A Novel Heterocycle-Stabilized Homoenolate Anion and Its Applications in the Syntheses of β-Propenoylcarboxylic Esters, Cyclopropanecarboxylic Esters, 1-Vinyl-1-ethoxy Epoxides, and γ-Lactones

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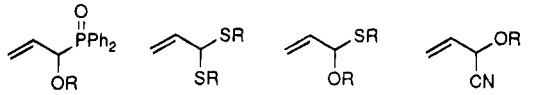
Functionalized allylic systems are versatile synthetic intermediates. The frequently used "allylic anion strategy" has been intensively studied in regard to both mechanism and synthetic applications and continues to receive much attention as evidenced by recent extensive reviews.[1] Among the most common precursors of 1,1-dihetero-stabilized allyl anions are β-unsaturated α-ethoxyphosphine oxides **1**,[2] α,β-unsaturated *S,S*-acetals **2**,[3] and α,β-unsaturated *O,S*-acetals **3**.[4] Reactions of lithiated

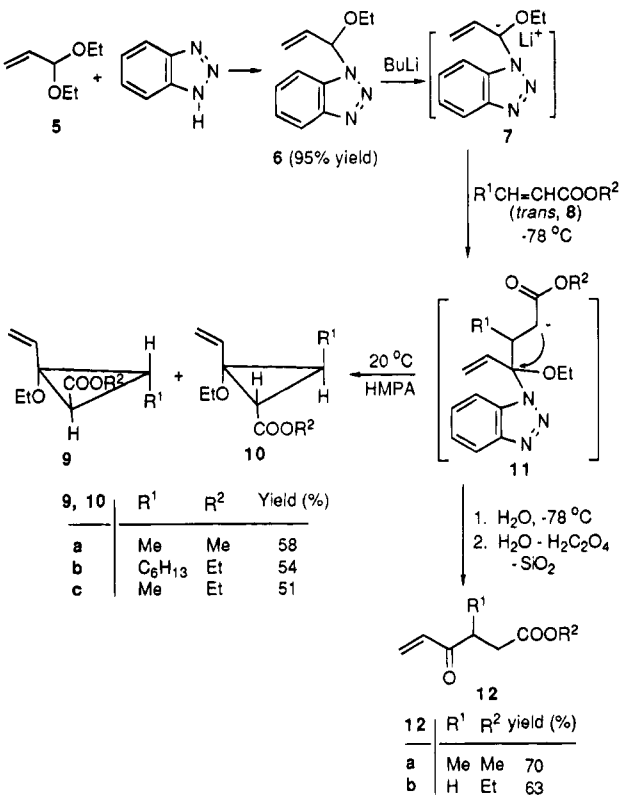


1 **2** **3** **4**

ethoxyallylphosphine oxide **1** and (alkylthio)allyl sulfides **2** with electrophiles give γ-alkylated products with high regioselectivity. Lithio derivatives of α-methoxyallyl sulfides **3** undergo only α-alkylation with halides to give α-alkylated hemithio ketals which are oxidized and then hydrolyzed to α-methylenated ketones.[4] However, the synthetic applications of **3** are limited by their instability and difficulty of preparation.[5] Protected cyanohydrins, including α,β-unsaturated derivatives **4**, have been reviewed as masked acyl anion equivalents.[6] However, little interest has been shown in homoenolate anions with an allyl carbon atom attached to a heterocyclic ring. We now report that the lithio derivative of *N*-(α-ethoxyallyl)-benzotriazole (**6**) is a novel heterocycle-stabilized homoenolate anion of type **7** and demonstrate its application in the syntheses of cyclopropanecarboxylic esters **9** and **10**, β-propenoylcarboxylic esters **12**, γ-lactones **15**, 1-vinyl-1-ethoxy epoxides **18**, β-alkoxyalkyl α-hydroxyalkyl ketones **19**, and vinyl α-hydroxyalkyl ketones **21**.

N-(α-Ethoxyallyl)benzotriazole (**6**) was prepared in a quantitative yield on a large scale from the reaction of

Scheme 1



9, 10	R¹	R²	Yield (%)
a	Me	Me	58
b	C_6H_{13}	Et	54
c	Me	Et	51

12	R¹	R²	yield (%)
a	Me	Me	70
b	H	Et	63

benzotriazole with the corresponding acetal **5** using performance fluid as an inert medium with a reversed Dean-Stark trap.[7]

The synthetic utility of homoenolate anion **7** is based on its ability to undergo α-alkylation with good regioselectivity to form intermediates with a labile benzotriazole moiety. The intermediates may either undergo an intramolecular substitution to form a three-membered ring or be hydrolyzed to yield vinyl ketones. Thus, treatment of **6** with butyllithium at −78 °C gave a deep green solution of **7** which, after stirring with α,β-unsaturated esters **8** at −78 °C for 2 h and then with HMPA for 24 h at 20 °C, gave *ca.* 50:50 mixtures of cyclopropanecarboxylic esters **9a–c** and **10a–c** in 51–58% yields (Scheme 1). The R^1 group in **8** is essential to form the three-membered ring as demonstrated by the attempted reaction of **7** with ethyl acrylate which gave no cyclopropane **9** or **10** under these conditions. All of the cyclopropanecarboxylic esters thus prepared are new, and the structures of the products were supported by NMR spectra and elemental analyses. Single isomers **9a–c** and **10a–c** were isolated by column chromatography [silica gel/hexane–diethyl ether (10:1)] and their structures were confirmed by NOE NMR spectra. For example, selective irradiation of (i) the methyl protons at 1.05 ppm (doublet) on the three-membered ring of **15c** or (ii) the cyclopropane proton at 1.69 ppm (doublet) each resulted in significant enhancement of the vinyl proton signals (doublet of doublet) at 5.68 ppm. The cyclopropane proton signals of **9** are overlapped at around 1.8 ppm, while the corresponding multiplet or quintet signals of **10** are shifted to a lower field (2.15 ppm) and the doublet signals to a higher field (1.70 ppm) presumably because of the field effect from the vinyl group or $COOR^2$ group of the three-membered ring.

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(6) Albright, J. D. *Tetrahedron* **1983**, *39*, 3207.

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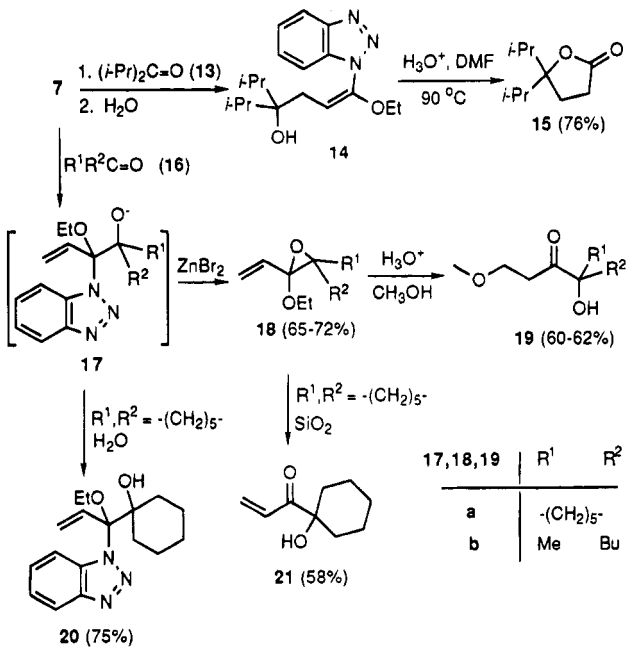
Scheme 2



The formation of **9** and **10** presumably proceeds *via* addition of the carbanion to the double bond of Michael acceptors **8** to give intermediates **11** at −78 °C followed by intramolecular displacement of lithium benzotriazolate at *ca.* 20 °C. As reported previously by our group,[8] the OR group of intermediates **11** should significantly assist the C−Bt scission in the intramolecular substitution (analogous to S_N1). However, unsuccessful attempts to form the cyclopropane ring from ethyl acrylate suggest that relief of the steric crowding in intermediate adducts **11** could be the driving force for the formation of the cyclopropane ring.

These considerations indicated the possibility of preparing β-propenoylcarboxylic esters. Indeed, treatment of **7** with either methyl crotonate or ethyl acrylate at −78 °C followed by quenching with H_2O at the same temperature yielded adduct **11**, which without purification was hydrolyzed by $H_2C_2O_4$−SiO_2−H_2O in CH_2Cl_2 in 10 min to afford β-propenoylcarboxylic esters **12** in 60−70% overall yields. The high regioselectivity toward α-alkylation and the facile hydrolysis of the resulting adducts **11** demonstrate the advantageous preparation of compounds of type **12**.

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The course of reaction of **7** with ketones depends on the degree of crowding about the ketonic carbonyl group. Interaction of **7** with cyclohexanone or hexan-2-one gave only α-alkylated adducts **17**, which were converted by $ZnBr_2$ at 20 °C into 1-vinyl-1-ethoxy epoxides **18** in 65−72% overall yields. The epoxide ring in **18** is generated by an intramolecular displacement of the benzotriazole group by the newly formed oxygen anion of **17**, but unlike the formation of cyclopropanes **9** and **10**, in the conversion of **17** or **18**, assistance from $ZnBr_2$ is required. In the absence of $ZnBr_2$, benzotriazole derivative **20** was isolated in 75% yield (Scheme 2).

The novel compounds **18** gave satisfactory elemental analyses and showed the expected proton and carbon NMR spectra. The two characteristic carbon signals of the epoxide ring appeared at around 69 and 89 ppm. Both ^1H and ^{13}C NMR spectra of **18b** showed two sets of signals, indicating a mixture of two stereoisomers. Compounds **18** are relatively stable and have synthetic potential. Thus, **18** are readily converted into β-methoxyalkyl α-hydroxyalkyl ketones **19** on acidic hydrolysis in CH_3OH and to vinyl α-hydroxyalkyl ketones **21** by silica gel chromatography.

By contrast, sterically hindered 2,4-dimethyl-3-pentanone (**13**) reacted with **7** to form only the γ-alkylated derivative **14** which was hydrolyzed by H_3O^+−DMF to give γ-lactone **15** in 76% overall yield.

In summary, readily accessible *N*-(α-ethoxyallyl)benzotriazole (**6**) is a useful precursor for novel heterocycle-stabilized homoenolate anions **7** which undergo exclusive α-alkylation with α,β-unsaturated esters, cyclohexanone, and hexan-2-one and exclusive γ-alkylation with the sterically hindered 2,4-dimethyl-3-pentanone. Although lithio derivatives of the previously documented **3** and **4** also undergo α-alkylation−oxidation−elimination and α-alkylation−hydrolysis, respectively (similar to the conversion of **7** to **12** *via* **11**), we could find no report of an intramolecular substitution of the resulting α-alkylation adducts of other homoenolate anions to form three-membered rings such as cyclopropanes **9** and **10** or epoxides **18**. Thus, the present method represents the first example of the preparation of vinyl substituted three-membered rings by an allylic anion strategy.

Supplementary Material Available: Experimental procedures and compound characterization data for compounds **6, 9, 10, 12, 15, 18, 19, 20** and **21** (6 pages).

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