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Novel Synthesis of Bicycles with Fused Pyrrole, Indole, Oxazole, and Imidazole Rings

Alan R. Katritzky,* Sanjay K. Singh, and Sergey Bobrov

Center for Heterocyclic Compounds, University of Florida, Department of Chemistry, Gainesville, Florida 32611-7200

katritzky@chem.ufl.edu

Received August 20, 2004

Abstract: Reactions of benzotriazol-1-yl(1*H*-pyrrol-2-yl)methanone **10** and benzotriazol-1-yl(1*H*-indol-2-yl)methanone **11** with diverse ketones, isocyanates, and isothiocyanates in the presence of base afforded pyrrolo[1,2-*c*]oxazol-1-ones **1**, oxazolo[3,4-*a*]indol-1-ones **2**, pyrrolo[1,2-*c*]imidazoles **3**, and imidazo[1,5-*a*]indoles **4** by a simple one-step procedure.

Pyrrolo[1,2-*c*]imidazole and imidazo[1,5-*a*]indole derivatives exhibit a wide spectrum of biological activity. Thus, pyrrolo[1,2-*c*]imidazole-1,3-diones **3** (X = O) are of interest due to their antidiabetic[1] and aldose reductase inhibitory activity.[2] Applications of imidazo[1,5-*a*]indoles **5** (X = O, S) derivatives include their use as central nervous depressants, analgesics,[3] and 5-NT_3 receptor antagonists.[4] Various 3-thioxo-2,3-dihydroimidazo[1,5-*a*]indol-1-ones **4** (X = S) have been evaluated as light-dependent TNF-α antagonists[5] and antifungals.[6] Several examples of oxazolo[3,4-*a*]indol-1-ones **2** (R = R^1 = Ar) from indolyl-2-carboxylic acid chloride and substituted 4,4′-bisalkylaminobenzophenones have all been reported by Fukui.[7] No pyrrolo[1,2-*c*]oxazol-1-ones **1** have been recorded.

5,6,7-Trisubstituted pyrrolo[1,2-*c*]imidazole-1,3-diones **3** (X = O) have previously been synthesized by cyclocondensation from the corresponding 2-pyrrolocarbonylaminoacetates with carbonyl diimidazole.[1,2] Papadopoulos[8,9] employed isocyanates and alkali salts of pyrroles to first generate the pyrrole-1-carboxamides **6**, which were then condensed with phosgene or thiophosgene in the presence of a base to give pyrrolo[1,2-*c*]imidazoles **3** (X = O; R = Ph and X = S; R = H, Ph) (Scheme 1 (i)). He also treated pyrrole-2-carboxamides **7** (R = Ph, CO_2Et) with phenyl isocyanate in the presence of a base to give **3** (X = O; R = Ph) (Scheme 1 (ii)).[10,11]

The synthetic strategies previously employed for compounds of type **4** are depicted in Scheme 2. Carter[5] condensed the appropriate indole-2-carboxylic acid **8** (R = alk, allyl; R^1 = alk, alkoxy; R^2 = H; Z = OH) or its methyl ester (Z = OMe) with isocyanate or isothiocyanate in the presence of triethylamine at high temperatures to give **4** (R^1 = alk, alkoxy; R^2 = H; X = O, S) in moderate to low yields (Scheme 2 (iii)). Unstable acid chloride **8** (R = H; R^1 = 5-Cl; R^2 = 2-fluorophenyl; Z = Cl) generated in situ was condensed with urethane to give imidazo[1,5-*a*]indole **4** (R = Ph; R^1 = 5-Cl; R^2 = 2-fluorophenyl; X = O) (Scheme 2 (iii)).[12] Papadopoulos also reacted indole-2-carbonyl compounds **8** (R^1 = R^2 = H; Z = NHPh, OEt) with phenyl isocyanate to form **4** (R^1 = R^2 = H; X = O) (Scheme 2 (iii)).[14] Compound **4** (R^1 = R^2 = H; R = H; X = S) has also been prepared in moderate yield by reaction of indole-2-carbonyl isothiocyanate **9** with sodium methanethiolate (Scheme 2 (iv)).[6,13]

The valuable and diverse biological properties of compounds incorporating the pyrrolo[1,2-*c*]imidazole or imidazo[1,5-*a*]indole ring system encouraged the development of efficient methods for their preparation. The pyrrolo[1,2-*c*]oxazoles **1** (Figure 1) represent rare types of fused heterocycles with a bridgehead nitrogen atom. This work reports a novel synthetic method for the ring closure to fused heterocyclic bicycles such as pyrrolo[1,2-*c*]oxazol-1-ones **1**, oxazolo[3,4-*a*]indol-1-ones **2**, pyrrolo[1,2-*c*]imi-

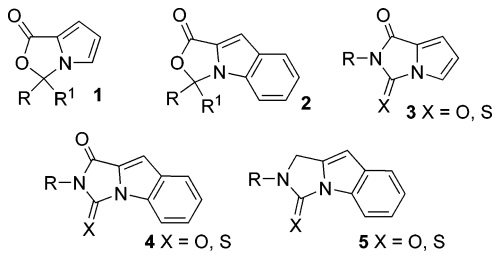
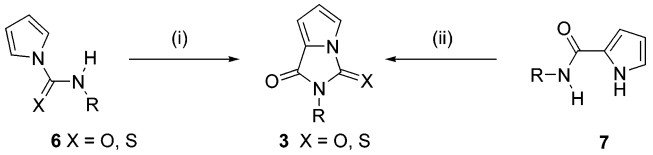
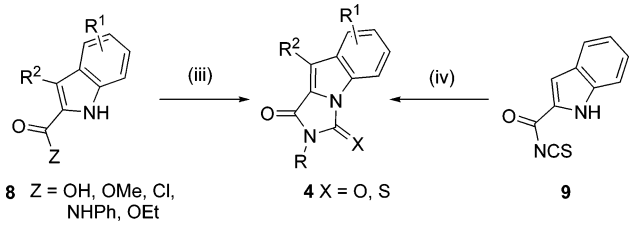


FIGURE 1. Pyrrolo[1,2-*c*]oxazol-1-ones **1**, oxazolo[3,4-*a*]indol-1-ones **2**, pyrrolo[1,2-*c*]imidazoles **3**, imidazo[1,5-*a*]indoles **4**, and imidazo[1,5-*a*]indoles **5**.

SCHEME 1



SCHEME 2



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10.1021/jo0485334 CCC: $27.50
Published on Web 11/12/2004

TABLE 1. Preparation of Pyrrolo[1,2-*c*]oxazol-1-ones 1a−h and Oxazolo[3,4-*a*]indol-1-ones 2a−d

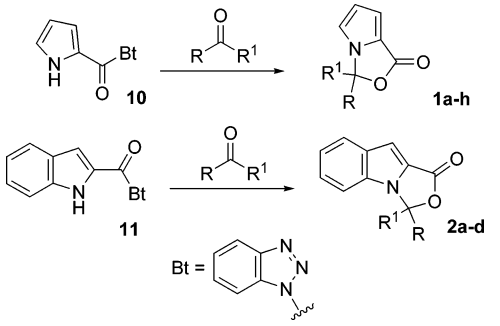
	compd	R	R^1	time (h)	product	yield (%)	mp (°C)
1	**10**	Me	Me	2	**1a**	80	52−53
2	**10**	*i*-Pr	H	2	**1b**	98	oil
3	**10**	$-(CH_2)_5-$		2	**1c**	80	99−100
4	**10**	*p*-Tol	H	2	**1d**	76	143−144
5	**10**	$-(CH_2)_4-$		2	**1e**	81	oil
6	**10**	Et	Et	2	**1f**	80	39−41
7	**10**	2-furyl	H	2	**1g**	64	76−77
8	**10**	Ph	Me	2	**1h**	47	oil
9	**11**	Me	Me	4	**2a**	50	81−82
10	**11**	*i*-Pr	H	4	**2b**	83	117−118
11	**11**	$-(CH_2)_5-$		4	**2c**	16	oil
12	**11**	*p*-Tol	H	4	**2d**	30[a]	143−144

[a] Product **12** was also isolated in 23% yield (see Scheme 4).

TABLE 2. Preparation of Pyrrolo[1,2-*c*]imidazoles 3a−g and Imidazo[1,5-*a*]indoles 4a−g

	compd	R	X	time (h)	product	yield (%)	mp (°C)
1	**10**	Bn	S	10	**3a**	41	75−76
2	**10**	Ph	S	10	**3b**[8,17]	26	138−139
3	**10**	Et	S	10	**3c**	77	60−61
4	**10**	*i*-Pr	S	10	**3d**	30	70−71
5	**10**	*p*-Tol	O	4	**3e**	71	194−195
6	**10**	Bn	O	4	**3f**[18]	75	75−76
7	**10**	Ph(Me)CH−	O	4	**3g**	95	63−64
8	**11**	Bn	S	10	**4a**	62	136−137
9	**11**	Ph	S	10	**4b**	21	200−201
10	**11**	Et	S	10	**4c**[5]	34	110−112
11	**11**	Me	S	10	**4d**[6]	27	185−186
12	**11**	*p*-Tol	O	4	**4e**	79	158−159
13	**11**	Bn	O	4	**4f**	81	153−154
14	**11**	Ph(Me)CH−	O	4	**4g**	87	105−106

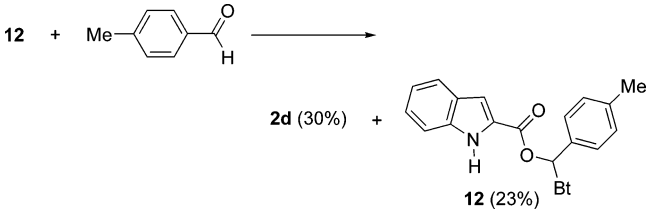
SCHEME 3



dazoles **3**, and imidazo[1,5-*a*]indoles **4**, by a simple one-step procedure starting from readily available and stable benzotriazol-1-yl(1*H*-pyrrol-2-yl)methanone **10** and benzotriazol-1-yl(1*H*-indol-2-yl)methanone **11** (Scheme 3).[15,16]

We found that the novel bicycle **1a**, a rare representative of the pyrrolo[1,2-*c*]oxazole ring system, was formed in low yield when compound **10** was treated with a stoichiometric amount of triethylamine or guanidine hydrochloride in refluxing acetone. Efficient conversion to the product **1a** in 80% yield, however, occurred when **10** was refluxed with the ketone in THF for 2 h in the presence of a strong, nonnucleophilic base (3 equiv), such as DBU

SCHEME 4



(Scheme 3, Table 1). These reaction conditions were applied to the reactions of **10** with various ketones and aldehydes to give pyrrolo[1,2-*c*]oxazoles **1a**−**h** in high yields (Scheme 3, Table 1). The reactions were monitored by TLC, which indicated completion of the reaction within 2−4 h with compounds **1a**−**h** being the sole products. As shown in Table 1, the reaction is of wide scope and works well with both enolizable and nonenolizable carbonyl compounds.

This result offered an opportunity to extend the synthetic method to oxazolo[3,4-*a*]indol-1-ones **2**, which was achieved by reactions of benzotriazol-1-yl(1*H*-indol-2-yl)-methanone **11** with carbonyl compounds to give **2a**−**d** (Scheme 3, Table 1). In contrast to **10**, compound **11**, under the same reaction conditions, reacted sluggishly with ketones and aldehydes to afford **2a**−**d** in lower yields sometimes together with side products. For example, reaction of **11** with *p*-tolualdehyde (entry 12, Table 1) produced **2d** in 30% yield and compound **12** in 23% yield (Scheme 4).

The formation of **12** probably occurred as a result of the opening of the lactam ring with the in situ generated nucleophilic benzotriazole in the presence of the base.

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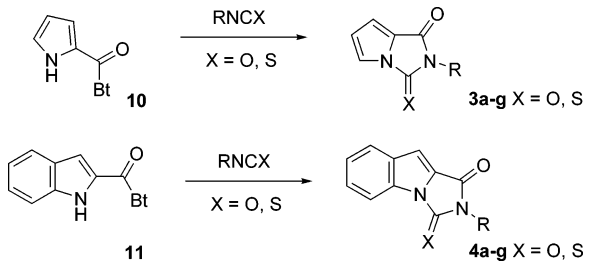
SCHEME 5



However, no such ring opening was observed in the reaction of **10** with *p*-tolualdehyde (entry 6, Table 1), which resulted in the formation of **1d** in 76% yield.

This methodology was extended to synthesize pyrrolo-[1,2-*c*]imidazoles **3a**−**g** and imidazo[1,5-*a*]indoles **4a**−**g** by treatment of **10** or **11**, respectively, with isocyanates or isothiocyanates (Scheme 5, Table 2). Reactions of **10** or **11** with isocyanates in THF under reflux for 4 h in the presence of DBU gave high yields of pyrrolo[1,2-*c*]-imidazoles **3e**−**g** and imidazo[1,5-*a*]indoles **4e**−**g**. The same condition when applied to the reactions of **10** or **11** with isothiocyanates gave low yields of **3a**−**d** and **4a**−**d** (Scheme 5, Table 2). Optimally, the preparation of **3a**−**d** and **4a**−**d** was achieved in the presence of triethylamine in a sealed tube at 130 °C over a period of 10 h (Scheme 5, Table 2). Employing the benzotriazole moiety as leaving group for the synthesis of **3a**−**g** and **4a**−**g** from **10** and **11** provides an alternative to the routes already available for their synthesis.[1,2,8−11]

In summary, we have developed novel and convenient methods for the syntheses of derivatives of pyrrolo[1,2-*c*]imidazole, imidazo[1,5-*a*]indole, oxazolo[3,4-*a*]indole, and pyrrolo[1,2-*c*]oxazole ring systems starting from readily available benzotriazol-1-yl(1*H*-pyrrol-2-yl)methanone **10** and benzotriazol-1-yl(1*H*-indol-2-yl)methanone **11**.

Experimental Section

General Procedure for the Reactions of Compound 10 or 11 with Ketones or Aldehydes. A solution of **10** or **11** (0.5 mmol) in freshly distilled dry THF (5 mL) was treated with 1.2 equiv of the appropriate ketone or aldehyde and 3 equiv of DBU under an atmosphere of argon (except for the preparation of **1a** and **2a**, where dry acetone was used as solvent). The reaction mixture was refluxed for the periods shown in Table 1. The cooled reaction mixture was concentrated under vacuum to give a crude, usually brown resin that was refined by flash chromatography on silica gel to give the products **1a**−**h** and **2a**−**d**.

General Procedure for the Reactions of Compound 10 or 11 with Isothiocyanates. Compound **10** or **11** (0.5 mmol) was placed in a tube with triethylamine (5 equiv, 1 mL) and 3 equiv of the appropriate isothiocyanate were added. The tube was sealed, and the reaction mixture was heated to 130 °C for a period of 10 h. Triethylamine was removed under reduced pressure, and the crude reaction mixture was subjected to flash chromatography to give the compounds **3a**−**d** and **4a**−**d**.

General Procedure for the Reactions of Compound 10 or 11 with Isocyanates. A solution of **10** or **11** (0.5 mmol) in freshly distilled dry THF (5 mL) was treated with 1.2 equiv of the appropriate isocyanate and 3 equiv of DBU under an atmosphere of argon. The mixture was heated under reflux for 5−7 h and monitored by TLC. The cooled solution was concentrated under vacuum, and the crude residue was refined by flash chromatography over silica gel (hexanes/ethyl acetate 45:5) to give compounds **3e**−**g** and **4e**−**g**.

Supporting Information Available: Characterization data for compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0485334