Three-carbon Homologations Employing Benzotriazole-Stabilized Allylic Anions

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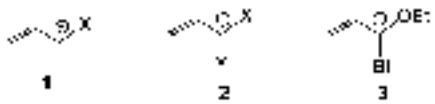
Contents

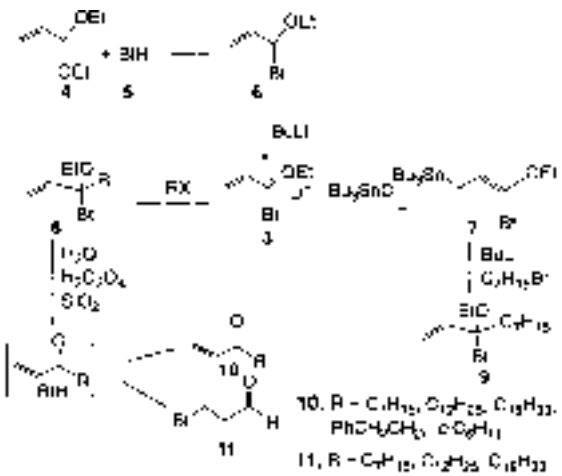
Heteroatom-stabilized allyl anion system **1** and **2**, formed by deprotonation of the corresponding allyl derivatives, are three-carbon homologating species. Their synthetic utility depends on (i) the degree of regioselectivity in their reactions with electrophiles at the α- or γ-position [1–5], (ii) the availability of their precursors and (iii) the ease of removal of the heteroatom at the end of the reaction sequence which frequently is achieved only with considerable difficulty [6–9]. In several cases the stabilizing group of **1** or **2** is benzotriazolyl [10]. We now survey reactions of allyl anion **3** with electrophiles and subsequent transformations.



1. Reactions of Benzotriazole-Stabilized Allylic Anions 3 with Alkyl Halides

N-(α-Ethoxyallyl)benzotriazole **6** is prepared in 95% yield on a large scale by treating benzotriazole **5** with acrolein diethyl acetal **4** (Scheme 1) [11, 12]. Allylic anion **3** is prepared *in situ* as a deep green solution in THF by stirring compound **6** with butyllithium at –78 °C. Reactions of the anion **3** with alkyl halides gave α-alkylated adducts **8**. No γ-alkylation products were detected even though attack at the γ-position is sterically more favorable. However, the reaction of anion **3** with tributyltin chloride under the same conditions gave only the γ-adduct **7** (Scheme 1). Significantly, when compound **7** was treated with butyllithium at –78 °C followed by heptyl bromide, the α-alkylated adduct **9** was generated exclusively. Thus, the regioselectivity of reactions of anion **3** with electrophiles represents the typical reactivity of a homoenolate anion and is not related to initial anion formation at the α-terminus or the γ-terminus.

Hydrolysis of adducts **8** into ketones **10** in 48–71% overall yield was readily achieved at ambient temperature by treatment with silica gel in the presence of catalytic amounts of $H_2C_2O_4$ and H_2O for ca. 30 min. Furthermore, small quantities of addition products **11** [12] are formed by Michael addition of benzotriazole to the product ketones **10**, and longer reaction times increased the amounts of **11** that were formed.



Scheme 1

In situ treatment of the α-alkylated intermediates **8** with Grignard reagents at reflux in THF caused substitution with simultaneous rearrangement of the C=C bond (S_N2' reaction) to give enol ethers **12**, which were hydrolyzed into ketones **13** (Scheme 2) [13]. The exclusive formation of the γ-alkylated products **12** can be rationalized by steric effects, *viz*, the bulky

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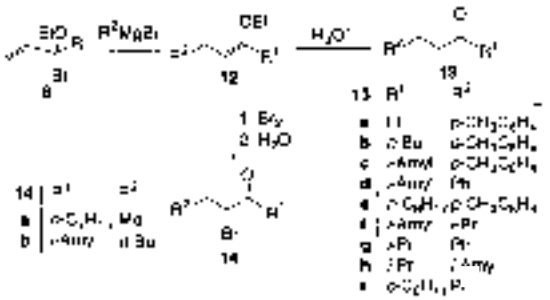
benzotriazolyl group coupled with the α-alkyl substituent makes it difficult for a nucleophile to attack at the α-position. In practice, reactions **6** → **13** (four steps) are all conveniently carried out in a one-pot sequence. Enol ethers **12** were also converted *in situ* into α-bromoalkyl ketones **14** in high yield.

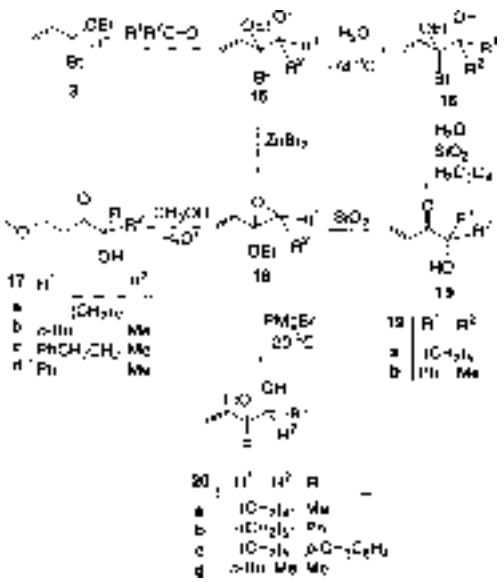


Scheme 2

2. Reactions of Benzotriazole-Stabilized Allylic Anions 3 with Aldehydes and Ketones

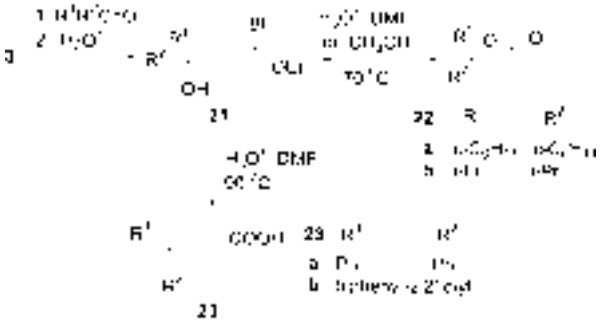
Anion **3** reacted with aldehydes, cyclic ketones or methyl alkyl ketones selectively at the α-position to afford secondary alcohols **16** in yields of 46 – 75% (Scheme 3) [12, 14]. Adducts **16** were quantitatively converted into vinyl 1-hydroxyalkyl ketones **19** by treatment with $H_2C_2O_4$–SiO_2–H_2O.

With the assistance of $ZnBr_2$, adducts **15** derived from ketones were cyclized to epoxides **18**, but no such cyclization of adducts **15** derived from aldehydes occurred. Partial hydrolysis of vinyl epoxides **18** occurred during work up, and complete hydrolysis on column chromatography gave the same vinyl 1-hydroxyalkyl ketones **19** as were obtained from **16** by hydrolysis with $H_2C_2O_4$–H_2O–SiO_2. However epoxides **18** were converted to 1-hydroxyalkyl 2-methoxyethyl ketones **17** at 70 °C by acidic hydrolysis in CH_3OH–H_2O–HCl *via* an S_N2'-mechanism. Grignard reactions on epoxides **18** gave alcohols **20** without rearrangement of the C=C bond.



Scheme 3

However for sterically hindered carbonyl compounds, a clear change in the stereochemistry occurred for reactions with **3**. Thus diaryl ketones, dicyclohexyl ketone and 2,4-dimethylpentanone reacted with anion **3** to give the γ-adducts **21** exclusively [14]. Adducts **21** derived from dialkyl ketones were hydrolyzed in DMF–HCl–H_2O or CH_3OH–HCl–H_2O to give γ-lactones **22** in good yield, while adducts **21** derived from diaryl ketones in DMF–HCl–H_2O at ca. 90 °C gave β,γ-unsaturated carboxylic acids **23** in quantitative yield.

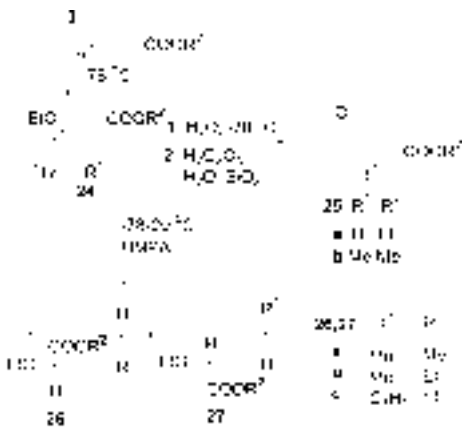


Scheme 4

3. Reactions of Benzotriazole-Stabilized Allylic Anion 3 with α,β-Unsaturated Esters and Ethyl α-Arylacetates

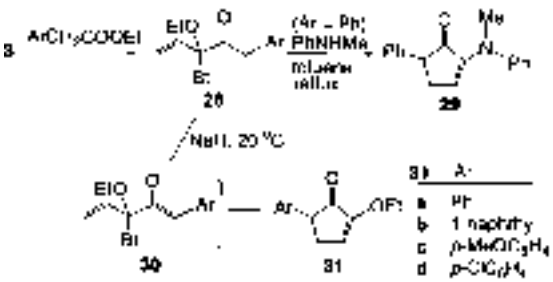
Reaction of anion **3** with ethyl acrylate followed by quenching with H_2O at –78 °C gave exclusively the 1,4-addition adduct **24**, as shown by H_2O–$H_2C_2O_4$–SiO_2 mediated hydrolysis to compound **25** in 63% overall yield (Scheme 5) [14]. Both the alkylation of anion **3** and the quenching with water must be carried out at –78 °C as higher temperatures resulted in mixtures of cyclopropanes **26** and **27** in ca. equal amounts in 51–58%. The formation of **26** and **27** involves an internal (S_N1 type) displacement of the benzotriazole moiety to generate the three-membered ring.

Reactions of anion **3** with ethyl α-arylacetates gave compound **28**, which on treatment with NaH at 20 °C gave directly 2-ethoxy-2-cyclopentenones **31** in good yield (Scheme 6) [13].



Scheme 5

Treatment of the phenyl adduct **28** with *N*-methylaniline afforded compound **29** in high yield. Ring formation involves enolate intermediates **30** which undergo internal S_N2' displacement of benzotriazole with a simultaneous rearrangement of the C=C bond.

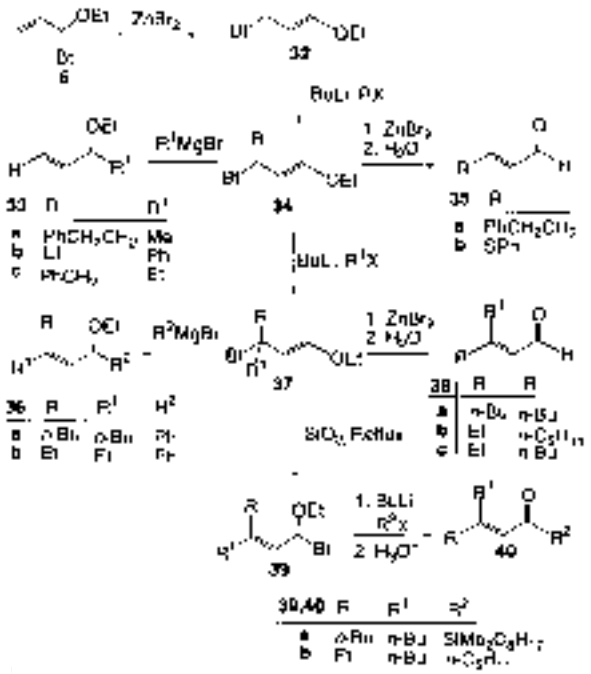


Scheme 6

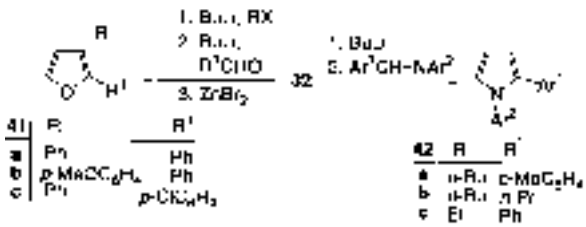
4. Rearrangement of *N*-(α-Ethoxyallyl)benzotriazole (6) to 3-(Benzotriazol-1-yl)-1-ethoxyprop-1-ene (32) and its Synthetic Applications

Treating compound **6** with $ZnBr_2$ in dry THF at 20 °C gives 3-(benzotriazole-1-yl)-1-ethoxyprop-1-ene (**32**) quantitatively as the *E*-isomer [15]. Reaction of compound **32** with butyllithium at –78 °C followed by reaction with a halide resulted in exclusive formation of the 3-alkylation product **34**. Further alkylation of **34** at the 3-position in a regiospecific manner can be easily accomplished to give **37** by deprotonation and subsequent reaction with another equivalent of halide. Mono- and dialkylated compounds **34** and **37** were converted into aldehydes **35** and **38**, respectively, by concomitant hydrolysis with $ZnBr_2$ and water, while S_N2 nucleophilic substitution reaction of **34** and **37** with Grignard reagents in refluxing toluene afforded allyl ethers **33** and **36**, respectively. In refluxing hexane with silica gel, the benzotriazole group of compound **37** migrated back to its original position α-to the ethoxy group to give the thermodynamically more stable alkene **39**. Alkenes **39** underwent exclusive α-alkylation with alkyl halides, and subsequent hydrolysis, to give substituted α,β-unsaturated ketones **40**.

Reaction of deprotonated **32** with diarylimines followed by intramolecular substitution and elimination of ethanol in the presence of $ZnBr_2$ yielded 1,2-diarylpyrroles **42** in 53–63% yields. Following a similiar protocol, substituted furans **41** were prepared from aldehydes [15].



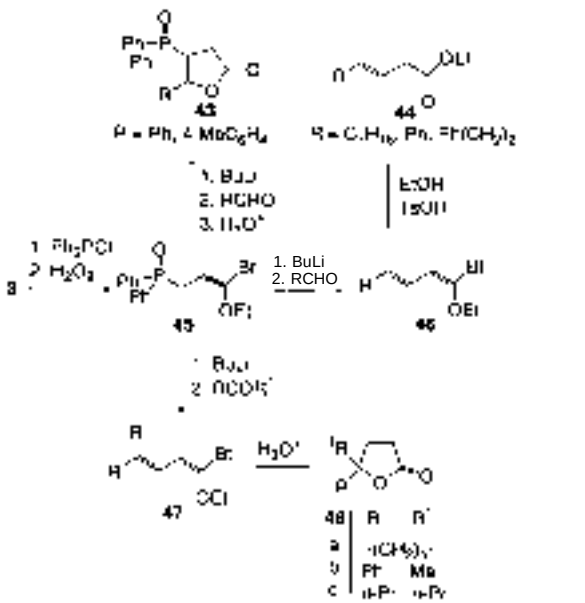
Scheme 7



Scheme 8

5. Exclusive γ-Alkylation of Benzotriazole-Stabilized Allylic Anion 3 *via* Intermediate 1-(Benzotriazol-1-yl)-3-(diphenylphosphoryl)-1-ethoxy-(*E*)-prop-1-ene (45)

Reaction of anion **3** with chlorodiphenylphosphine gave exclusively the γ-product, which is subsequently smoothly oxidized *in situ* to generate 1-(benzotriazol-1-yl)-3-(diphenylphosphoryl)-1-ethoxy-(*E*)-prop-1-ene **45**. Phosphine oxide **45** [16] underwent stereoselective Horner reactions to yield substituted dienes; subsequent hydrolysis, afforded convenient routes to both β,γ-unsaturated esters **44** and γ-lactones **48**, depending on the conditions employed. In contrast to Scheme 4, where only sterically hindered ketones generated γ-alkylated



Scheme 9

compounds, the method of Scheme 9 provides for the regiospecific γ-alkylation of anion **3** with aldehydes and nonhindered ketones.

Conclusion

Readily available heterocyclic-stabilized allylic anion **3** has been shown to be a useful and versatile three carbon homologating equivalent. Compared with similar reagents, the use of *N*-(α-ethoxyallyl)benzotriazole exhibits a number of advantages: high regioselectivity of either α-alkylation or γ-alkylation, easy removal of (and if desired, easy recovery of) the benzotriazole group, no requirement for the use of HCN or sulfur compounds, readily available reagents and simple procedures. The intramolecular and intermolecular displacements of the benzotriazole group represent new reactions of heterocycle-stabilized allyl anions.

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