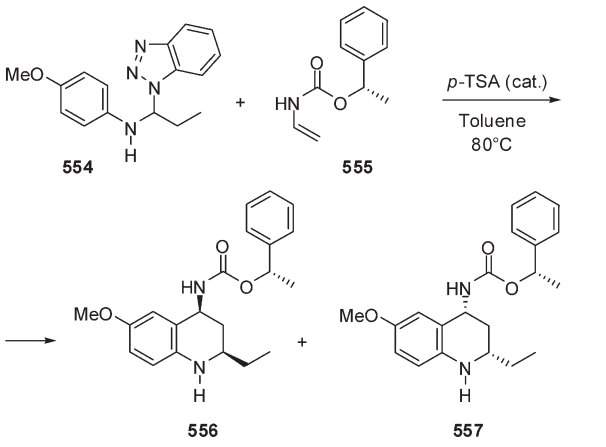
Scheme 114



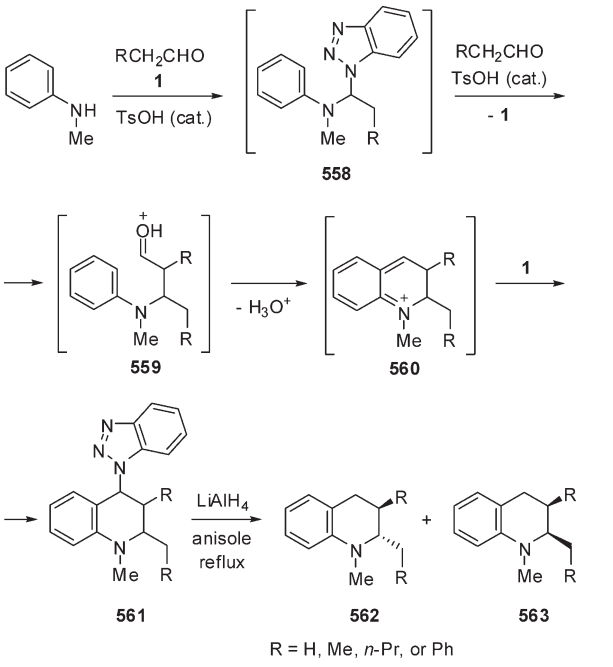
Scheme 115



Scheme 116



Scheme 117



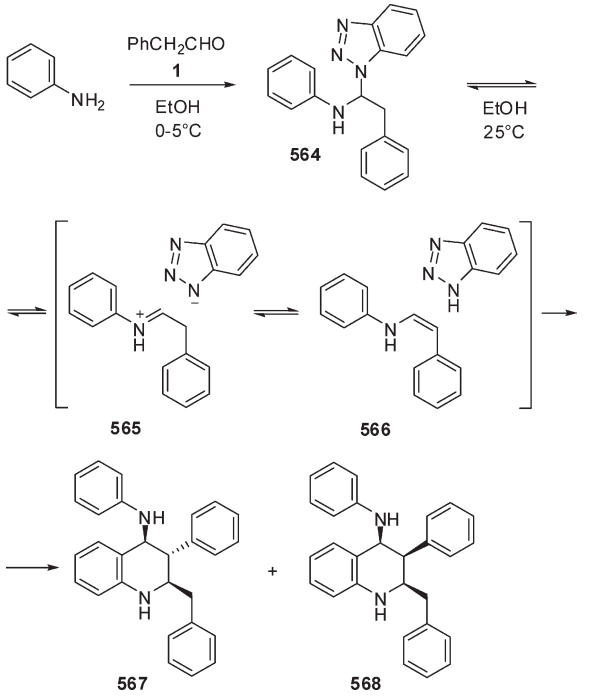
In another approach, a chiral auxiliary is attached to the *N*-vinyl carbamate. Thus, in an example given in Scheme 116, *N*-(1-benzotriazol-1-ylpropyl)anisidine (**554**) reacts with (*S*)-1-phenylethyl *N*-vinylcarbamate (**555**) to give a mixture of tetrahydroquinolines **556** and **557**, from which the predominant (2*R*,4*S*) enantiomer **556** is separated by recrystallization from isopropyl ether.[131]

11.1.4. 1,2,3,4-Tetrahydroquinolines with Three or More Substituents. Condensations of *N*-methylaniline with benzotriazole and aldehydes RCH_2CHO give products **558**, which are unstable and difficult to handle oils. However, when the aldehydes are used in an excess, the reactions proceed further to furnish stable tetrahydroquinolines **561**. The reaction mechanism leading through intermediate forms **559** and **560** is believed to be analogous to that outlined in Scheme 108. Because of three asymmetric carbon atoms and benzotriazol-1-yl/2-yl isomerization, every reaction provides a complex mixture of isomeric tetrahydroquinolines **561**. Treatment with $LiAlH_4$ in refluxing anisole eliminates one asymmetric center and the problem of benzotriazolyl regioisomers, reducing the complex mixture to two stereoisomers **562** and **563**. With acetaldehyde, R = H, a single product, 1,2-dimethyl-1,2,3,4-tetrahydroquinoline **562**, is obtained in 88% yield. For propionaldehyde derivatives (R = Me), the reaction mixture is separated by column chromatography to give *trans*-1,2,3-trisubstituted 1,2,3,4-tetrahydroquinoline **562** (45%) and its cis isomer **563** (39% yield). The prevalence of trans isomers seems to be increasing with increased size of the substituents, as for R = *n*-Pr, the isolated yields are 55% (for **562**) and 33% (for **563**), and only the trans isomer, **562** (78% yield), was isolated for R = Ph (Scheme 117).[125]

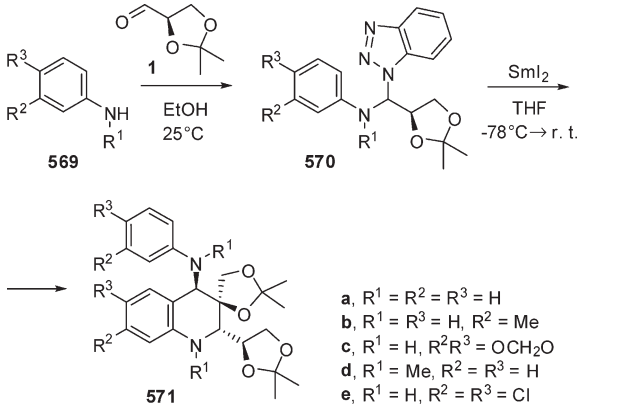
When benzotriazole is added to equimolar amounts of aniline and phenylacetaldehyde, a rapid reaction occurs without any

dx.doi.org/10.1021/cr200031r |*Chem. Rev.* 2011, 111, 7063–7120

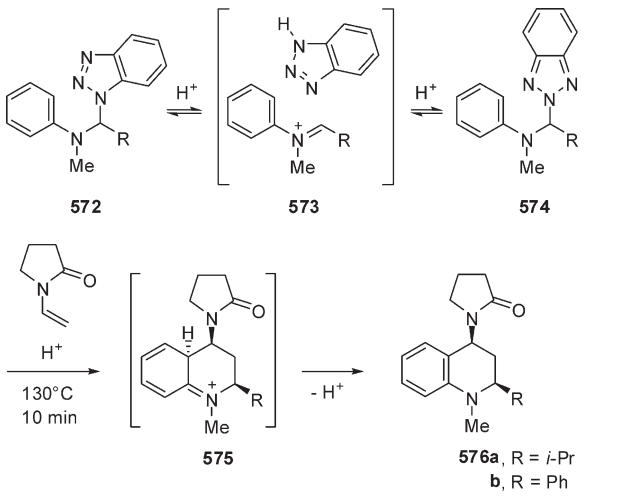
Scheme 118



Scheme 119



Scheme 120



catalyst. At low temperatures, regular condensation product **564** can be separated. However, at room temperature, a mixture of tetrahydroquinolines **567** and **568** is obtained in 86% yield in a ratio of 76:24. This unique reaction of phenylacetaldehyde, due to high acidity of its α-protons, is explained by dissociation of **564** to a benzotriazolide anion and cation **565** that further equilibrates with neutral form **566**. Addition of cation **565** to enamine **566** leads to tetrahydroquinolines **567** and **568** (Scheme 118) via a normal process described above.[132] Use of polymer-bound benzotriazole in reactions with phenylacetaldehyde and various substituted anilines allows for one to run this reaction in a combinatorial fashion and provides high yields of the corresponding tetrahydroquinolines.[133]

Products derived from reactions of other aldehydes with anilines and benzotriazole require Lewis acid catalysis for cyclization to tetrahydroquinolines. Thus, condensation of (*R*)-glyceraldehyde acetonide with benzotriazole and anilines **569** gives derivatives **570**, which in the presence of SmI_2 (10 mol %) undergo cyclization to optically active tetrahydroquinolines **571**, separated in 64% (**571c**) to 88% (**571a**) yields (Scheme 119).[132]

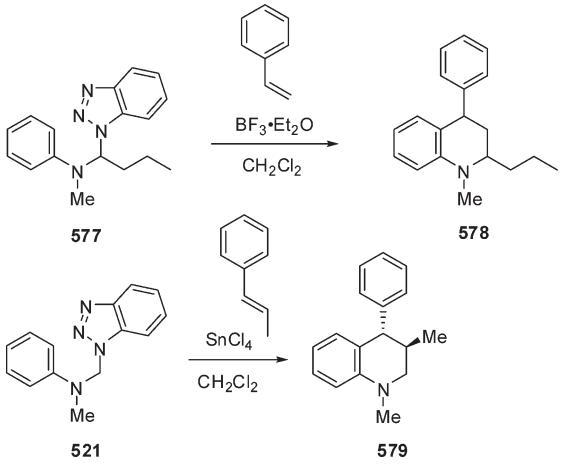
N-Methylated analogues of **544** can be converted to the corresponding 1,2,3,4-tetrahydroquinolines more efficiently. Thus, condensation of *N*-methylaniline with isobutyraldehyde and benzotriazole in ethyl ether over molecular sieves gives quantitatively a mixture of benzotriazol-1-yl derivative **572a** and it 2-yl analogue **574a** in a ratio of 65:35. For products obtained from benzaldehyde, **572b** and **574b**, the ratio is 69:31. In solutions, both isomers equilibrate quickly through intermediate iminium cation **573**, especially in the presence of acids.[3] Brief heating of the mixtures of **572** and **574** with 1-vinyl-2-pyrrolidinone and catalytic *p*-TsOH results in formation of 1,2,4-trisubstituted 1,2,3,4-tetrahydroquinolines **576**, isolated as enantiomeric mixtures of 64% (**576a**) and 89% (**576b**). Again, the steric reasons described above cause the cis-orientation of the substituents at C-2 and C-4 in intermediates **575** and, hence, in the final tetrahydroquinolines **576** (Scheme 120).[127]

However, not much stereoselectivity is observed in a reaction of derivative **577** with styrene catalyzed by $BF_3 \cdot O(Et)_2$, as two diastereomeric tetrahydroquinolines **578** are obtained in almost equal amounts, ratio 1.4:1. The reason for this may be a different mechanism operating here than in the case of product **576**. Furthermore, formation of the exclusively trans-substituted tetrahydroquinoline **579** (98% yield) from **521** and *trans*-1-phenyl-1-propene, and its cis analogue from *cis*-1-phenyl-1-propene, indicates concerted cationic [4 + 2]-cycloaddition rather than a two-step ionic process assigned for the reactions with enolizable aldehydes, vinyl ethers, and *N*-vinylamides (Scheme 121).[128]

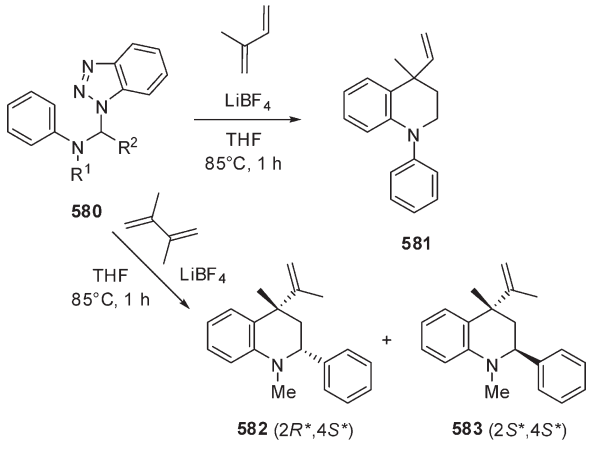
In a reaction of 1-(*N*,*N*-diphenylaminomethyl)benzotriazole (**580**, R^1 = Ph, R^2 = H) with isoprene catalyzed by $LiBF_4$, 1,4,4-trisubstituted 1,2,3,4-tetrahydroquinoline **581** is obtained in 60% yield. In this case, involvement of the more substituted double bond of isoprene suggests rather a stepwise mechanism with formation of the more stable ionic intermediate (analogue of **541**). Compound **580** (R^1 = Me, R^2 = Ph), derived from *N*-methylaniline, benzaldehyde, and benzotriazole, reacts with

dx.doi.org/10.1021/cr200031r |*Chem. Rev.* 2011, 111, 7063–7120

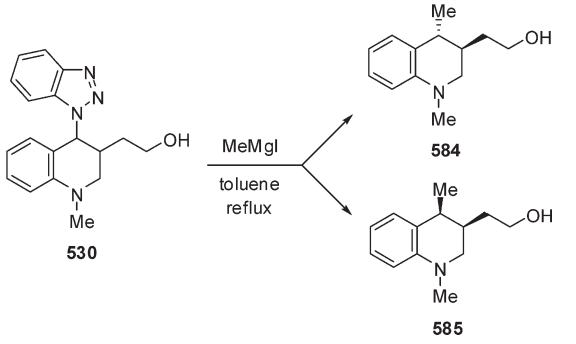
Scheme 121



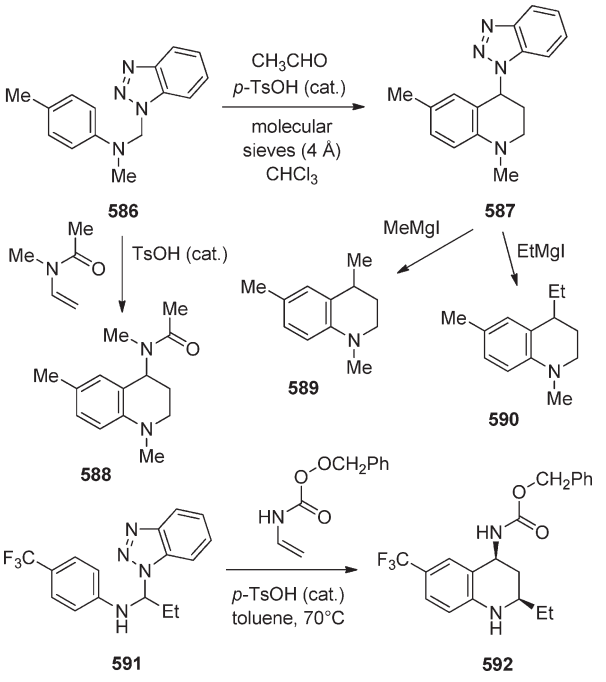
Scheme 122



Scheme 123



Scheme 124



2,3-dimethyl-1,3-butadiene to give a diastereomeric mixture of 1,2,4,4-tetrasubstituted 1,2,3,4-tetrahydroquinolines **582** and **583** in a ratio of 2.5:1, respectively. This observation agrees with the previous findings (structures **548** and **576**) that larger substituents at C-2 and C-4 tend to be on the same side of the tetrahydroquinoline ring (Scheme 122).[134]

In a reaction of **530** with methylmagnesium iodide in refluxing toluene, the benzotriazole moiety is substituted with a methyl group, giving rise to an equimolar mixture of 1,3,4-trisubstituted 1,2,3,4-tetrahydroquinolines **584** and **585** (Scheme 123). The mixture is easily separated by column chromatography. A homologue of **530** obtained from 3,4-dihydro-2*H*-pyran reacts with methylmagnesium iodide in a similar fashion providing the 3-(3-hydroxypropyl) analogues of **584** and **585**.[126]

11.1.5. Substituent on the Aromatic Ring. The benzotriazolyl derivative of *p*-toluidine **586** is prepared and behaves analogously to its parent molecule **521**. Thus, in a reaction with acetaldehyde, it gives tetrahydroquinoline **587** in 76% yield. Substitution of the benzotriazole moiety in **587** with alkyls from Grignard reagents is also not affected by the additional methyl group giving 1,4,6-trisubstituted 1,2,3,4-tetrahydroquinolines **589** (82% yield) and **590** (61% yield).[125,126] In a reaction with *N*-methyl-*N*-vinylacetamide, **586** gives 1,2,3,4-tetrahydroquinoline **588** (86% yield) with an acetamido group at C-4.[127] It can be expected that other para-substituted anilines with electron-donating groups would behave similarly. The last example in Scheme 124 shows that even para-electron-withdrawing substituents in anilines have no effect on the reaction course, as compound **591** derived from 4-(trifluoromethyl)aniline reacts with benzyl *N*-vinylcarbamate to give tetrahydroquinoline **592** in 76% yield.[129] Analogous to the reactions of *N*-vinylamides (see Schemes 114 and 120), this reaction is highly stereoselective, giving exclusively the cis product. The effects of ortho and meta substituents in anilines on formation of 1,2,3,4-tetrahydroquinolines have not yet been evaluated.

The influence of ortho substituents on the aniline ring on formation of 1,2,3,4-tetrahydroquinolines can be illustrated by reactions of derivatives **593** with allylsilanes (Scheme 125). It appears that blocking one of the potential reaction centers by an ortho methyl group affects only slightly the reaction, as tetrahydroquinoline

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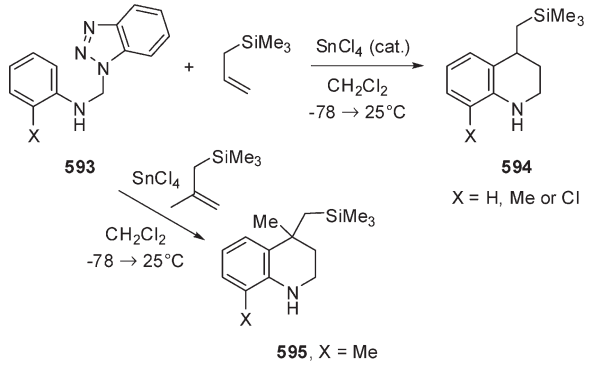
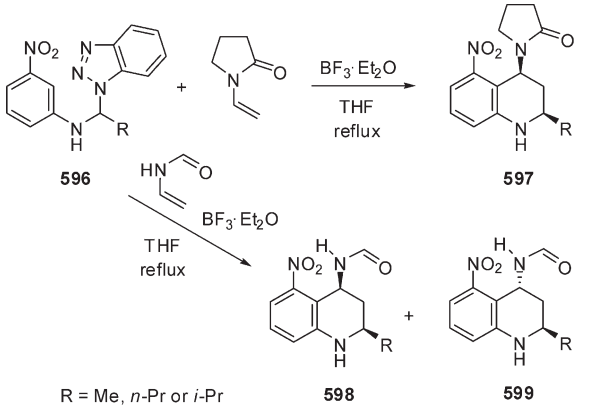
Scheme 125



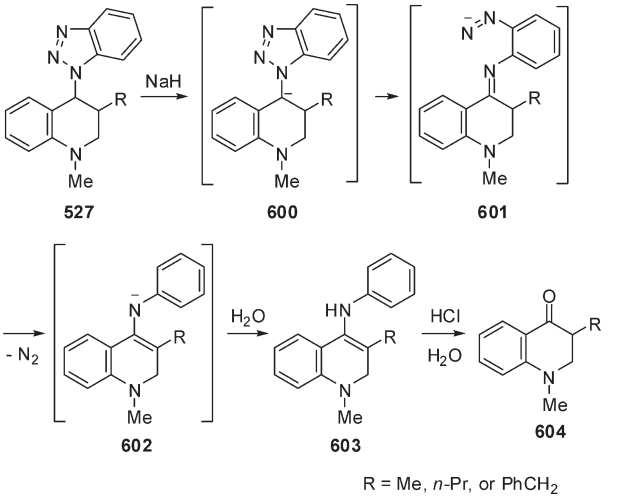
Scheme 126



594 (R = Me) is obtained in 76% yield, versus 85% yield for unsubstituted **594** (R = H). Even sterically hindered (2-methylallyl)silane reacts relatively well to give 4,4,8-trisubstituted 1,2,3,4-tetrahydroquinoline **595** in 67% yield. The electron-withdrawing chloro substituent further lowers the yield of **594** (R = Cl) to 62%, probably by diminishing reactivity of the remaining unsubstituted *ortho*-carbon due to an inductive effect. However, all these influences are not strong enough to preclude application of this approach to the synthesis of C-8-substituted 1,2,3,4-tetrahydroquinolines.[135]

Quite unusual regioselectivity is observed in a reaction of *N*-(benzotriazol-1-yl)alkyl-3-nitroanilines **596** with *N*-vinylamides. Thus, in a reaction with *N*-vinyl-2-pyrrolidinone catalyzed by BF_3 etherate, derivatives **596** are converted into 2,4,5-trisubstituted 1,2,3,4-tetrahydroquinolines **597** in 61−78% yields. The preference for the ortho position that is sterically hindered and less nucleophilic is difficult to explain without more studies. In analogy to other reactions of this type (see Scheme 114), only cis isomers of tetrahydroquinolines **597** are produced; however, the reactions of **596** with *N*-vinylformamide give mixtures of *cis*- (**598**) and *trans*- (**599**) 1,2,3,4-tetrahydroquinolines in an approximate ratio of 4:1 (Scheme 126).[136]

Scheme 127



11.2. 1,2-Dihydroquinolines and 2,3-Dihydro-4-quinolones

All reactions of 4-(benzotriazol-1-yl)-1,2,3,4-tetrahydroquinolines **527** described in section 5.1 are based on substitution of the benzotriazolyl moiety with nucleophiles. Other useful abilities of the benzotriazolyl substituent include increasing the acidity of the C-α protons and ring-opening with elimination of nitrogen. Thus, heating of tetrahydroquinolines **527** with NaH in refluxing dioxane generates anions **600** that shift the electron to benzotriazolyl N-2 with ring-opening to give anions **601**. Elimination of nitrogen produces more stable anions **602** that take protons from water during workup to furnish 4-(phenylamino)-1,2-dihydroquinolines **603** in 65−75% yields. Hydrolysis in refluxing 36% HCl converts dihydroquinolines **603** into 2,3-dihydro-4-quinolones **604** in 62−91% yields (Scheme 127).[125]

Condensation of *N*-methylaniline with phenylacetaldehyde and benzotriazole generates a mixture of stereoisomers **561**. Simple crystallization from ethyl ether allows separation of the most abundant trans−trans isomer **605** in 39% yield. In a reaction with sodium hydride, the triazolyl ring is destroyed, leading to 4-(phenylimino)-1,2,3,4-tetrahydroquinoline **606** (57% yield). An unexpected result of the reaction of **606** with methylmagnesium iodide, giving 1,2-dihydroquinoline **607** in 89% yield instead of the corresponding 4-methyl-1,2,3,4-tetrahydroquinoline, can be attributed to the phenyl substituent at C-3 making the attached proton more acidic (Scheme 128).[125]

1,2-Dihydroquinolines **608** can be obtained directly from the cycloaddition reactions of an iminium cation generated from **521** with alkynes. In air, derivatives **608** are rapidly oxidized to quinolinium salts **609**. The quinolinium salts are easily separated as crystalline hexafluorophosphates after addition of NH_4PF_6 to the reaction mixture. Treatment of crude **609** with Grignard reagents furnishes C-2 substituted 1,2-dihydroquinolines in 74, 54, and 71% yields, for **610a**, **b**, and **c**, respectively (Scheme 129).[137]

11.3. Fully Aromatic Quinoline and Quinolones

Because of versatility of the benzotriazolyl substituents, introduction of a benzotriazolyl group to the quinoline system may be of interest. The benzotriazol-1-yl substituent can be directly attached to the quinoline ring in reactions of chloroquinolines with benzotriazole (**1**). Thus, under microwave irradiation, the reaction of **1** with 2-chloroquinolines **611** gives smoothly 2-(benzotriazoly-1-yl)quinolines **612a** and **b** in 85% and 94% yields, respectively.[138] One-carbon linkage between the benzotriazole and quinoline moieties can be obtained in reactions of **1**

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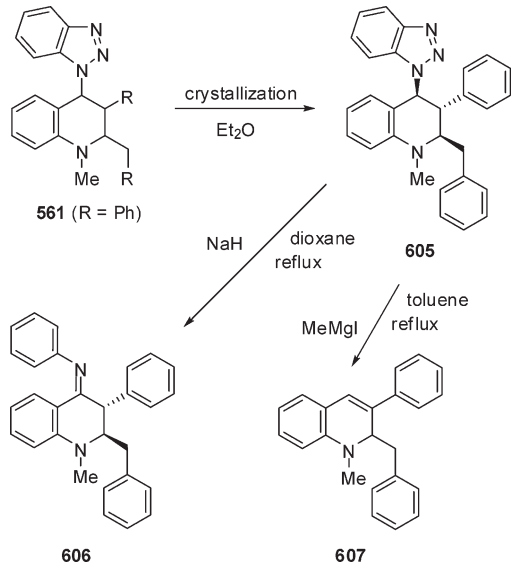
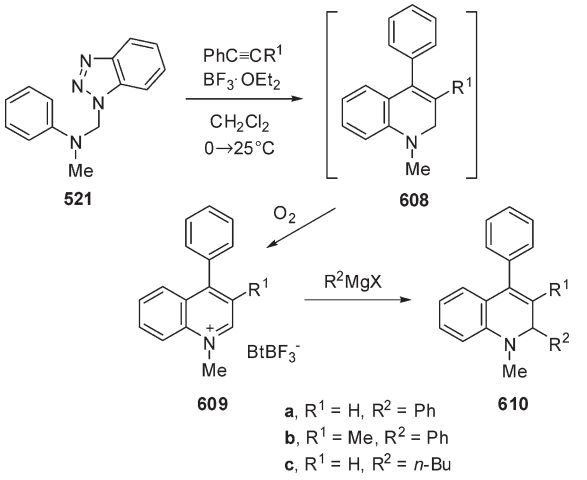
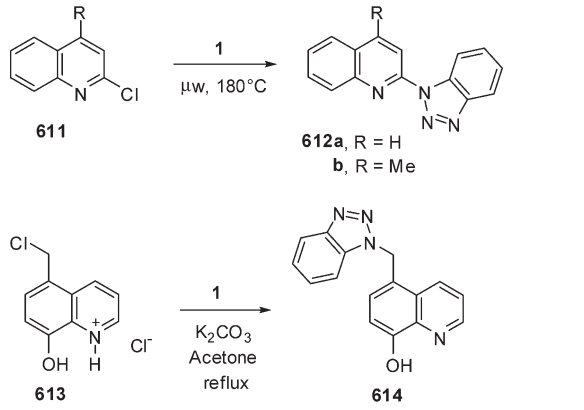
Scheme 128



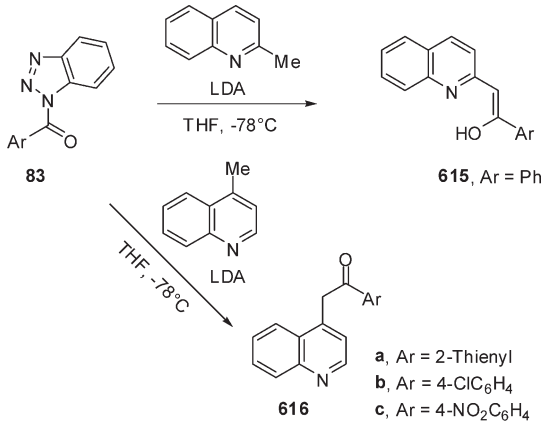
Scheme 129



Scheme 130



Scheme 131



with chloromethylquinolines. In this way, 5-(chloromethyl) quinolin-8-ol (**613**) is converted to 5-(benzotriazol-1-ylmethyl)quinoline-8-ol (**614**) in 85% yield (Scheme 130).[139]

Treatment of lithiated quinaldine with 1-benzoylbenzotriazole (**83a**, Ar = Ph) provides enol **615** in 91% yield; according to NMR in $CDCl_3$, the keto/enol ratio is 8:92. Similar reactions carried out with lithiated lepidine provide 4-(aroylmethyl) quinolines in 66% (**616a**) to 87% (**616b**) yields, exclusively as keto tautomers. The remarkable shift of the keto/enol equilibrium for **615** must result from stabilization of its enol form by strong intramolecular hydrogen bonding between the oxygen and nitrogen atoms (Scheme 131).[140]

Condensation of *N*-phenylimines **617**, obtained from aniline and ketones, with iminium chloride **219** provides vinamidinium salts **618** in virtually quantitative yields. The reaction is distinguished by its remarkable regioselectivity—always involving only the less sterically hindered methylene group, even if the difference between the groups is small. Upon refluxing of salts **618** in THF, an electrophilic attack of the iminium carbon atom on the aromatic ring is followed by elimination of dimethylammonium chloride to give quinolines **619** in 65−82% yields (Scheme 132).[141]

When heated in a sealed tube at 210 °C for 24 h, mixtures of 1-acylbenzotriazoles **621** with excess amounts of aryl isocyanates **620** are converted into 2,4-di(arylamino)quinolines **624** in 64−85% yields. On the reaction pathway, condensation of two molecules of aryl isocyanate produces carbodiimide **622** that reacts with **621** to give 4-quinolone **623**. The formation of a heterocyclic ring may consist of addition of **621** to the C═N bond followed by *ortho*-acylation with elimination of benzotriazole or thermal decomposition of **621** to the corresponding ketene that undergoes cycloaddition to **622**. In the final step, condensation of **623** with an additional molecule of **620** generates final quinoline **624** (Scheme 133).[142]

Flash vacuum pyrolysis at 450 °C of ethyl (*E*)-3-(benzotriazol-1-yl)acrylate (**625**), obtained by addition of **1** to ethyl propiolate,[45] gives (1*H*)-2-ethoxyquinolin-4-one **630** in 57% yield. The proposed mechanism involves extrusion of a molecule of nitrogen to produce diradical **626** that by a hydrogen shift is converted to ketenimine **627**. The subsequent 1,3-migration of the ethoxy group leads to ketene **628** that cyclizes to give **630** via intermediate **629** (Scheme 134).[43]

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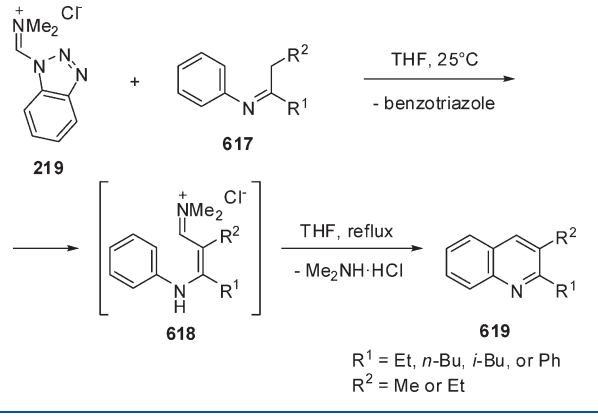
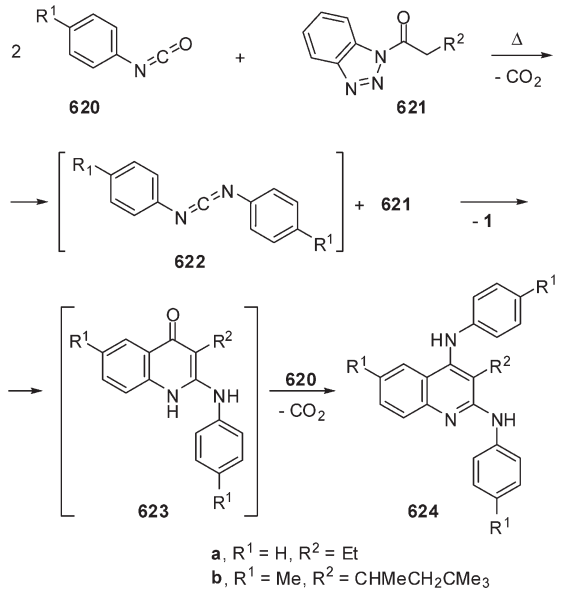
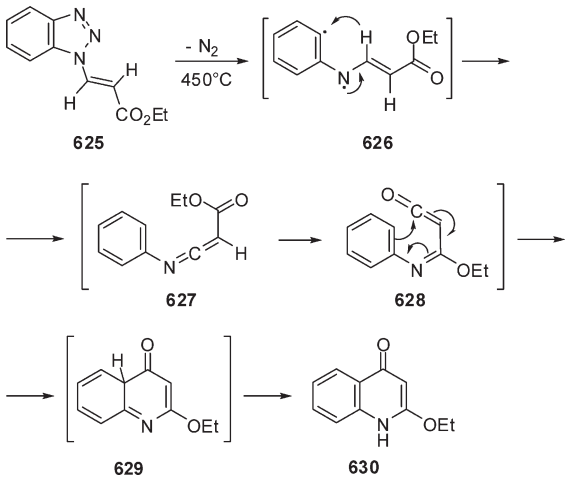
Scheme 132



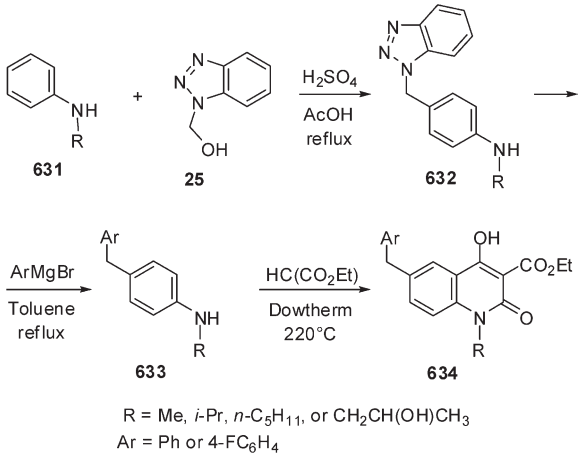
Scheme 133



Scheme 134



Scheme 135



Condensation of *N*-alkylanilines **631** with **25** in refluxing acetic acid provides 4-substituted anilines **632** in 23−54% yields. Substitution of the benzotriazolyl moiety in **632** by an aryl from Grignard reagents occurs in refluxing toluene to give 4-benzylanilines **633** in 21−51% yields. Anilines **633** cyclize with triethyl methanetricarboxylate in Dowtherm to provide ethyl 1-alkyl-6-benzyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylates **634**, precursors for HIV-1 integrase inhibitors, in 15−38% yields (Scheme 135).[143]

11.4. Isoquinoline

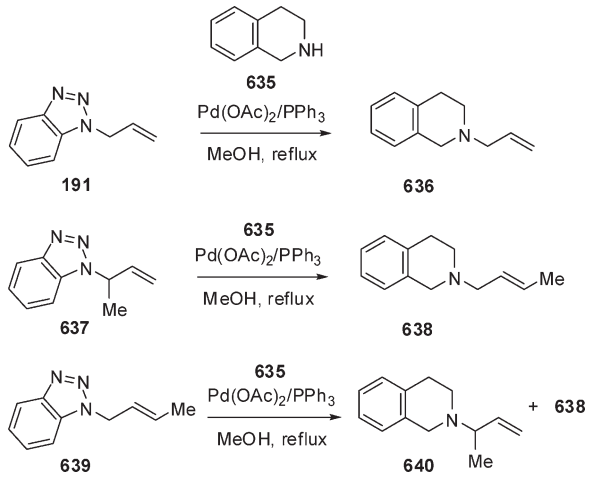
11.4.1. 1,2,3,4-Tetrahydroisoquinolines. 1,2,3,4-Tetrahydroisoquinoline (**635**) is effectively *N*-allylated with 1-allylbenzotriazole (**191**) in the presence of a palladium catalyst to give derivative **636** in 85% yield. Under the same conditions, α-methylated starting material **637** gives 2-(*E*-2-buten-1-yl)-1,2,3,4-tetrahydroisoquinoline (**638**) in a mixture with its *Z*-isomer (*E*/*Z* = 4) in the total yield of 85%, whereas γ-methylated material **639** gives mostly **638** (70% yield) and minor amounts (20% yield) of 2-(1-buten-3-yl)-1,2,3,4-tetrahydroisoquinoline (**640**). The reaction course leads probably through an allyl−palladium-complex intermediate, and the amine attacks favorably the least substituted terminus of the allyl group. Because 2-allylbenzotriazoles react similarly, mixtures of **191**, **631**, or **639** with the corresponding 2-allylbenzotriazoles are conveniently used as starting materials without need of their separation (Scheme 136).[144]

Reaction of 1,2,3,4-tetrahydroisoquinoline (**635**) with **25** in ethanol proceeds rapidly, giving 2-(benzotriazol-1-ylmethyl)-1,2,3,4-tetrahydroisoquinoline (**641**) in practically quantitative yield (Scheme 137).[145] Derivative **641** is a convenient starting material for synthesis of *N*-substituted 1,2,3,4-tetrahydroquinolines via aminomethylation of various nucleophiles.[146,147]

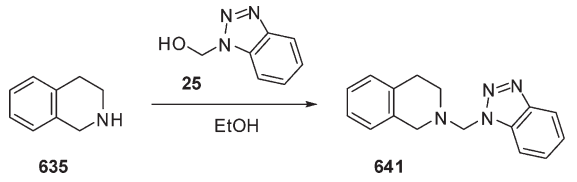
Condensation of 1,2,3,4-tetrahydroisoquinolines **642** with formaldehyde and benzotriazole provides their *N*-(benzotriazol-1-yl) methyl derivatives **643**, together with their minor benzotriazol-2-yl isomers, in practically quantitative yields. Compounds **643** are convenient intermediates for a variety of *N*-substituted 1,2,3,4-tetrahydroisoquinolines. Thus, in their reactions with organomagnesium reagents, the benzotriazolyl moiety is substituted with phenyl, alkyl, or vinyl groups to give 1,2,3,4-tetrahydroisoquinolines

dx.doi.org/10.1021/cr200031r |*Chem. Rev.* 2011, 111, 7063–7120

Scheme 136



Scheme 137

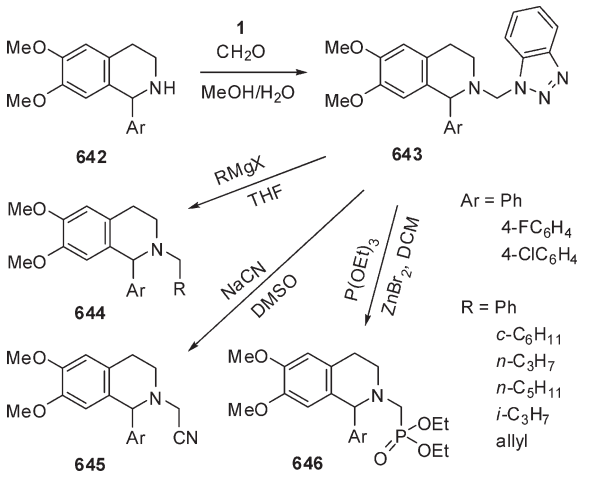


644 in 65−73% yields. Similarly, in reactions of **643** with NaCN, nitriles **645** are obtained in 85−89% yields; and in reactions with triethyl phosphite, phosphates **646** are formed in 76−84% yields (Scheme 138).[148]

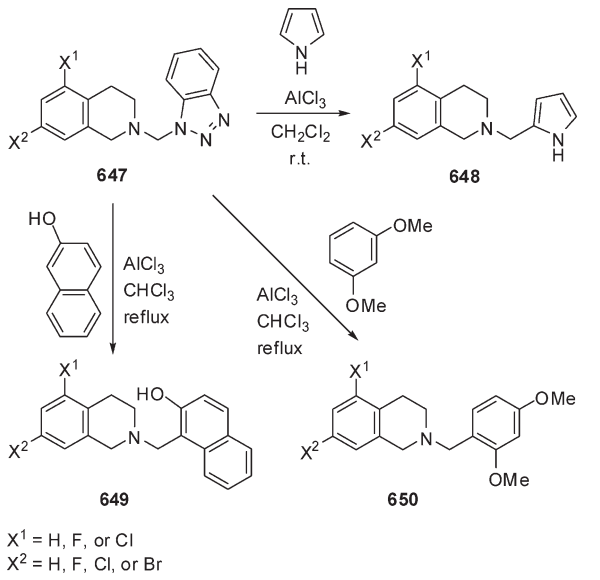
In the presence of $AlCl_3$ as a Lewis acid catalyst, the benzotriazolyl moiety in *N*-(benzotriazol-1-yl)methyl-1,2,3,4-tetrahydroisoquinolines **647** can be readily substituted with electron-rich aromatic rings. The reaction with pyrrole occurs readily at room temperature to give *N*-(pyrrol-2-yl)methyl-1,2,3,4-tetrahydroisoquinolines **648** in 86−95% yields. The reaction with 2-naphthol requires heating at reflux in chloroform to provide *N*-(2-hydroxynaphth-2-yl)methyl-1,2,3,4-tetrahydroisoquinolines **649** in 83−97% yields. Similarly, the reaction with 1,3-dimethoxybenzene gives *N*-(2,4-dimethoxyphenyl)methyl-1,2,3,4-tetrahydroisoquinolines **650** in 93−96% yields. Sodium borohydride converts derivatives **647** into the corresponding *N*-methyl-1,2,3,4-tetrahydroisoquinolines (Scheme 139).[149]

Condensation of phenethylamines **651** with **25** in the presence of a dehydrating agent (sodium sulfate) gives the corresponding *N*,*N*-bis(benzotriazol-1-yl)methyl derivatives **652**, together with minor quantities of their benzotriazol-2-yl isomers. Treatment of **652** with aluminum chloride generates imines **653** which, in an electrophilic attack on the *ortho*-carbon atom, undergo cyclization to *N*-(benzotriazol-1yl)methyl-1,2,3,4-tetrahydroisoquinolines **654**, and their minor benzotriazol-2-yl isomers, in high total yields (Scheme 140).[150,151] Concentrated sulfuric acid can also be used as a catalyst for the cyclization to give 1,2,3,4-tetrahydroisoquinolines **654** in 69−86% yields.[149] In an one-pot approach, phenethylamines **651** are simultaneously treated with **25** and aluminum chloride, used both as a dehydrating agent and a Friedel−Crafts catalyst, to give 1,2,3,4-tetrahydroisoquinolines **654** in 69−95% yields.[152]

Scheme 138



Scheme 139

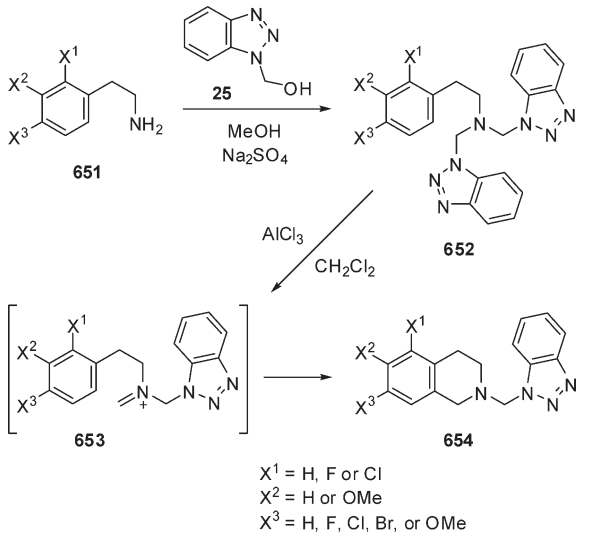


Condensation of (*S*)-phenylalanine methyl ester **655a** with formaldehyde and benzotriazole gives derivative **656a** as a sole benzotriazol-1-yl isomer in 92% yield. In the presence of aluminum chloride, an iminium ion generated from **656a** attacks the *ortho*-carbon atom of the phenyl ring, leading to methyl (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**657a**), isolated in 70% yield. A similar reaction sequence of amides **655b** and **655c** furnishes 3-substituted 1,2,3,4-tetrahydroisoquinolines **657b** and **657c** in 80% and 72% yields, respectively. All products **657** are isolated as pure enantiomers without any evidence of racemization during the transformations (Scheme 141).[151]

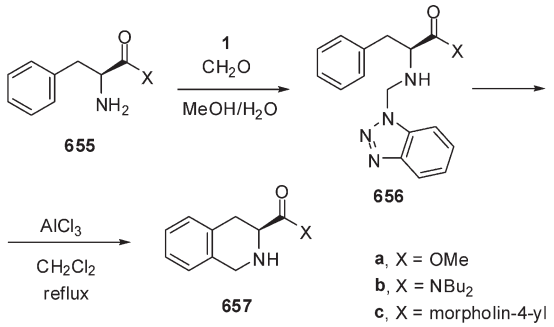
A similar approach is used for conversion of (*S*)-tyrosinol into 3-hydroxymethyl-7-methoxy-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid **661**, which is a convenient intermediate in the synthesis of aphanorphine, a natural product with potent analgesic activity. Thus, in the crucial steps, condensation of (*S*)-tyrosinol derivative **658** with ethyl glyoxylate and benzotriazole

dx.doi.org/10.1021/cr200031r |*Chem. Rev.* 2011, 111, 7063–7120

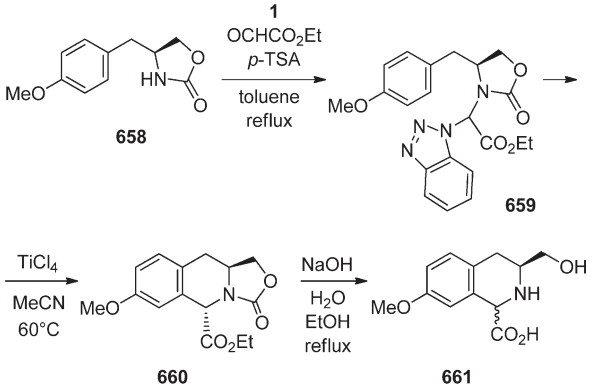
Scheme 140



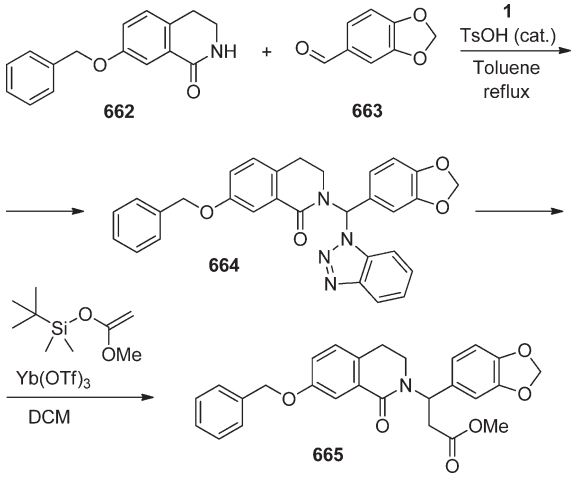
Scheme 141



Scheme 142



Scheme 143



provides 2-(benzotriazol-1-yl)glycinate **659** in 84% yield, which is subsequently subjected to cyclization in the presence of $TiCl_4$ to give tricyclic system **660** in 76% yield. Finally, the protective groups are removed by basic hydrolysis to furnish acid **661** in 88% yield, as a mixture of two diastereomers in the ratio of 3:1 (Scheme 142).[153]

11.4.2. Dihydroisoquinolones. Reaction of 3,4-dihydro-2-isoquinolone **662** with piperonal (**663**) and benzotriazole in the presence of a *p*-toluenesulfonic acid catalyst gives adduct **664** in 55% yield. The benzotriazolyl moiety in **664** is readily substituted in a reaction with 1-(*tert*-butyldimethylsilyloxy)-1-methoxyethene and ytterbium triflate to give derivative **665** in 75%, which is an intermediate in the synthesis of α_v-integrin antagonists (Scheme 143).[154,155]

Condensation of arylacetamides **666** with benzaldehydes and benzotriazole, carried out in refluxing toluene in the presence of a *p*-TSA catalyst, provides *N*-substituted derivatives **667** in 53−65% yields. Treated with aluminum chloride in dichloromethane, amides **662** undergo ring-closure with elimination of benzotriazole to afford 2-aryl-1,4-dihydro-3-isoquinolones **668** in 47% (**d**) to 95% (**a**) yields. The significantly lower yields of the products derived from (4-methoxyphenyl)acetamide may originate from the suspected side-reactions: intermolecular attacks of the iminium ions generated from **667d** and **667e** on the more reactive positions ortho in relation to the methoxy group (Scheme 144).[156]

11.4.3. Fully Aromatic Isoquinolines and Isoquinolones. Nucleophilic displacement of the benzotriazolyl substituent in 1-(triphenylphosphorylideneaminomethyl)benzotriazole, betmip (**669**), with an anion generated from diethyl phosphite provides intermediate phosphate **670**. Further treatment with *n*-BuLi results in a phosphonate carbanion, an equivalent of 1,2-monoazabisylide, that can be trapped with various dielectrophiles to form heterocyclic rings. Thus, in its reaction with 1,2-(4-toluoyl)benzene, 1,4-disubstituted isoquinoline **671** is obtained in 25% yield, whereas in a reaction with phthalaldehyde, unsubstituted isoquinoline **672** is formed in 55% yield (Scheme 145).[157,158]

N-Acylation of acetal **674** obtained from L-isoleucine with 1-acylbenzotriazole **673** gives amide **675** in 68%. Treatment of **675** with KOH removes the tosylate protecting group, and the following treatment with camphorsulfonic acid in refluxing toluene causes cyclization and *O*-demethylation to produce 1-isoquinolone **676** in 71% yield (Scheme 146).[159]

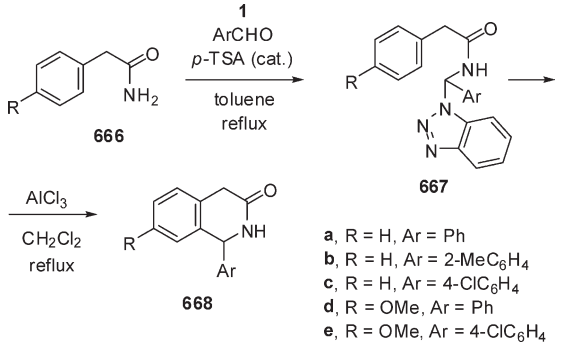
12. (6,6)-C_9O RING SYSTEMS

12.1. Chromanes

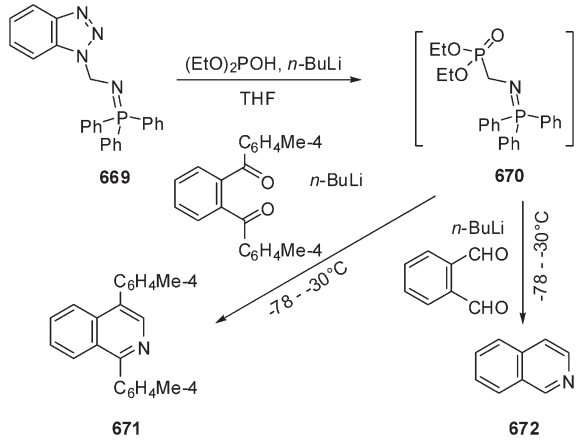
Alkylation of 1-(arylmethyl)benzotriazoles **677** with β-bromophenetole provides 3-aryl-3-(benzotriazol-1-yl)propyl phenyl ethers **678** in 76−99% yields. Heated at 170 °C with zinc bromide in 1,2-dichlorobenzene, ether **678a** undergoes cyclization to

dx.doi.org/10.1021/cr200031r |*Chem. Rev.* 2011, 111, 7063–7120

Scheme 144



Scheme 145

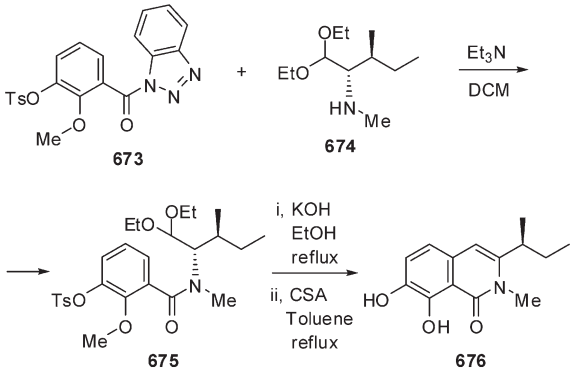


4-phenylchromane (**679a**), isolated in 70% yield. The relatively high temperature of this reaction is needed for cleavage of the bond with benzotriazole to generate a carbocation that subsequently attacks the phenyl ring. The strongly electron-donating substituent in **679b** facilitates the process, allowing the reaction to proceed in refluxing dichloromethane (40 °C), but the yield of chromane **679b** is low, probably due to competition from intermolecular quaternization of the dimethylamino group. The moderately electron-donating thienyl group in **678c** facilitates somewhat the reaction (run at 120 °C) and allows a good yield of chromane **679c** (76%).[160,161] Alternatively, lithiated ether **678a** is additionally alkylated with 1-iodobutane to give derivative **680** in 80% yield. The quaternary carbon atom in **680** promotes cleavage of the bond with benzotriazole, with the reaction occurring at 115 °C with formation of 4,4-disubstituted chromane **681** in high yield (94%) (Scheme 147).[161]

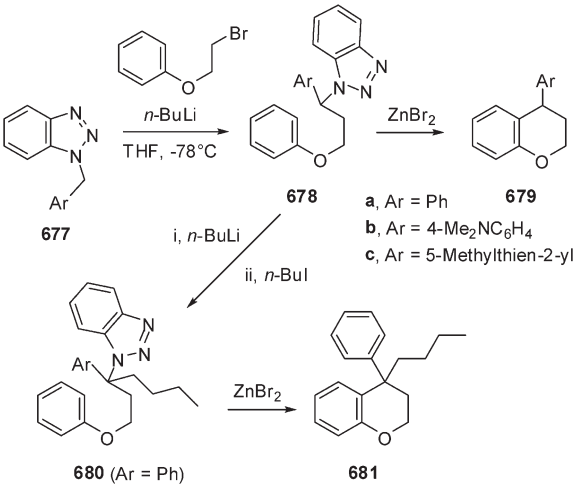
2-[(Benzotriazol-1-yl)methyl]phenols **683** are readily prepared in 59−71% yields by heating solutions of phenols **682** and 1-(hydroxymethyl)benzotriazole (**25**) in acetic acid at reflux.[25] Upon heating with ethyl vinyl ether at 150 °C in sealed tubes, phenols **683** are converted to 2-ethoxychromanes **685** in 91−93% yields. The reactions presumably involve intermediate *ortho*-quinone methides **684** that are formed by thermal elimination of benzotriazole from **683** (Scheme 148).[162]

Treatment of Boc-protected 1-aminobenzotriazole **686** with *n*-BuLi in the presence of cerium trichloride generates dianion **687** that is trapped with 1,2-diiodoethane to give 7-iodo derivative **688** in 97% yield. Coupling of **688** with propargyl alcohols

Scheme 146



Scheme 147



gives 7-(alkyn-1-yl)benzotriazoles **689** in 72−92% yields. Reduction of the triple bond in **689** gives 3-(benzotriazol-7-yl)propanols **690**, in which the amino group is consecutively deprotected with TFA. Obtained amines **691** are treated with excess amounts of *N*-iodosuccinimide (NIS) to give 8-iodochromanes **693** in 78−90% yields. In the first step of this process, the amino group in **691** is oxidized and two molecules of nitrogen are eliminated with formation of benzyne **692** that subsequently adds iodine (from NIS) and the hydroxy group from an *ortho*-(3-hydroxyalkyl) substituent to cyclize to **693** (Scheme 149).[163] This approach is effectively applied to the synthesis of analogues of α-tocopherol.[164]

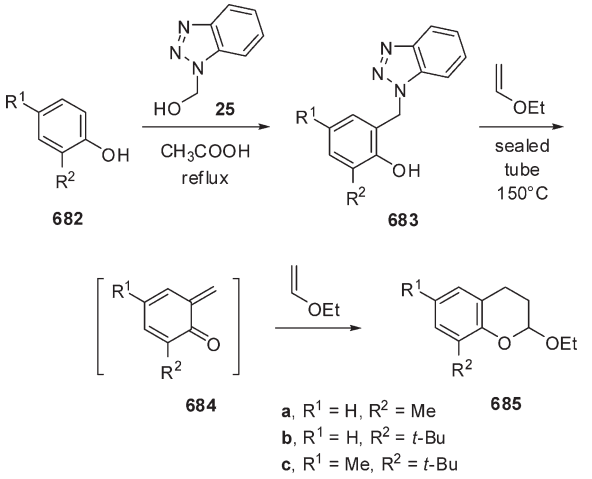
12.2. Chromenes and Benzopyrylium Salts

Slight modification of the process described in Scheme 149 allows synthesis of 2*H*-chromenes. Thus, instead of hydrogenation over a palladium catalyst, alkynes **689** are reduced with Rieke zinc to alkenes in 60% (**694c**) to 94% (**694b**) yields. Deprotection of the amino group in **694** with TFA gives amines **695** that are treated with NIS to provide 2*H*-chromenes **696** in 63−83% yields (Scheme 150).[163]

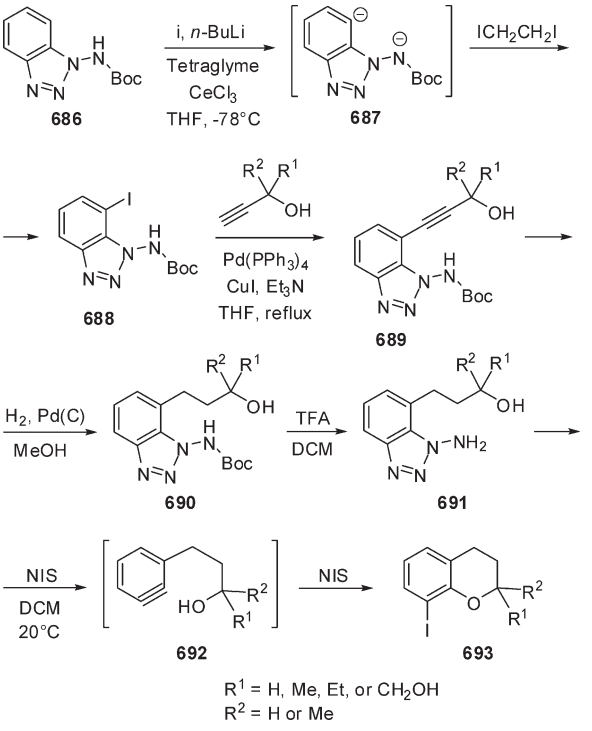
Benzotriazole is a convenient auxiliary in alkylation of benzo[*b*]pyrylium salts at C-4. Thus, treatment of benzo[*b*]pyrylium

dx.doi.org/10.1021/cr200031r |*Chem. Rev.* 2011, 111, 7063–7120

Scheme 148



Scheme 149

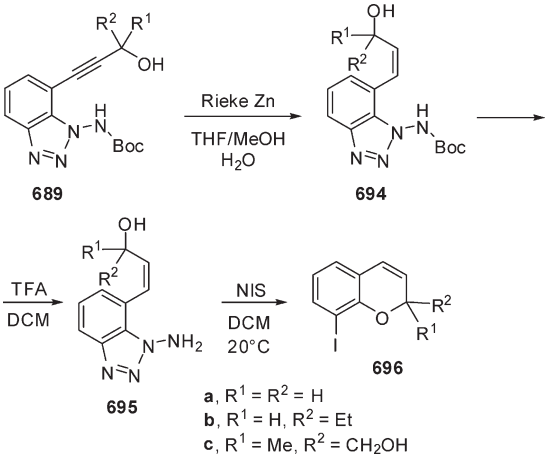


tetrafluoroborates **697** with sodium benzotriazolide, generated from benzotriazole (**1**) and NaH, provides 4-(benzotriazol-1-yl)-4*H*-chromenes **698**, together with their minor benzotriazol-2-yl isomers, in practically quantitative yields. Anions **699**, generated by treatment of **698** with *n*-BuLi, react readily with alkyl bromides, and finally the benzotriazolyl moiety is eliminated to furnish 4-substituted benzo[*b*]pyrylium salts that are precipitated as perchlorates **700** in 48−70% yields (Scheme 151).[165]

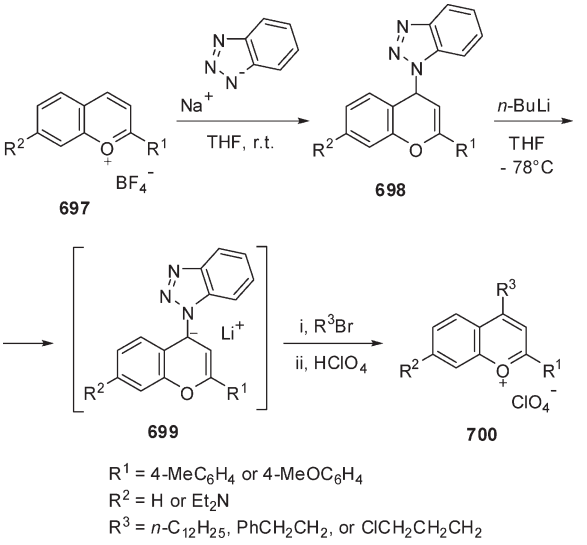
12.3. Chromen-2-ones and -4-ones

Condensation of 2-hydroxyacetophenone (**701**) with (benzotriazol-1-yl)acetic acid (**322**) in the presence of $POCl_3$ gives ester **702** in 80% yield. Treated with KOH, ester **702** undergoes

Scheme 150



Scheme 151



cyclization to 3-(benzotriazol-1-yl)-4-methylcoumarin (**705**) that is separated in 82% yield. This process proceeds through generation of anion **703**, its intramolecular attack on the acetyl group to give anion **704**, and final elimination of a hydroxyl group (Scheme 152).[166,167]

Reaction of coumarin-3-carboxylic acid (**706**) with benzotriazole and thionyl chloride gives 3-(benzotriazol-1-ylcarbonyl) coumarin (**707**) in 87% yield. Derivative **707** is a convenient reagent for attachment of a fluorescent coumarin tag to various natural products containing an amino group to produce amides **708** (Scheme 153). Thus amino acids,[168] peptides,[168] and amino sugars[169] are efficiently labeled this way. Regular sugars can also be labeled with **707** as esters **709**.[169] In a similar manner, (7-methoxycoumarin-4-yl)acetic acid is converted to the corresponding 1-acylbenzotriazole and used for fluorescent labeling of peptides.[170]

Condensation of 4,13-diaza-1,7,10,16-tetraoxacyclooctadecane (diaza-18-crown-6) with 2 mol equiv of 1-(hydroxymethyl) zbenzotriazole (**25**) gives derivative **710** in 91% yield. In a

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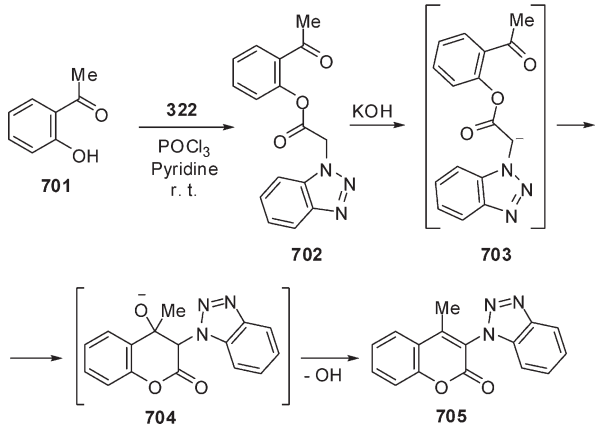
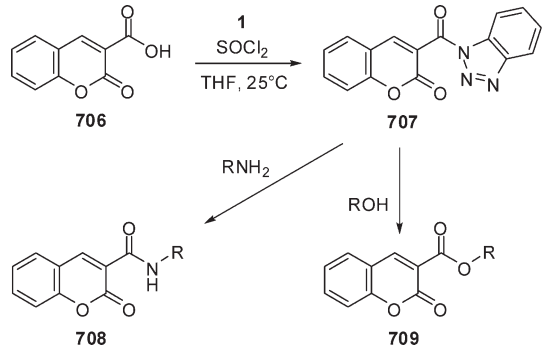
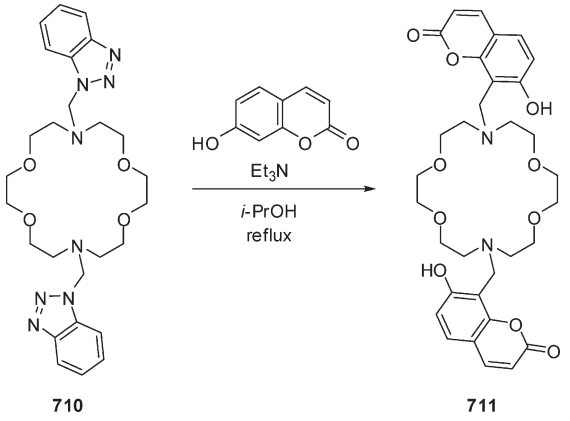
Scheme 152



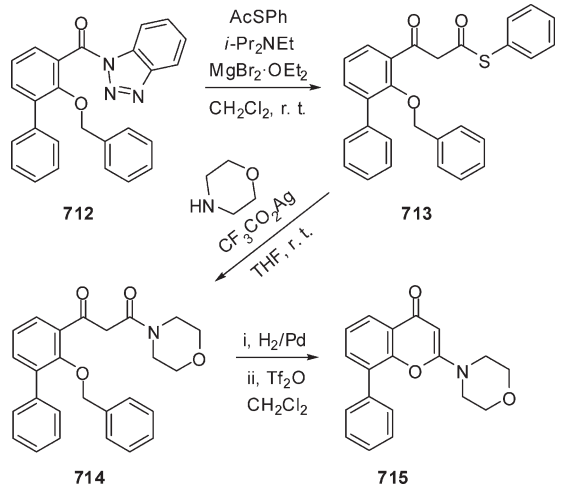
Scheme 153



Scheme 154



Scheme 155



reaction with 7-hydroxycoumarin, the benzotriazolyl groups in **710** are replaced with 7-hydroxypyran-2-one-8-yl substituents to provide fluorescent crown ether **711** in 31% yield (Scheme 154).[171]

1-Acylbenzotriazole **712** is prepared in 90% yield from commercially available 3-phenylsalicylic acid by benzylation of its hydroxy group and subsequent treatment with benzotriazole and thionyl chloride. Crossed-Claisen coupling of **712** with phenyl thioacetate provides β-keto thioester **713** in 86% yield. In the presence of silver trifluoroacetate, the phenylthio group in **714** is readily exchanged for morpholinyl to give amide **714** in 93% yield. Deprotection of the hydroxy group in **714** and cyclization of the obtained phenol catalyzed by triflic anhydride provides smoothly 2-morpholino-8-phenyl-4*H*-chromen-4-one (**715**), an important PI3-K inhibitor, in 93% yield (Scheme 155).[172]

Total synthesis of Vitexin (**719**), a naturally occurring flavonoid, is based on a similar concept. Thus, in a key step, 2-hydroxyacetophenone derivative **716** is acylated with 1-(4-benzyloxybenzoyl)benzotriazole to give β-diketone **717** in 95% yield. Cyclization of **717** catalyzed by Amberlyst 15 provides 4*H*-chromen-4-one **718** in 58% yield, in which the hydroxy groups are deprotected by hydrogenation to give **719** (Scheme 156).[173]

12.4. Isochromanes

1-Chlorobenzotriazole (**721**) is an effective reagent for derivatization of aliphatic ethers at C-α. The reaction is catalyzed by Lewis acids, especially $TiCl_4$. In the case of isochromane (**720**), derivative **722** is obtained in 76% yield (Scheme 157).[174] The benzotriazolyl moiety in α-(benzotriazol-1-yl)benzyl ethers can be readily substituted with nucleophiles.[38,175]

The acid chloride generated from commercially available acid **723** is treated with 1-(trimethylsilylmethyl)benzotriazole (**212**) to give ketone **724** that is subsequently subjected to a reaction with triflic anhydride and 2,6-lutidine to produce enol triflate **725** in 86% yield. Alcoholysis of **725** with sodium methoxide generates ester **726** in 87% yield. In the following three steps, ester **726** is converted to ketone **727**. Formylation of **727** with triethyl *ortho*-formate results in aldehyde **728** (75% yield) that is treated with lead tetraacetate and *para*-toluenesulfonic acid to give 6*H*-isochromene-6,8-dione **729** in 48% yield (Scheme 158).[176]

13. (6,6)-C_8N_2 RING SYSTEMS

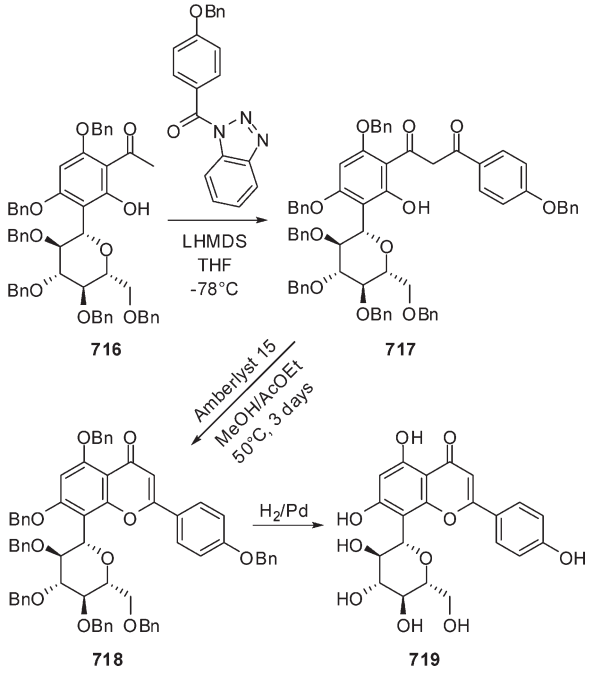
Of 15 potential structures with such ring formula, derivatives of four, cinnoline (**730**), quinazoline (**730**), quinoxaline (**732**), and naphthyridine (**733**), have been synthesized with the aid of benzotriazole chemistry (Figure 9).

13.1. Cinnoline

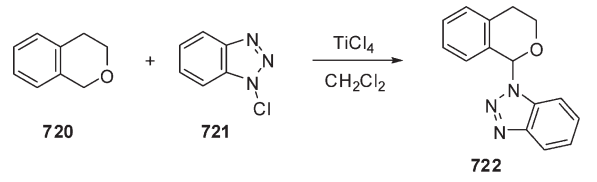
Phenylhydrazone **734** is readily prepared by coupling of (benzotriazol-1-yl)acetone (**295**) with benzenediazonium chloride.[116]

dx.doi.org/10.1021/cr200031r |*Chem. Rev.* 2011, 111, 7063–7120

Scheme 156



Scheme 157

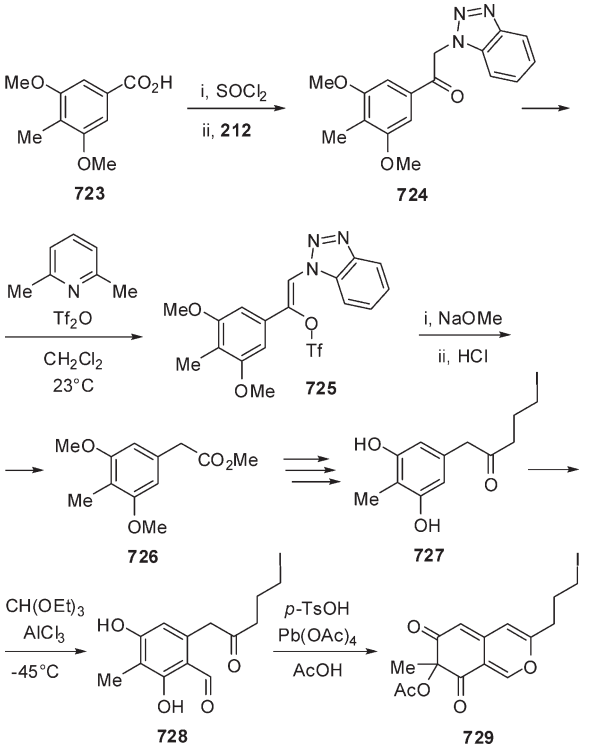


When heated in refluxing xylene in the presence of piperidine as a catalyst, **734** undergoes cyclization to 3-(benzotriazol-1-yl)-4-methylcinnoline (**735**), isolated in 80% yield (Scheme 159).[177]

13.2. Quinazoline

Condensation of 2-aminobenzylamine (**736**) with 3 mol equiv of formaldehyde (37% aqueous solution) and 2 equiv of benzotriazole (**1**) provides 1,3-(benzotriazol-1-yl)methyl-1,2,3,4-tetrahydroquinazoline (**737**) in 88% yield. In reactions of **737** with organomagnesium reagents, the benzotriazolyl substituents are readily replaced with alkyl, alkenyl, or aryl groups to furnish 1,3-disubstituted 1,2,3,4-tetrahydroquinazolines **738** in 81−95% yields. Treatment of **737** with 1-phenylvinyl trimethylsilyl ether in the presence of boron trifluoride etherate gives 1,3-di(3-oxo-3-phenylpropyl)-1,2,3,4-tetrahydroquinazoline **738** in 70% yield. In a reaction of **737** with triethyl phosphite catalyzed by zinc bromide, diphosphonate **740** is obtained in 75% yield (Scheme 160). Because of higher reactivity of the (benzotriazol-1-yl)methyl substituent at N-3 than at N-1, asymmetrically substituted analogues of **738** are obtained when **737** is successively treated with two different organomagnesium reagents, e.g., in this way, 1-allyl-3-(4-methylphenethyl)-1,2,3,4-tetrahydroquinazoline is synthesized in 66% yield.[178]

Scheme 158



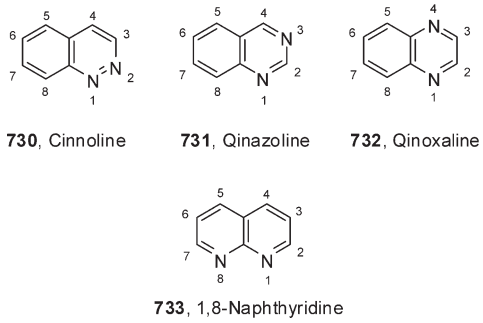


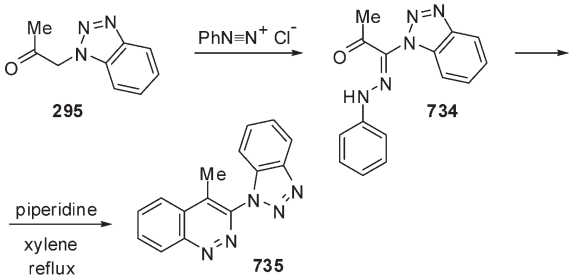
Figure 9. Atom numbering in (5,5)-C_8N_2 ring systems.

Microwave-assisted cyclocondensation of methyl anthranilate (**741**) with bis(benzotriazol-1-yl)methanetione (**742**) and *n*-octyl- or benzylamine in the presence of catalytic DBU provides 2-thioxo-1,2,3,4-tetrahydroquinazolin-4-ones **743** in 92 and 90% yields, respectively. Under similar conditions, the reactions with 2-amino-4-arylthiazoles provide products **744** in 84−87% yields. Analogously, 3-(1,3,4-oxadiazolyl) **745** (X = O) and 3-(1,3,4-thiadiazoly) **745** (X = S) derivatives are obtained in 80−90% yields (Scheme 161).[179] Under classical conditions, reactions of ester **741** with **742** and amines are carried out in refluxing DCM to give 2-thioxo-1,2,3,4-tetrahydroquinazolin-4-ones **743** in 54−89% yield.[180]

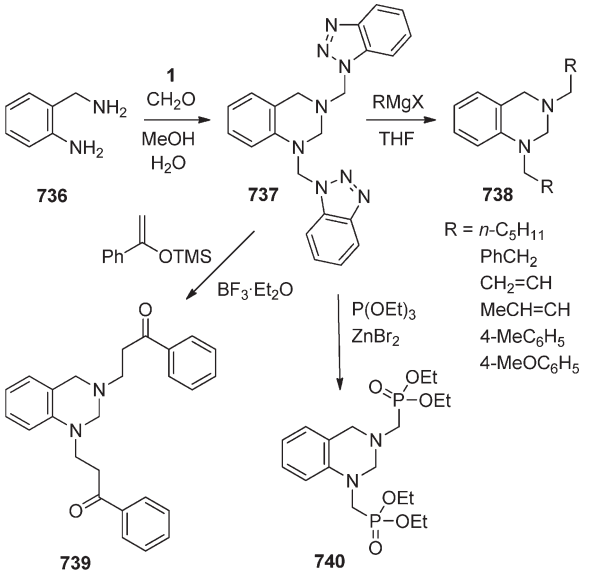
Addition of **722** to *p*-tolyl isocyanide provides carboximidoyl chloride **746** and its minor benzotriazol-2-yl isomer in the total yield of 85%. Secondary amines convert **746** into carboximidamides **747** in 78−81% yields. In a reaction of **747** (mixtures of benzotriazolyl isomers) with potassium thiocyanate and zinc bromide, carried out in refluxing DME, the benzotriazolyl moiety

dx.doi.org/10.1021/cr200031r |*Chem. Rev.* 2011, 111, 7063–7120

Scheme 159



Scheme 160

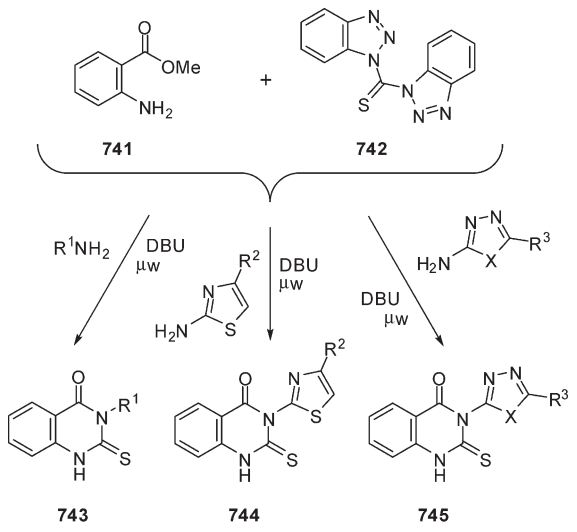


is substituted with an −N═C═S group to give intermediate **748** that subsequently cyclizes to 2-amino-(3*H*)-quinazolin-4-thione **749**. Because of their tautomerism, compounds **749** are difficult to purify and characterize and are isolated as methylated derivatives **750** in 52−70% yields (Scheme 162).[181]

Lithiated 1-benzylbenzotriazoles **751** add to aryl nitriles to give enamines **752** in 10% (Ar^1 = 4-$MeOC_6H_4$, Ar^2 = Ph) to 56% (Ar^1 = Ph, Ar^2 = 4-$MeOC_6H_4$) yields. Heating in refluxing toluene converts enamines **752** into 2,4-diarylquinazolines **757** in 30% (Ar^1 = 4-$MeOC_6H_4$, Ar^2 = Ph) to 74% (Ar^1 = 4-MeC_6H_4, Ar^2 = Ph) yields. The proposed mechanism consists of ring-opening of benzotriazole generating betaine **753** that loses nitrogen to give intermediate **754**, which undergoes rapid ring-closure to 2,3,3-trisubstituted (3*H*)-indole **755**. The crucial step, separation of the aryl-bearing carbon atoms, occurs by addition of the amino group to the C═N bond and cleavage of the C−C bond in resultant aziridine **756**. To generate **757**, this step must also involve elimination of molecular hydrogen or oxidation by atmospheric oxygen (Scheme 163).[182]

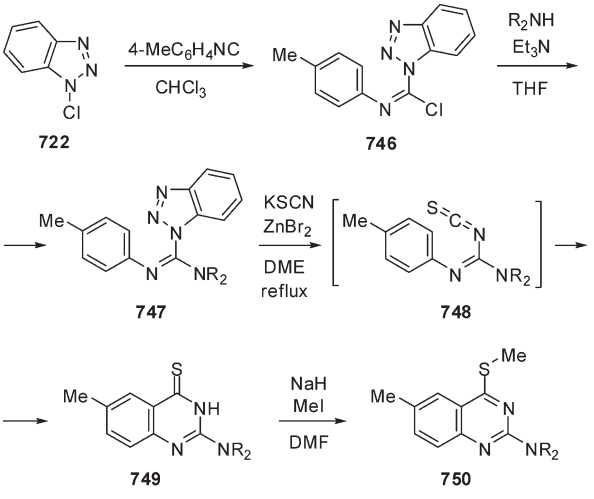
α-(Benzotriazol-1-yl)arylmethyl isopropyl ethers **758** are readily prepared by condensation of aryl aldehydes with benzotriazole and isopropanol in the presence of an acid catalyst (*p*-TSA).[38] Lithiated ethers **758** spontaneously eliminate nitrogen, and the resultant species **759** can be trapped by various electrophiles.

Scheme 161



R^1 = *n*-C_8H_{17} or $PhCH_2$; R^2 = Ph or 4-MeC_6H_4
R^3 = Ph, 3-HOC_6H_4, 4-HOC_6H_4, 4-$MeOC_6H_4$, 3-$O_2NC_6H_4$, or 4-$O_2NC_6H_4$; X = O or S

Scheme 162



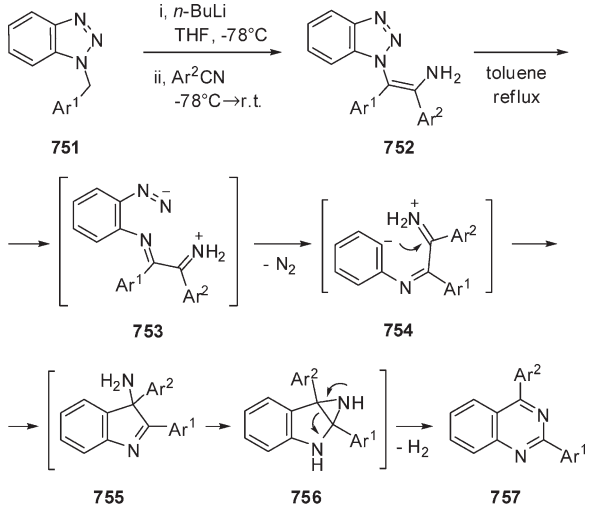
R_2NH = Et_2NH, piperidine, or morpholine

When aryl nitriles are used, 2,4-diarylquinazolines **760** are obtained in 47−81% yields. In the case of phenyl isothiocyanate, (3*H*)-quinalolin-4-thiones **761** are formed in 67−74% yields. The reaction with Schiff bases provides 2,3,4-triaryl-3,4-dihydroquinazolines **762** in 71−83% yields (Scheme 164).[183]

Reaction of quinazolone **763** with BOP and DBU provides 4-(benzotriazol-1-yloxy)quinazoline (**767**) in 82% yield. In the first step of this reaction, phosphonium intermediate **764** forms with elimination of anion **765**. The subsequent nucleophilic attack of **765** on quinazoline C-4 results in elimination of HMPA with formation of **767**. However, when the reaction is carried out in the presence of benzotriazole, the anion generated from benzotriazole acts as a dominant nucleophile, and 4-benzotriazol-ylquinazoline (**766**) is obtained instead in 66% yield (Scheme 165).[184]

dx.doi.org/10.1021/cr200031r |*Chem. Rev.* 2011, 111, 7063–7120

Scheme 163



Ar^1 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, or 4-Br-C_6H_4
Ar^2 = Ph, 4-MeC_6H_4, or 4-$MeOC_6H_4$

13.3. Quinoxaline

Treating a mixture of 2-chloroquinoxaline (**768**) and benzotriazol-1-ylacetonitrile (**481**) with 2.5 mol equiv of sodium hexamethyldisilazane (NaHMDS) results in formation of nitrile **769** in 89% yield. When *meta*-chloroperbenzoic acid is added to the reaction mixture, amide **772** (66% yield) is the only detected product. This outcome of the reaction can be explained by initial formation of cyanohydrin **770** that eliminates HCN to form 1-acylbenzotriazole **771**. Addition of NaHMDS to **771** followed by hydrolysis of the adduct during workup provides final amide **772** (Scheme 166).[185]

13.4. 1,8-Naphthyridine

Treated with benzotriazole and thionyl chloride, 1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (**773**) is converted to 1-acylbenzotriazole **774** in 90% yield. In reactions of **774** with various amino acids, amides **775**, potential antibiotics, are obtained in 39% (from L-Asp) to 88% (DL-Ala) yields (Scheme 167).[186]

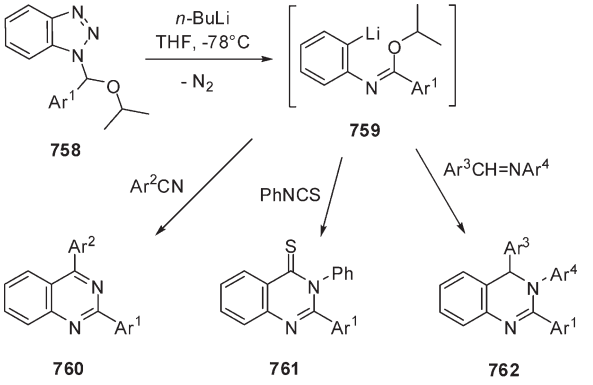
14. OTHER (6,6)-RING SYSTEMS WITH TWO OR MORE HETEROATOMS

A few other (6,6)-ring systems with oxygen and nitrogen (**776** and **777**), two oxygen (**778**), sulfur and nitrogen (**779**), or three nitrogen atoms (**780** and **781**) have been synthesized with the aid of benzotriazole derivatives. Core structures of these systems are presented in Figure 10.

An anion generated from 1-(α-isopropoxybenzyl)benzotriazole (**758a**), upon its treatment with *n*-BuLi, undergoes spontaneous opening of the triazole ring with extrusion of nitrogen to give the corresponding anion **759a** that adds to carbonyl groups of aldehydes and ketones to form alkoxides **782**. In the consecutive steps, intramolecular addition of the alkoxide anions to the C=N bond followed by elimination of isopropoxide furnishes (4*H*)-3,1-benzoxazines **783** in 53−70% yields (Scheme 168).[183]

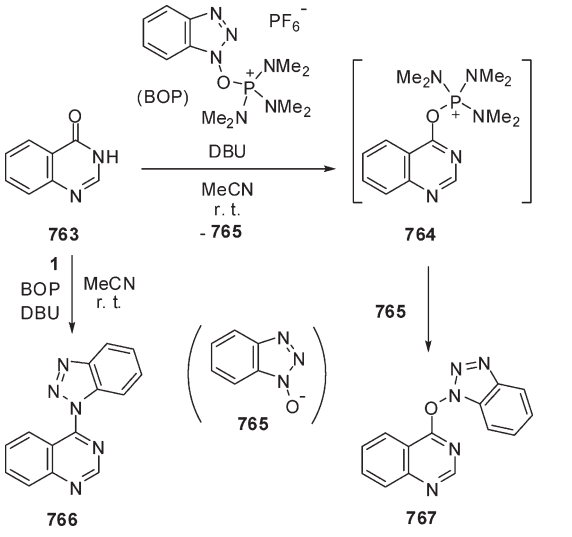
1-(2-Hydroxybenzoyl)benzotriazoles **784** are obtained in high yields in reactions of the corresponding salicylic acids with benzotriazole and thionyl chloride.[187] Treatment with isocyanates

Scheme 164



Ar^1 = Ph, 4-MeC_6H_4, or 1-naphthyl; Ar^2 = Ph or 4-MeC_6H_4;
Ar^3 = Ph, 4-MeC_6H_4, or 4-$MeOC_6H_4$; Ar^4 = Ph or 4-MeC_6H_4

Scheme 165



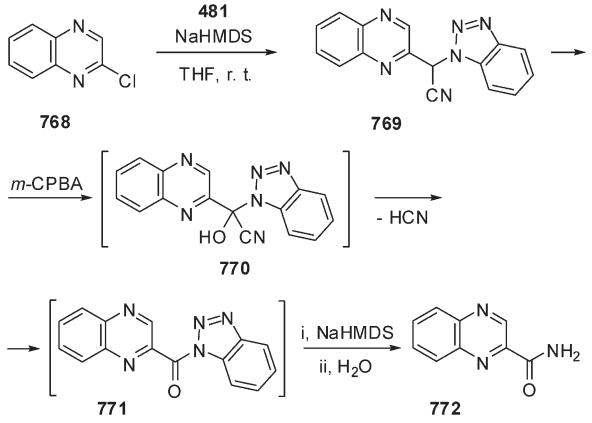
and triethylamine converts derivatives **784** into (3*H*)-1,3-benzoxazin-2,4-diones **785** in 96−99% yields. Reactions of **784** with aldehydes provide 1,3-benzodioxin-4-ones **786** in 52−94% yields (Scheme 169).[188]

Addition of benzotriazole to the carbonyl groups of glyoxal provides quantitatively 1,2-bis(benzotriazol-1-yl)ethane-1,2-diol (**787**).[189] Treatment with thionyl chloride converts diol **787** into 1,2-dichloro derivative **788** in 90% yield. The reactive chlorine atoms in **788** can be readily substituted with nucleophiles. Use of 2-aminobenzenethiol as a dinucleophile allows substitution of both chlorine atoms with ring formation to give (2*H*)-3,4-dihydro-1,4-benzothiazine system **789** in 90% yield. Because of a low energy barrier of isomerization between benzotriazol-1-yl and 2-yl isomers in **789**, the product constitutes a complex mixture of regio- and stereoisomers, but because it allows easy substitution of the benzotriazolyl groups with nucleophiles, it may be considered as a valuable starting material for various 2,3-disubstituted (2*H*)-1,4-benzothiazines (Scheme 170).[190]

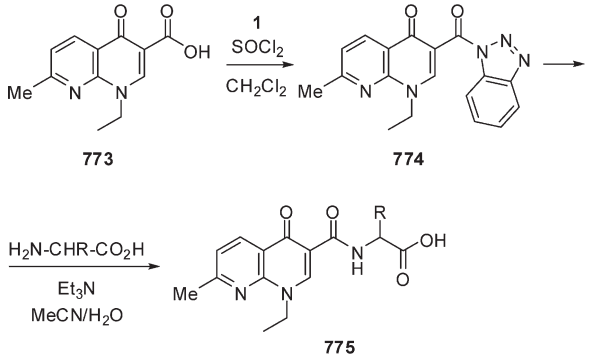
α-(Benzotriazol-1-yl)benzyl ketones, readily available from reactions of lithiated 1-benzylbenzotriazoles with carboxylic

dx.doi.org/10.1021/cr200031r |*Chem. Rev.* 2011, 111, 7063–7120

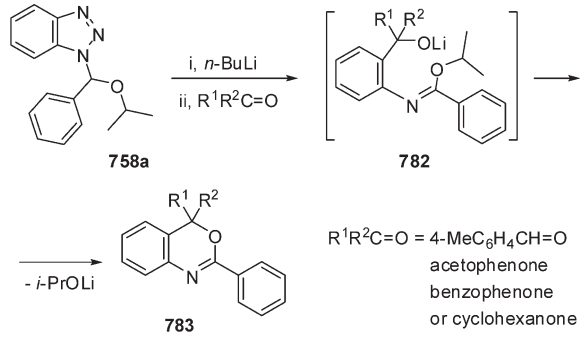
Scheme 166



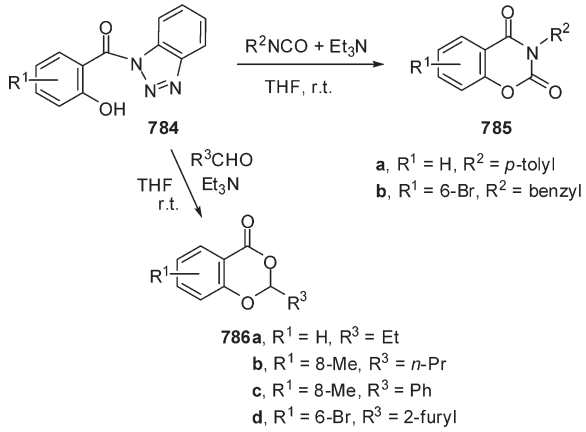
Scheme 167



Scheme 168



Scheme 169



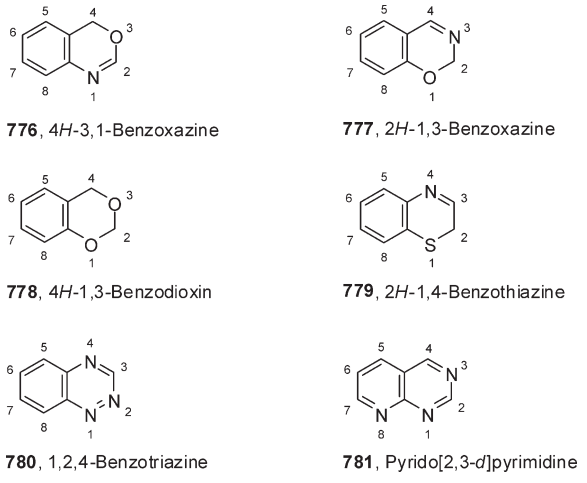


Figure 10. (6,6)-Ring systems discussed in section 14.

esters,[39] are converted to tosylhydrazones **790** in 72−98% yields. Dianions **791**, obtained by treatment of **790** with 3 mol equiv of *n*-BuLi in the presence of TMEDA, undergo rearrangement by opening of the triazole ring to give dianions **792** and ring-closure involving the benzylic carbon atom to give the six-membered ring of 1,2,4-benzotriazine systems **793**. In the case of R^2 = aryl, just generated dianions **793** are stable and during workup are converted to hydrazones **794** in 75−79% yields; however, for R^2 = alkyl (n-C_7H_{15} or $PhCH_2CH_2$), the whole hydrazone functionality is eliminated to furnish 3-aryl-1,2,4-benzotriazines **795** in 76−79% yields (Scheme 171).[40]

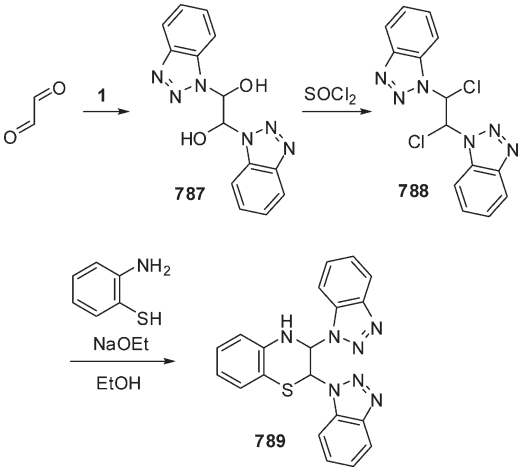
Phosphonium chloride **796** is prepared in 90% yield by reacting 1-(chloromethyl)benzotriazole (**76**) with tri-*n*-butylphosphine. Treated with 2 equiv of *n*-butyllithium followed by acetyl chloride, salt **796** is converted to ylide **797** in 69% yield. Flash vacuum pyrolysis of **797** at 450 °C gives 3-acetyl-1,2,4-benzotriazine **799** (26% yield) resulting from elimination of tri-*n*-butylphosphine followed by rearrangement of intermediate carbene **798** (Scheme 172).[191]

Combinatorial synthesis of 1,2,7-trisubstituted 1*H*-pyrido[2,3-*d*]pyrimidin-4-ones **805** starts from a reaction of resin-bound amines with dibenzotriazolylmethanimine producing derivatives **800**. Acylation of **800** with 2,6-dichloronicotinyl chloride gives **801**, in which the benzotriazolyl moiety is subsequently displaced with amines to give guanidines **802**. In the following steps, **802** are cyclized to 1*H*-pyrido[2,3-*d*]pyrimidin-4-ones **803**, the chlorine atom is displaced with amines to give **804**, and finally the bond with the resin is cleaved to give **805** in 42−71% total yields (Scheme 173).[192]

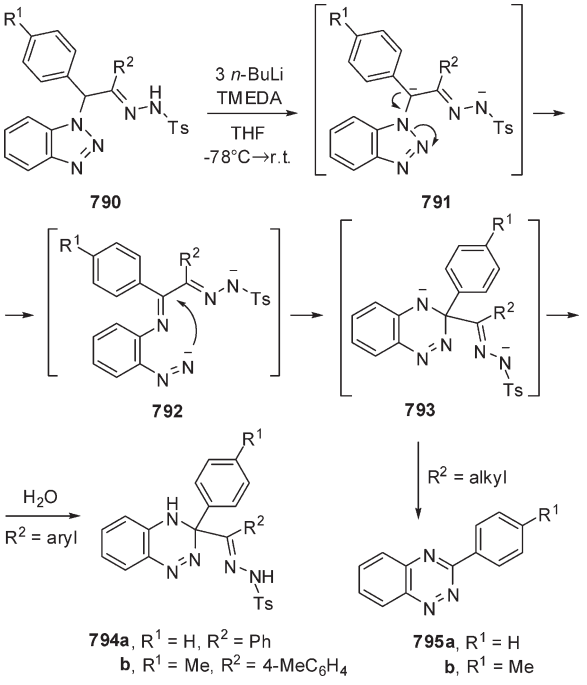
In another approach to the 1*H*-pyrido[2,3-*d*]pyrimidine system, the pyrimidine ring is assembled first, and then the pyridine ring is build on it. Thus, in an example given in Scheme 174, amino acid **806** is converted to 1-acylbenzotriazole **807** in 54% yield, using EDCI as a dehydrating agent. Treatment of **807** with

dx.doi.org/10.1021/cr200031r |*Chem. Rev.* 2011, 111, 7063–7120

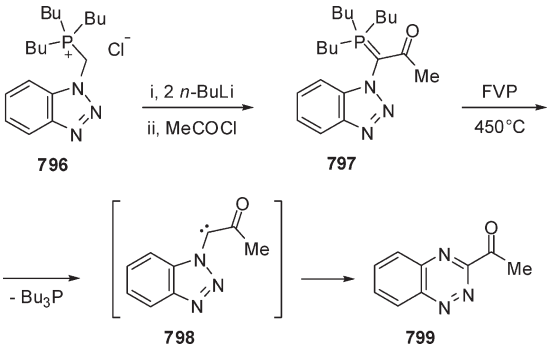
Scheme 170



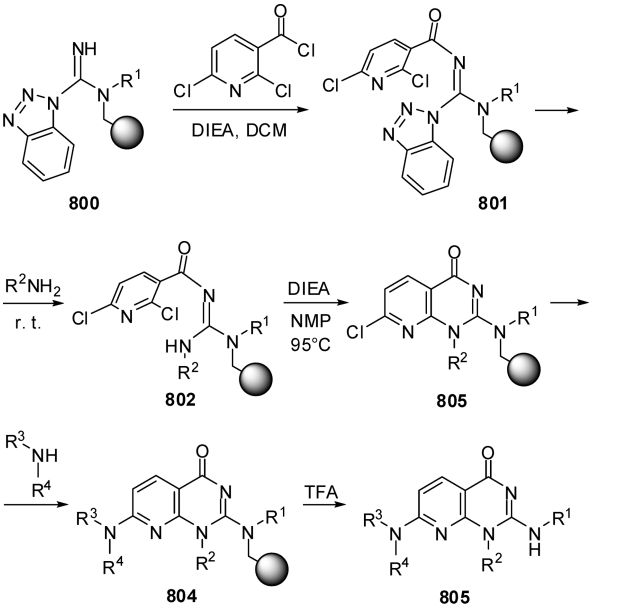
Scheme 171



Scheme 172



Scheme 173



lithiated ethyl acetate gives β-keto ester **808** in 42% yield. Heated with DBU and *N,N*-diisopropylethylamine, **808** undergoes cyclocondensation to form 8-cyclopentyl-5-hydroxy-2-methylsulfanyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (**809**) in 97% yield.[193]

15. (6,7)-RING SYSTEMS

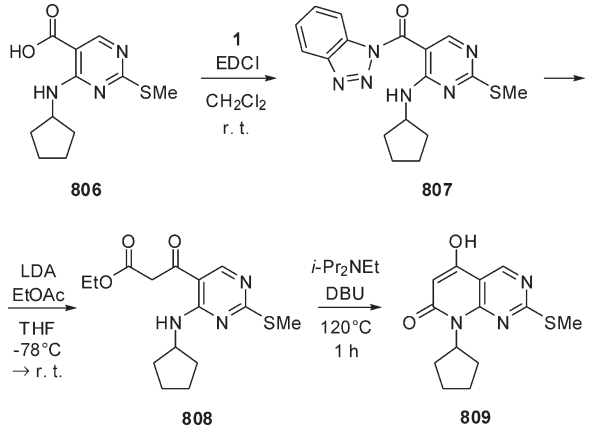
In most popular heterocycles of this category, the six-membered ring is represented by benzene or pyridine, and the seven-membered ring contains nitrogen, oxygen, and/or sulfur atoms. The benzotriazole methodology has been involved in preparation of derivatives of three mono- (**810**−**812**), six di- (**813**−**818**), and one tetraheteroatom (**819**) (6,7)-bicyclic systems shown in Figure 11.

15.1. One Heteroatom

Condensation of 3-phenyl-1-propylamine (**820**) with formaldehyde and benzotriazole (**1**) in aqueous methanol provides *N,N*-bis(benzotriazol-1-ylmethyl)-3-phenyl-1-propylamine (**821**), exclusively as benzotriazol-1-yl regioisomers, in 62% yield. In the presence of aluminum chloride, an electrophilic attack of an iminium cation generated by cleavage of one of the (benzotriazol-1-yl)-methylene bonds in **821** on the phenyl *ortho*-carbon atom results in 2-(benzotriazol-1-ylmethyl)-2,3,-4,5-tetrahydro-1*H*-2-benzazepine (**822**) and its benzotriazol-2-yl analogue in total 70% yield and isomeric ratio of 4.4:1. The isomerization from benzotriazol-1-yl to benzotriazol-2-yl regioisomers must occur during the cyclization, probably promoted by aluminum chloride. However, because there is no difference in

dx.doi.org/10.1021/cr200031r |*Chem. Rev.* 2011, 111, 7063–7120

Scheme 174



reactivity of these isomers with electrophiles, the whole mixture is used in subsequent reactions. Thus, treatment of **822**, together with its benzotriazol-2-yl isomer, with Grignard reagents allows substitution of the benzotriazolyl moiety with alkyl, aryl, or phenylethynyl groups resulting in 2-substituted 2,3,4,5-tetrahydro-1*H*-2-benzazepines **823** in 43% (**f**) to 78% (**c**) yields. Similarly, reaction of **822** with triethyl phosphite and zinc bromide gives phosphonate **824** in 87% yield. Treatment of **822** with sodium borohydride in methanol causes its decomposition, but reduction of the benzotriazol-1-ylmethyl to methyl group can be achieved when the reaction is run in THF; 2-methyl-2,3,4,5-tetrahydro-1*H*-2-benzazepine is separated as a complex with borane (**825**) in 83% yield (Scheme 175).[194]

Condensation of 3-arylpropionamides **826** with aldehydes and benzotriazole gives derivatives **827** in practically quantitative yields. In the presence of aluminum chloride as Lewis acid, molecules **827** generate cations **828**, which attack the aryl *ortho*-carbon atom to give 1-aryl-4-phthalimidoyl-1,2,4,5-tetrahydro-2-azepin-3-ones **829** in 30−31% yields (X^1 = H) to 68−71% yields (X^1 = MeO). In all cases, formation of only cis stereoisomers of **829** is observed (Scheme 176).[195]

Reaction of betmip (**669**) with methylenetriphenylphosphorane, generated by treatment of triphenylmethylphosphonium bromide with *n*-butyllithium, gives phosphonium salt **830** that in situ is deprotonated by addition of more *n*-butyllithium to give 1-aza-1,3-bis(triphenylphosphoranylidene)propane (**831**). Subsequent treatment of the reaction mixture with phthalaldehyde results in formation of 3*H*-2-benzazepine (**832**) in 62% yield (Scheme 177).[158,196]

Condensation of cycloheptanone with 3-aminocrotononitrile in the presence of titanium tetrachloride and triethylamine provides 3-amino-2-(1-cyclohepten-1-yl)-2-butenenitrile (**833**) in 84% yield. Reaction of **833** with iminium salt **219**, a Vilsmeier-type reagent, gives relatively stable intermediate **834**, which can be stored in solutions for several days without decomposition. However, treatment of the reaction mixture with 2N aqueous NaOH causes rapid cyclocondensation of **834** with elimination of dimethylamine to furnish 3-methyl-6,7,8,9-tetrahydro-5*H*-cyclohepta[*c*]pyridine-4-carbonitrile (**835**) in 68% yield (Scheme 178).[67]

Condensation of readily available dialdehydo sugar **836** with benzotriazole and benzylamine provides piperidine **837** (together with the corresponding benzotriazol-2-yl isomers) in

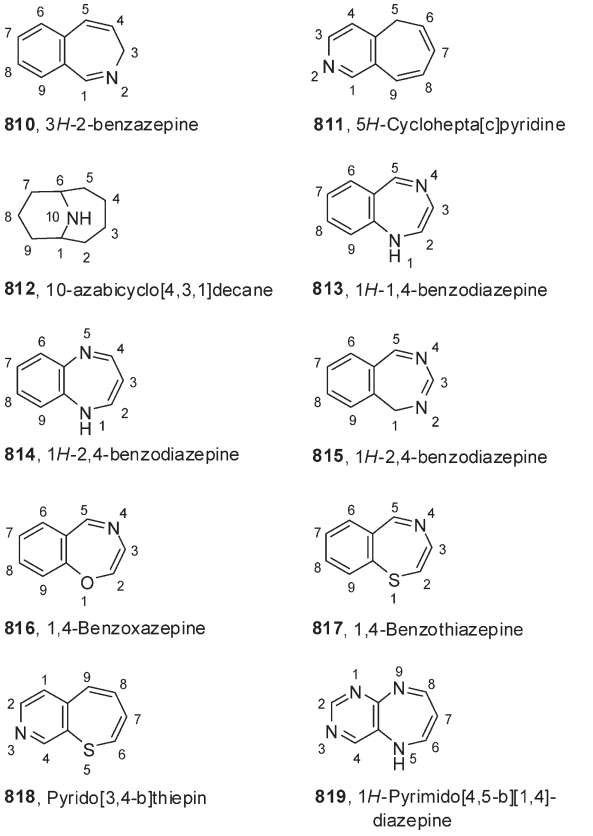
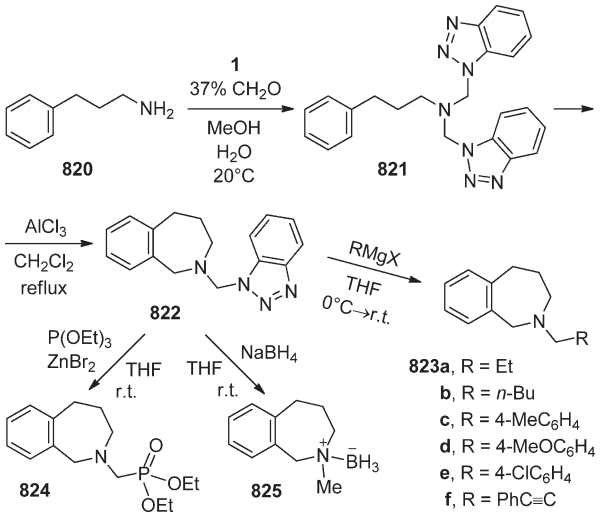


Figure 11. Atom numbering in (6,7)-ring systems.

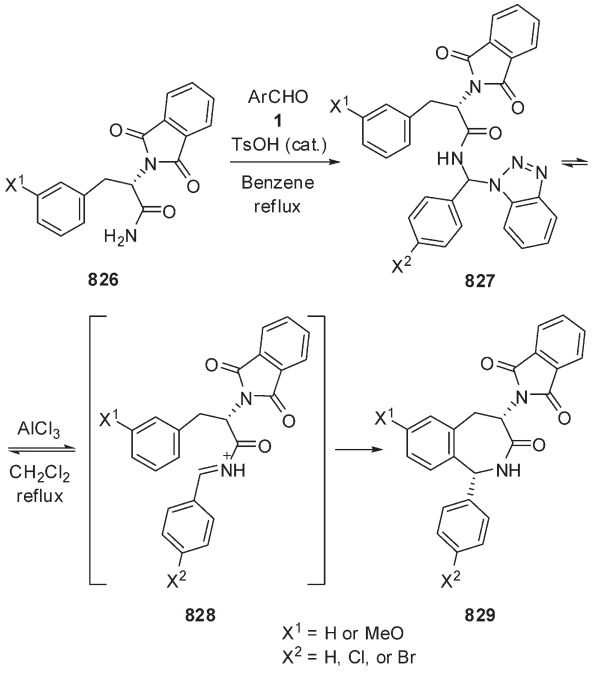
Scheme 175



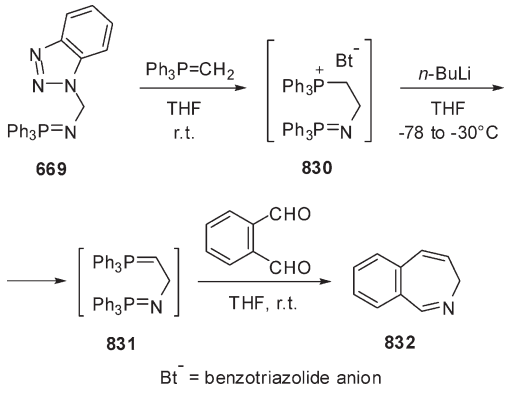
45% yield. Replacement of the benzotriazolyl substituents in **837** with allyl groups and acetylation of the hydroxy groups gives a mixture of stereoisomers of 2,6-diallylpiperidines **838** in 57% yield. Removal of the benzyl group with CAN gives a mixture of stereoisomers, from which **839** is chromatographically separated in 29% yield. Finally, protection of the piperidinyl nitrogen with 2,2,2-trichloroethyl chloroformate gives derivative **840**, which when subjected to Grubbs' catalyst undergoes metathesis with

dx.doi.org/10.1021/cr200031r |*Chem. Rev.* 2011, 111, 7063–7120

Scheme 176



Scheme 177

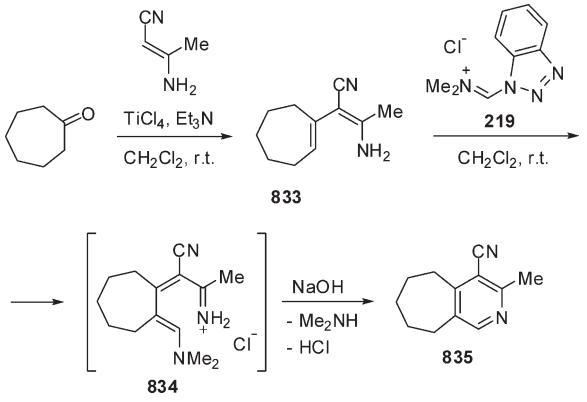


closing of the seven-membered ring to give 10-azabicyclo-[4,3,1]decane derivative **841** in 98% yield (Scheme 179).[197]

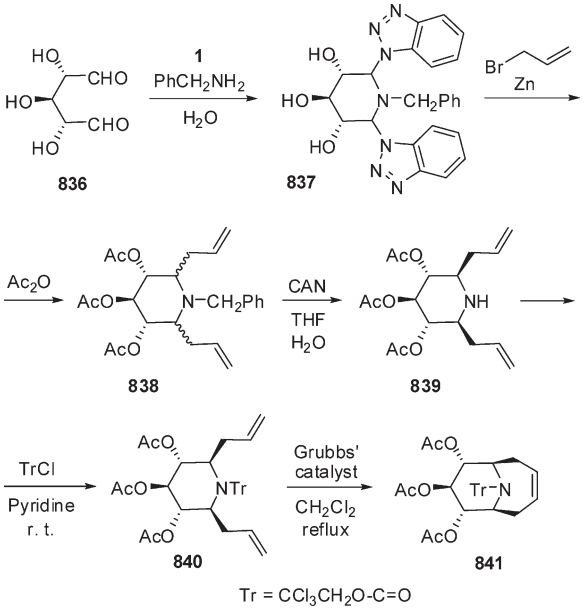
15.2. Benzodiazepines

Condensation of diamine **842**, obtained in 90% yield from a reaction of *N*-methylaniline with oxazolidin-2-one, with aqueous formaldehyde and benzotriazole provides *N*,*N*-bis(benzotriazol-1-ylmethylated) product **843** in 92% yield. In the presence of aluminum chloride, the iminium cation generated from **843** attacks the aniline *ortho*-carbon atom, closing a seven-membered ring to give 4-(benzotriazol-1-ylmethyl)-1-methyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine **844** and its minor benzotriazol-2-yl isomer in the total yield of 86%. Because in this case both isomers give the same products in reactions with nucleophiles, the mixture is used further without separation. Substitution of the benzotriazolyl moiety in **844** and its benzotriazol-2-yl isomer

Scheme 178



Scheme 179



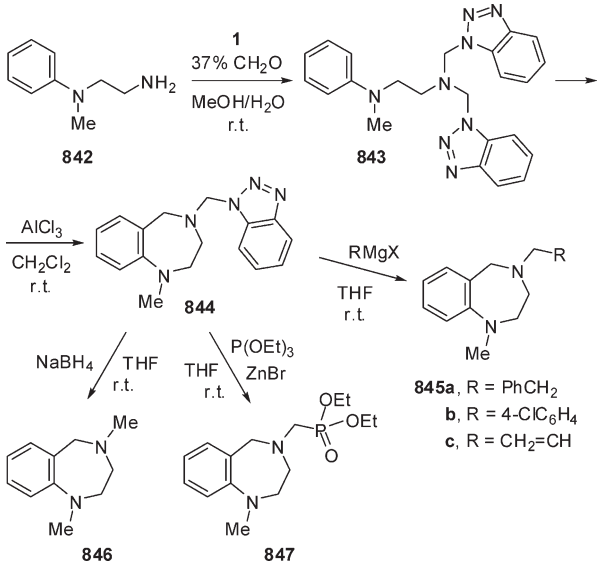
with Grignard reagents leads to 1,4-disubstituted 2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepines **845a**−**c** in 68−76% yields. Reduction of **844** with sodium borohydride gives 1,4-dimethyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine **846** in 73% yield, whereas diethyl phosphonate **847** is obtained in 69% yield from a reaction of **844** with triethyl phosphite and zinc bromide (Scheme 180).[198]

Condensation of aniline **848** with acid **849**, obtained from benzyl carbamate, glyoxylic acid, and benzotriazole,[28] in the presence of oxalyl chloride and *N*-methyl maleimide (NMM) gives amide **850**. In its crude form, **850** is treated with ammonium hydroxide in methanol to provide 1*H*-2,3-dihydro-1,4-benzodiazepin-2-one **851**, an intermediate in the synthesis of potent γ-secretase inhibitors, in 45% overall yield (Scheme 181).[199] In a similar way, **849** is used in the synthesis 1*H*-2-amino-2,3-dihydro-1,4-benzodiazepin-2-ones with various substituents on the rings as agents for treating hepatitis C infection[200] and as analgesics.[201]

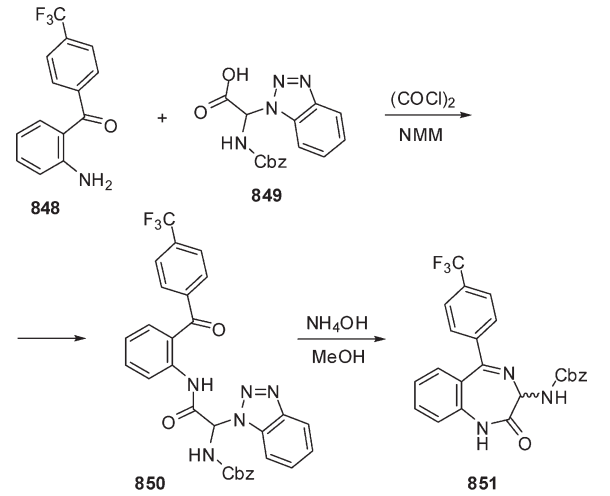
Addition of *ortho*-phenylenediamine to α,β-unsaturated 1-acylbenzotriazoles **852** followed by cyclocondensation of

dx.doi.org/10.1021/cr200031r |*Chem. Rev.* 2011, 111, 7063–7120

Scheme 180



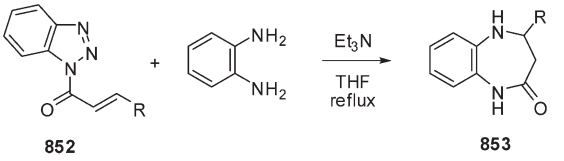
Scheme 181



the obtained intermediates results in 1*H*-2,3,4,5-tetrahydro-1,5-benzodiazepin-2-ones **853**, isolated in 76−85% yields (Scheme 182).[202,203]

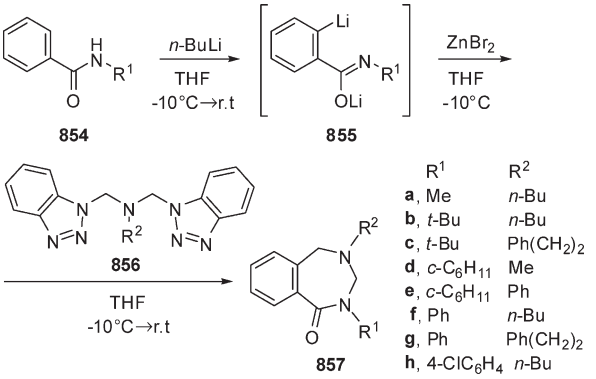
Double lithiation of benzamides **854** with *n*-BuLi gives organolithium derivatives **855** that are subsequently converted to the corresponding organozinc reagents by addition of zinc bromide. Cyclocondensation of just generated zinc derivatives with *N*,*N*-bis(benzotriazol-1-ylmethyl)amines **856**, readily available from reactions of primary amines with formaldehyde and benzotriazole, furnishes 2,4-disubstituted 2,3,4,5-tetrahydro-1*H*-2,4-benzodiazepin-1-ones **857** in 36% (**c**) to 82% (**b**) yields. The driving force of this reaction is high affinity of zinc cations to benzotriazole, as strong complexation with zinc expedites the benzotriazolyl−N−Cα bond scission. The experiments carried out with lithio-derivatives **855** showed that they do not react themselves with **856** (Scheme 183).[204]

Scheme 182

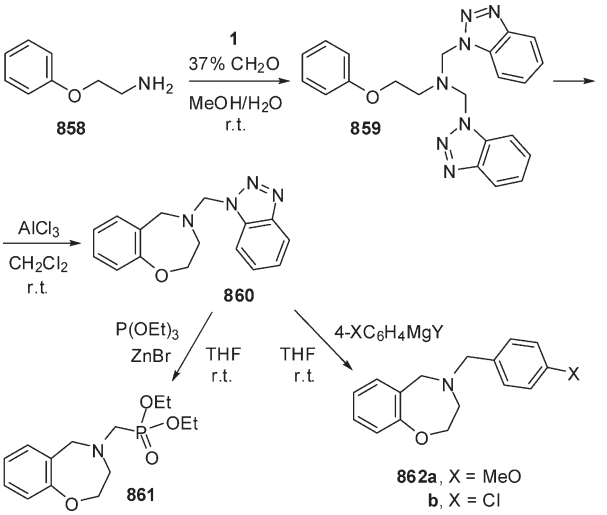


R = Me, Ph, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-O$_2$NC$_6$H$_4$, or 2-furyl

Scheme 183



Scheme 184



15.3. C$_9$NO and C$_9$NS Systems

N,*N*-Bis(benzotriazol-1-ylmethylation) of 2-phenoxyethylamine **858** with benzotriazole and formaldehyde in methanol/water provides crystalline derivative **859** in 78% yield. Catalyzed by aluminum chloride, intramolecular aminomethylation in **859** closes a seven-membered ring leading to 4-(benzotriazol-1-ylmethyl)-2,3,4,5-tetrahydro-1,4-benzoxazepine (**860**) and its minor benzotriazol-2-yl isomer (isomeric ratio 5.6:1) in 66% total yield. Because both isomers react similarly with nucleophiles, the mixture is directly used in further transformations.

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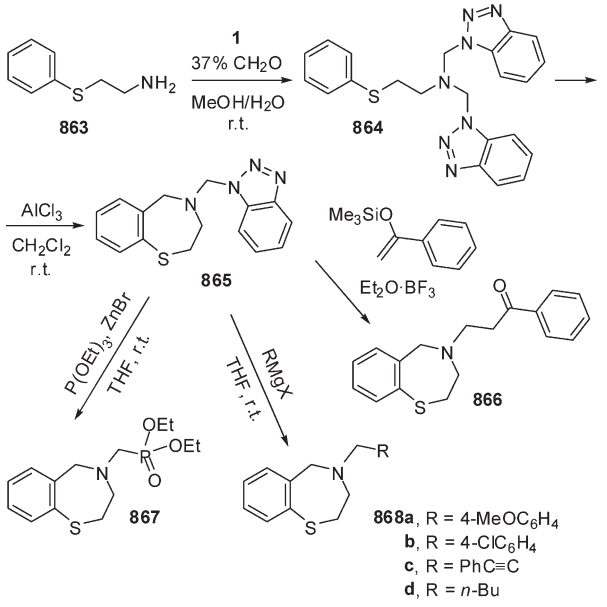
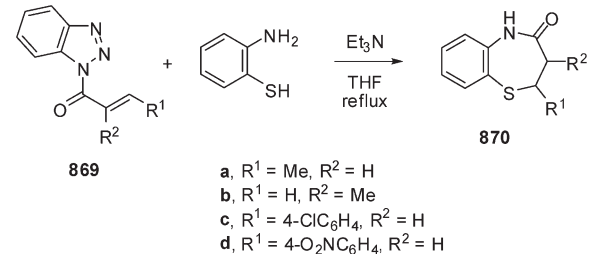
Scheme 185



Scheme 186

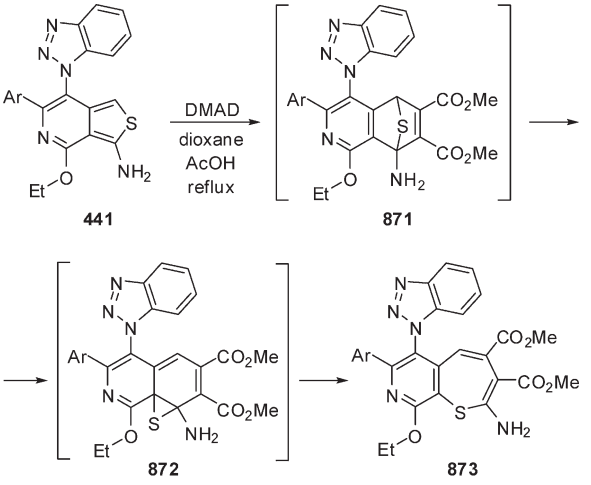


Thus, in its reaction with triethyl phosphite catalyzed by zinc bromide, phosphonate **861** is obtained in 70% yield, whereas the reactions with arylmagnesium reagents give 4-arylmethyl-2,3,4,5-tetrahydro-1,4-benzoxazepines **862** in 74% (**a**) and 84% (**b**) yields (Scheme 184).[198]

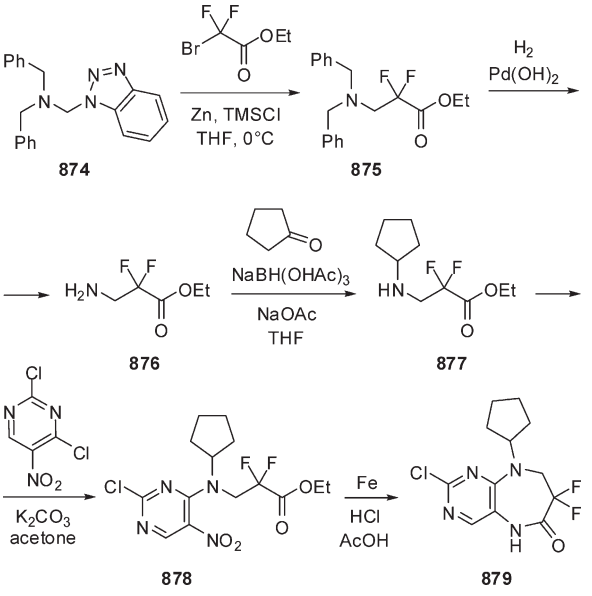
Similarly to its oxygen analogue **858**, 2-(phenylsulfanyl) ethylamine (**863**) is converted to *N*,*N*-bis(benzotriazol-1-ylmethylated) derivative **864** (90% yield). Cyclization of **864** in the presence of aluminum chloride provides 4-(benzotriazol-1-ylmethyl)-2,3,4,5-tetrahydro-1,4-benzothiazepine (**865**) together with its minor benzotriazol-2-yl isomer in 81% total yield. Treatment of this mixture with boron trifluoride etherate and 1-phenylvinyl trimethylsilyl ether results in 4-(2-benzoylethyl)-2,3,4,5-tetrahydro-1,4-benzothiazepine (**866**) in 44% yield. In a reaction of **865** with triethyl phosphite and zinc bromide, phosphonate **867** is generated in 79% yield. Substitution of the benzotriazolyl moiety in **865** (and its benzotriazol-2-yl isomer) with aryl, phenylethynyl, or *n*-butyl groups from Grignard reagents gives 4-substituted 2,3,4,5-tetrahydro-1,4-benzothiazepines **868** in 88−93% yields (Scheme 185).[198]

In analogy to the synthesis of 1*H*-2,3,4,5-tetrahydro-1,5-benzodiazepin-2-ones **853**, α,β-unsaturated 1-acylbenzotriazoles **869** react with 2-aminobenzothiol to give 2,3,4,5-tetrahydro-1,5-benzothiazepin-4-ones **870** in 69−78% yields (Scheme 186).[203]

Scheme 187



Scheme 188



Reaction of dimethyl acetylenedicarboxylate (DMAD) with thieno[3,4-*c*]pyridine **441** in refluxing dioxane/acetic acid provides dimethyl 2-amino-6-(benzotriazol-1-yl)-9-ethoxy-7-(4-methoxyphenyl)pyrido[3,4-*b*]thiepin-3,4-dicarboxylate (**873**) in 74% yield. The suggested mechanism of this reaction involves Diels−Alder cycloaddition of DMAD to **441** with formation of tricyclic system **871** that subsequently rearranges to **872** and finally to **873** (Scheme 187).[107]

15.4. More than Two Heteroatoms

Condensation of 1-(hydroxymethyl)benzotriazole (**25**) with dibenzylamine provides 1-(dibenzylaminomethyl)benzotriazole (**874**) together with its benzotriazol-2-yl isomer in quantitative

dx.doi.org/10.1021/cr200031r |*Chem. Rev.* 2011, 111, 7063–7120

yield. Treatment of this mixture with ethyl bromodifluoroacetate and zinc gives ethyl 3-dibenzylamino-2,2-difluoropropionate (**875**) in 50% yield. Deprotection of the nitrogen atom in **875** gives 3-amino-2,2-fluoropropionate **876** in 94% yield, which is used in the synthesis of 2-chloro-9-cyclopentyl-7,7-difluoro-6,7,8,9-tetrahydro-5*H*-pyrimido[5,4-*b*][1,4]diazepin-6-one (**879**), via intermediates **877** and **878** (Scheme 188).[205] A series of 7,7-difluorinated 6,7,8,9-tetrahydro-5*H*-pyrimido[5,4-*b*][1,4]diazepin-6-ones with various substituents on the rings have been obtained in this way as potential anticancer agents.[206]

16. CONCLUSION

Tremendous progress has been achieved since the first reports in the 1980s on application of benzotriazole as a synthetic auxiliary in organic synthesis. Benzotriazole methodology is spreading now from universities to industrial laboratories and processes. Although many fields benefit, aid of benzotriazole to the synthesis and derivatization of heterocyclic systems is especially profound. Many structures involving all basic heterocycles can be now much more easily obtained due to benzotriazole chemistry. In this review, part 2 of a series, we are focusing on bicyclic heterocycles, the area to which the benzotriazole methodology has brought recently most contribution.

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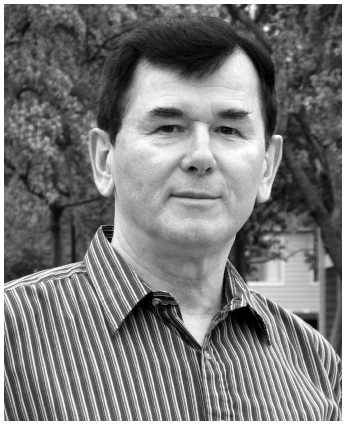
BIOGRAPHIES

Alan Katritzky is Kenan Professor of Chemistry and Director for Center of Heterocyclic Compounds at the University of Florida. He studied, researched, and taught in the U.K. at the Universities of Oxford, Cambridge, and East Anglia before crossing the Atlantic to take up his present post in 1980. He has researched in diverse areas of organic and physical-organic chemistry but none more deeply than in the chemistry of benzotriazole, a topic which blossomed in his group after Stan Rachwal joined him in 1983. Benzotriazole chemistry was first summarized in Chemical Reviews in 1998; that manuscript has since received 264 citations. It is a particular pleasure for him to have been asked by Dr. Rachwal to share in the authorship of the present summary, which updates part of the earlier review.



Stanislaw Rachwal was born in Jodlowka and was raised in Krakow, Poland. He received a Ph.D. in organic chemistry from Jagiellonian University in Krakow and was nominated to a position of Adjunct Professor at that university in 1980. His main research at that time was focused on chemistry of ferrocenophanes. During a sabbatical leave in 1984, he joined Professor Alan R. Katritzky at University of Florida to lay a foundation for application of benzotriazole in organic synthesis. He returned to University of Florida in 1988, where as a group leader, he effectively contributed to the research on derivatives of benzotriazole. His collaboration with Professor Katritzky resulted in over 40 scientific papers on benzotriazole. Since 1993, he has worked in the pharmaceutical industry, specializing in CNS drugs with a primary focus on heterocyclic compounds.

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