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Geminal Benzotriazolyl Ethoxy Derivatives – Efficient Auxiliaries in the Synthesis of Unsaturated Carbonyl Compounds

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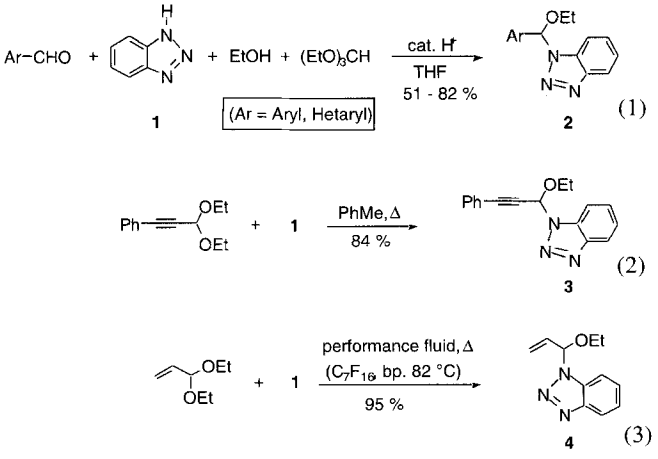
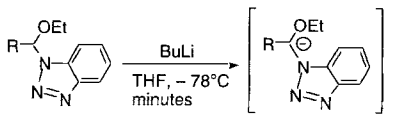
The versatility of 1*H*-Benzotriazole **1** as an efficient auxiliary in various fields of organic synthesis has been impressively developed over the years by Katritzky and coworkers [1–4] and certain aspects thereof were recently highlighted in this journal [5]. The utility of **1** to mediate a broad range of organic transformations rests on a unique combination of properties: **1** is easily introduced into a large variety of molecular frameworks, allows nucleophilic functionalization by its ability to serve as a good leaving group, activates adjacent CH positions for heterolytic bond cleavage thereby opening routes to subsequent CC bond forming reactions, and, having achieved its task, is readily removed from the now modified skeleton. The plethora of synthetic applications of **1** has been expanded recently by the finding that geminal benzotriazolyl ethoxy derivatives like, for example, **2–4** may function as masked acyl anion equivalents [6–10] that lead to unsaturated carbonyl compounds which are obtained only with difficulty by alternative methods. We would like to present herein a brief account of these latest developments.

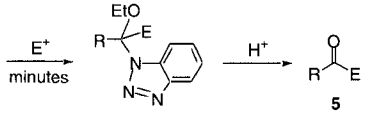


Scheme 1 Examples for the preparation of unsaturated α-(benzotriazol-1-yl)-ethoxy-derivatives.

Benzotriazole derivatives like **2–4** are easily prepared (Scheme 1) either by direct conversion of aldehydes with **1**, ethanol, and triethyl orthoformate in THF under acid catalysis (eq 1) [9], or more indirectly, by reaction of the preformed diethyl acetals with **1** in refluxing toluene (eq 2) [8]. In cases where the removal of liberated ethanol poses problems, the use of the so-called "performance fluid", a commercially available perfluorocarbon solvent [11], in combination with a reverse Dean-Stark trap (eq 3) is suggested [7]. All three preparative methods show yields from excellent to good; the products can be prepared on large scale and can be stored over extended periods of time without special precautions.

In conjunction with its facile incorporation into substrates, the electron-withdrawing, yet aromatic benzotriazole moiety in compounds like **2–4** is unsurpassed in its ability to promote proton abstraction from the neighboring CH group and to stabilize the resulting anionic charge for periods sufficiently long to allow reaction with added electrophiles (Scheme 2). Thus, deprotonation of α-(benzotriazol-1-yl)-ethoxy derivatives such as **2–4** with butyllithium, followed by treatment with electrophiles and mild acidic workup (oxalic acid, dilute HCl, or TsOH, depending on the substrate) provides an easy access to, *inter alia*, unsaturated ketones [6–9], α-hydroxy- [8, 9], α-amino-ketones [8, 12], and acyl-silanes [10], some of which with connectivity patterns previously not reported. This convenient methodology is not restricted to the generation of functionalized α,β-unsaturated ketones, but can be extended to the synthesis of 1,2-diketones, a fundamental substructure for which a variety of synthetic procedures has been developed [13]. However, the majority of them is based on oxalic acid derivatives that are often problematic starting materials for unsymmetrically functionalized 1,2-diones and the procedures are not widely applicable to all, in particular unsaturated, substrates. The general protocol depicted in Scheme 2 circumvents these problems and, by treatment of the deprotonated benzotriazole intermediates with carboxylic acid esters, dialkyl carbonates, and isocyanates, yields the corresponding 1,2-diketones, α-keto esters, and α-keto amides, respectively [8].

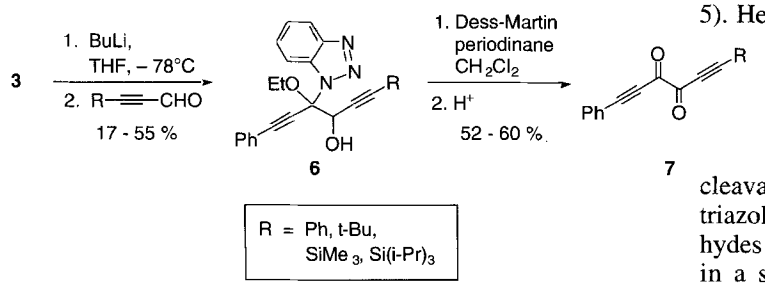




E^+	5
alkyl halides	ketones
aldehydes, ketones	α-hydroxyketones
imines	α-aminoketones
trialkylchlorosilanes	acyl silanes
carboxylic acid esters	1,2-diketones
dialkyl carbonates	α-keto esters
isocyanates	α-keto amides

Scheme 2 General scheme for the conversion of α-(benzotriazol-1-yl)ethoxyderivatives to carbonyl compounds.

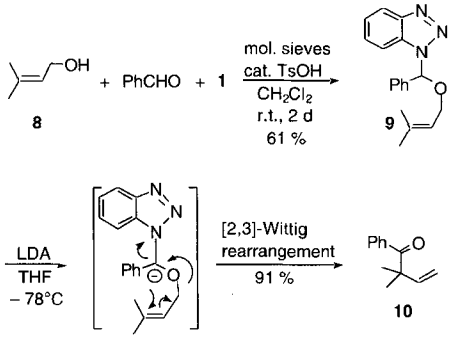
The versatility and the gratifyingly mild conditions of the benzotriazole-mediated diketone synthesis were recently highlighted by the first preparation of dialkynyl-1,2-diones **6** [14] (Scheme 3). Although a number of alternative synthetic routes to **6** were explored, only the benzotriazole-assisted methodology proved to be successful in this case. Hence, treatment of deprotonated **3** with various alkynyl carbaldehydes smoothly gave the very acid-sensitive propargylic alcohols **6** which in turn were oxidized with Dess–Martin periodinane [15]. Acid hydrolysis then furnished the novel acetylenic 1,2-diketones. Meanwhile, the procedure depicted in Scheme 3 could be extended to compounds with different terminal substitutents and to other homologous acetylenic oxocarbons [16].



Scheme 3 Synthesis of dialkynyl-1,2-diones starting from α-(benzotriazol-1-yl)-propargyl ether.

1*H*-Benzotriazole proves its value as a reagent not only in the field of α,β-unsaturated ketones and diketones but also in the synthesis of β,γ-unsaturated ketones [17] (Scheme 4). An attractive route to such compounds is the anionic [2, 3]-Wittig rearrangement of deprotonated methyl allyl ethers, a procedure bearing hazards with respect to its stereochemical outcome and to subsequent prototropic rearrangement of the products to the thermodynamically favored conjugated ketones. Furthermore, the activating group necessary for a smooth deprotonation of the methyl ether, usually remains part of the molecular framework during this transformation and, if desired and possible, has to be removed in a separate step.

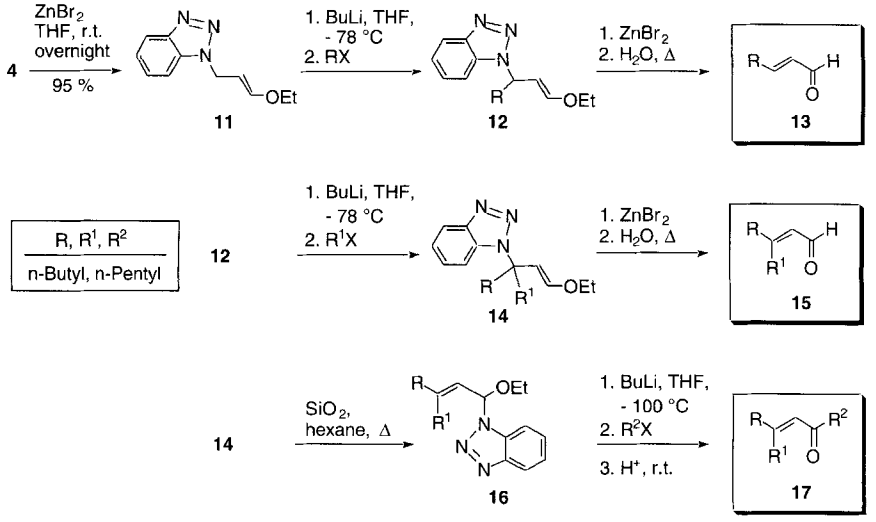
Again, benzotriazole functions as a perfect auxiliary: Starting from allylic alcohol **8**, allyl ether **9** is readily prepared and, upon treatment with LDA, rearranges under expulsion of the benzotriazole moiety to the β,γ-unsaturated ketone **10** (Scheme 4). Variation of the substitution pattern of both double bond and allyl position shows that complete stereocontrol is achieved in the course of the reaction, resulting in an *E* configuration at the newly formed double bond. Ketones of the type **10** can then be carried on to provide tertiary homoallylic alcohols that were previously not accessible by Wittig-rearrangements.



Scheme 4 Benzotriazole as a mediator in [2, 3]-Wittig rearrangements.

The scope of the benzotriazole-mediated syntheses of unsaturated carbonyl compounds could recently been broadened by the finding [18] that compound **4** is easily isomerized to the thermodynamically more stable ethoxy vinyl ether **11** under mild Lewis acid catalysis with zinc bromide (Scheme 5). Hence, **11** can be alkylated to **12** and yields, after ether cleavage with $ZnBr_2$ and hydrolytic removal of the benzotriazole auxiliary, the monosubstituted α,β-unsaturated aldehydes **13**. Similarly, twofold alkylations of **11** can be performed in a stepwise fashion via **12** and **14**, from which the disubstituted aldehydes **15** are obtained. The steric congestion at the quaternary center of **14** provides a convenient driving force to allow the SiO_2-induced allylic rearrangement of the benzotriazole moiety back to its original position as in **4** and opens a way to introduce yet another substitutent into the framework of **16** to furnish the α,β-unsaturated ketones **17**. In general, the yields for the generation of the substituted carbonyl compounds **13**, **15**, and **17** are very satisfactory, ranging from 50–82% overall from **11**.

This short summary of the role of benzotriazole in the synthesis of fundamentally important unsaturated carbonyl compounds has really only scratched the surface of the strikingly rich chemistry of this unique heterocycle. It is becoming more and more obvious that benzotriazole has much



Scheme 5 Functionalizaton of α,β-unsaturated carbonyl derivatives by allylic migration of benzotriazole.

to offer to the organic chemist and is a convenient tool for the functionalization of organic compounds. A comprehensive survey about the synthetic possibilities of benzotriazole will appear shortly [19].

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