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Designing efficient synthetic routes to polyfunctionality*

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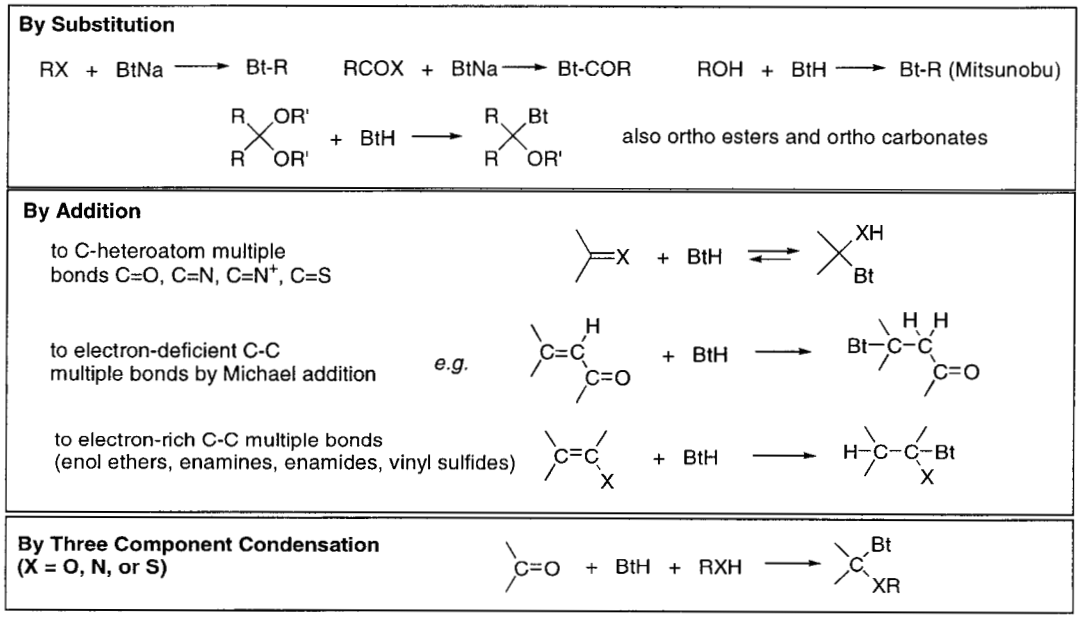
Abstract: Benzotriazole-mediated methodology was successfully applied for the preparation of many classes of polyfunctional organic compounds.

INTRODUCTION

During the last two decades, our group at the University of Florida has explored diverse applications of heteroaromatic moieties, and particularly the benzotriazolyl group, as selective auxiliaries and masked synthons for the preparation of many classes of polyfunctional organic compounds.

The results demonstrate clearly the potential of the benzotriazolyl moiety as a powerful tool for the synthetic manipulations. Benzotriazolyl group can be introduced into a molecule by substitution, addition, or condensation reactions (Scheme 1). Once introduced, a Bt-group influences significantly the reactivity of a molecule; the multiple possibilities for further transformations are illustrated in Scheme 2.



Scheme 1 Benzotriazole is easily inserted into a molecule.

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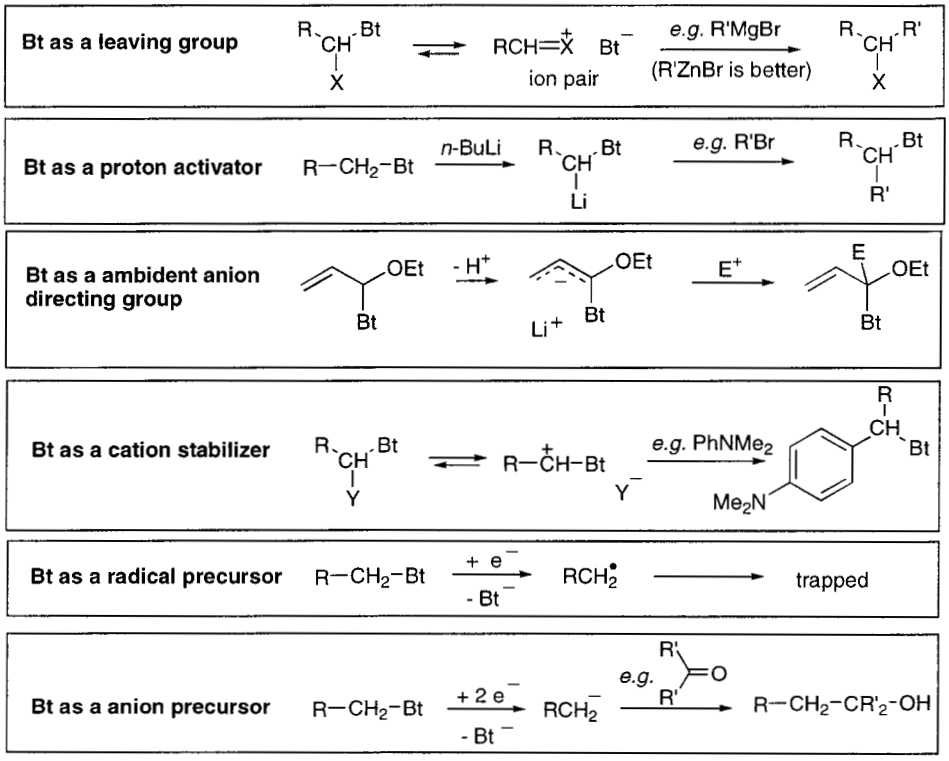


Scheme 2 A benzotriazole residue conveys multiple activating influences on molecules to which it is attached.

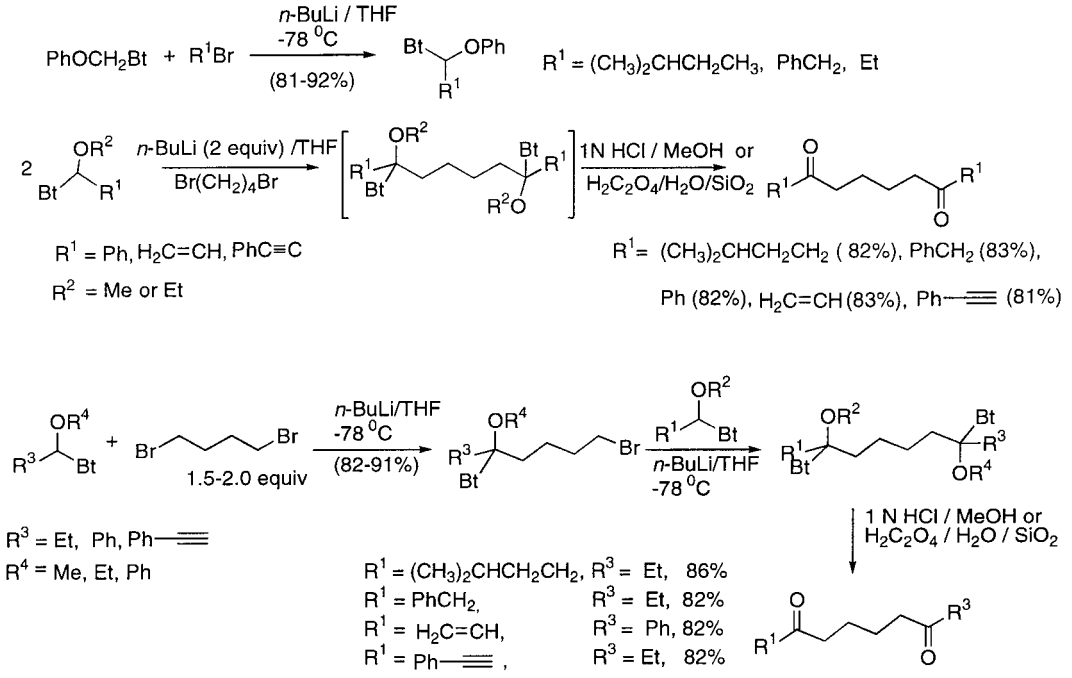
Our work through 1996 was comprehensively reviewed [1]; more recent specific reviews deal with (i) various benzotriazole-based reagents [2], (ii) Michael additions of benzotriazole-stabilized carbanions [3], and (iii) [3+3] benzannulations [4].

The present short account discusses some more recent approaches to various polyfunctional compounds using benzotriazole-assisted methodology.

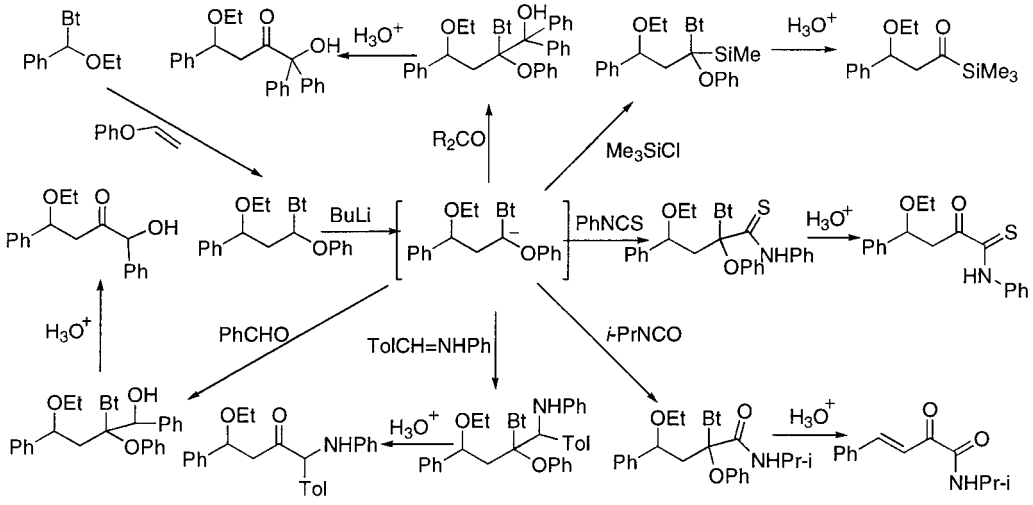
RESULTS AND DISCUSSION

Benzotriazole-based acyl anion synthons

Recently, we applied well-established [5-7] Bt-derived acyl anion synthon methodology to the preparation of symmetrical and unsymmetrical 1,6-diketones [8] (Scheme 3) and β-alkoxy ketones [9] (Scheme 4).



Scheme 3 Preparation of symmetrical and unsymmetrical 1,6-diketones.

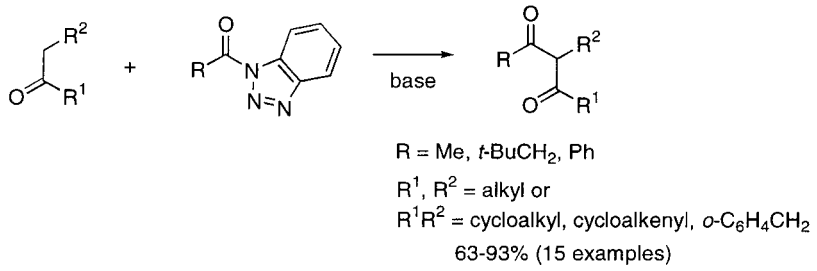


Scheme 4 Synthesis of β-alkoxy ketones.

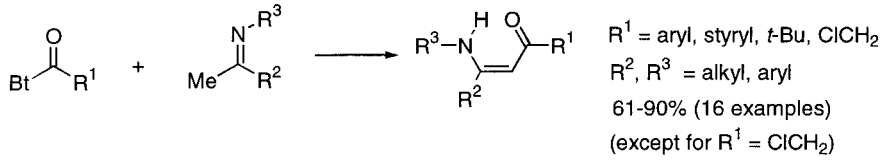
N-Acylbenzotriazoles as acylating reagents

N-Acylimidazoles and *N*-acylpyrazoles have long been used as acyl group donors [10]. Recently readily available [11,12] *N*-acylbenzotriazoles have been shown to be excellent acylating agents, both at

nitrogen and carbon atoms. Thus, *N*-acylbenzotriazoles react regio- and stereoselectively with alkyl ketones [13] (Scheme 5) and imines [14] (Scheme 6) to produce 1,3-diketones and enaminones, respectively.



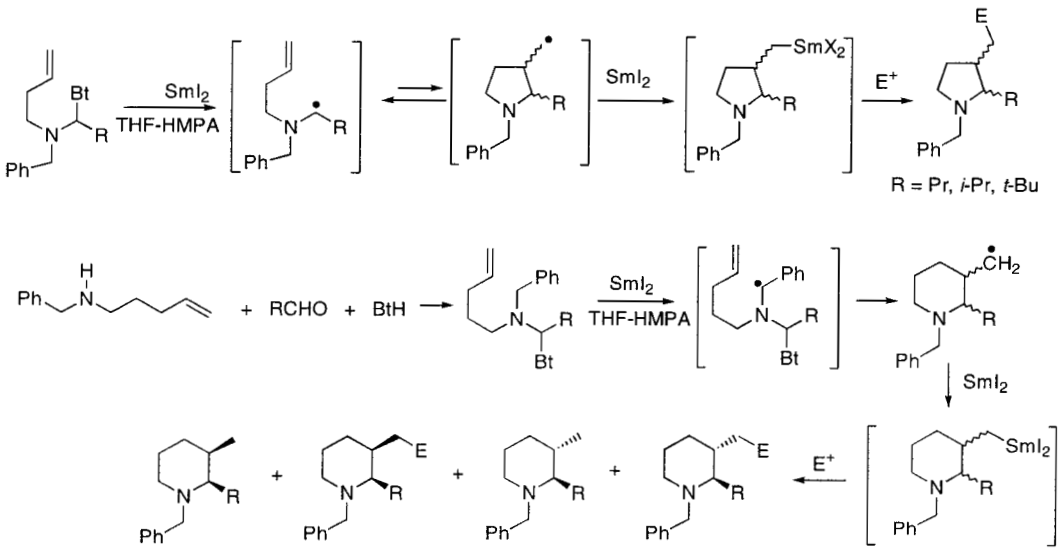
Scheme 5 *C*-acylation of ketones



Scheme 6 Imine acylation: preparation of enaminones.

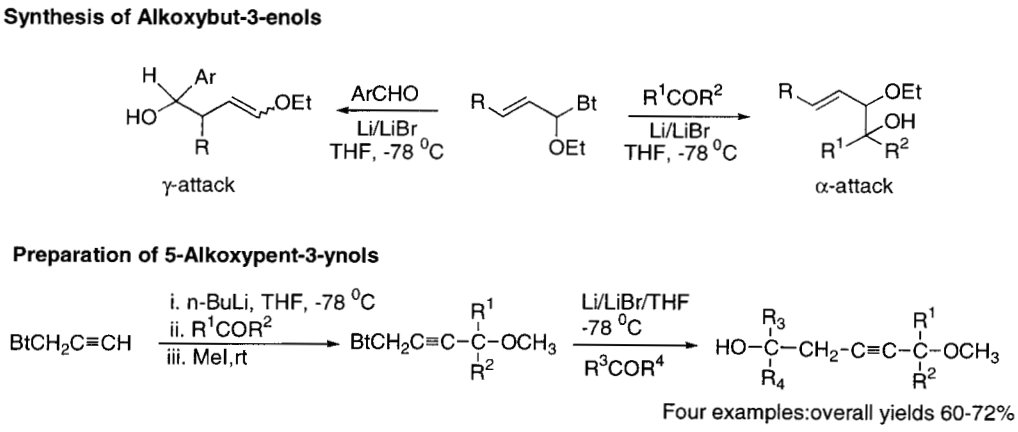
Precursors for radicals and carbanions

A benzotriazolyl group can be eliminated by the addition of one or two electrons, giving the corresponding radicals or carbanions, respectively, which can be trapped (cf. Scheme 2).



Scheme 7 Preparation of pyrrolidines and piperidines by radical cyclization.

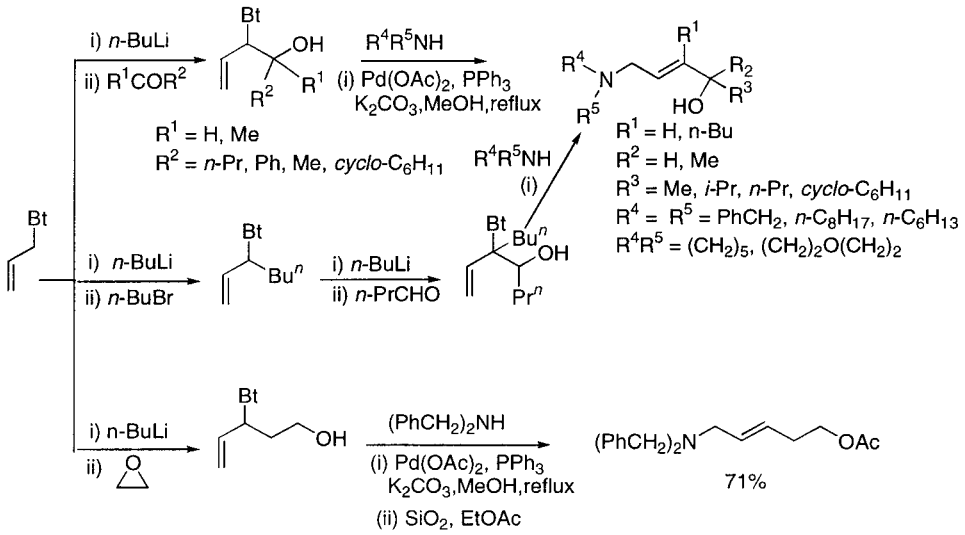
This reaction is particularly useful for the generation of α-amino-stabilized radicals. Thus, treatment of α-benzotriazolylalkylamines with SmI_2 leads to the elimination of the Bt group and formation of intermediate radicals, which, if a suitable located terminal double bond is available, undergo intramolecular cyclization affording the corresponding pyrrolidines and piperidines [15,16] (Scheme 7).



Scheme 8 Conversions of Bt-derivatives *via* carbanion intermediates.

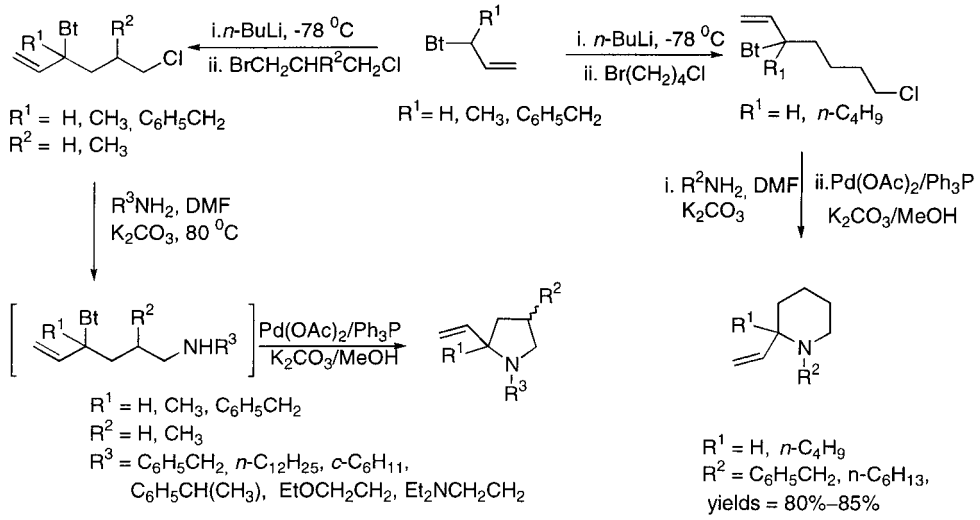
The elimination of a benzotriazolyl moiety leading to an intermediate carbanion has been achieved by treatment of the appropriate allylic [17] and propargylic [18] substrates with a Li/LiBr reducing system (Scheme 8). Subsequent treatment of the carbanions formed with carbonyl compounds resulted in the formation of alkoxybut-3-enols and 5-alkoxypent-3-ynols, respectively.

Palladium-catalyzed benzotriazole replacement



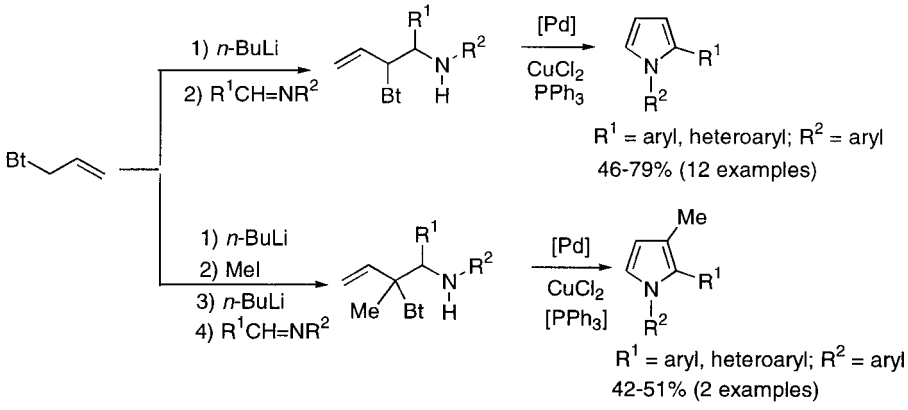
Scheme 9 Preparation of functionalized allylamines.

Allylbenzotriazoles undergo nucleophilic displacement of the benzotriazolyl group with amines in the presence of a Pd(II) catalyst. This procedure provides a versatile preparation of functionalized allylamines [20] (Scheme 9).



Scheme 10 Synthesis of 2-vinyl-pyrrolidines and -piperidines.

Intramolecular cyclization can occur if a suitably located secondary amino group is present in the allylbenzotriazole molecule. The outcome of such reactions depends strongly on the length of the carbon chain between the benzotriazolyl and amino groups, and can lead to either 2-vinylpyrrolidines or 2-vinylpiperidines [21] (Scheme 10) or pyrroles [22] (Scheme 11).



Scheme 11 Preparation of 1,2-di- and 1,2,3-tri-substituted pyrroles.

CONCLUSIONS

In this brief summary of the work carried out in the benzotriazole area at the University of Florida during the last few years, it has not been possible to more than skim the surface. The unique characteris-

tics of the benzotriazole group, the possibility to introduce it into molecules in many different ways, its multiple mechanisms of activation of molecules, combined with the inertness of the ring system of benzotriazole itself, make it a powerful synthetic auxiliary. Further work published during the period 1998–2000 in the area has dealt *inter alia* with the following topics:

1. Bt-mediated benzannelation in the preparation of various benzo-fused heterocycles [23–28];
2. α-functionalized β-silyl benzotriazolylethanes as two-, three-, and four-carbon synthons in organic synthesis [29–34];
3. the benzotriazolyliminium salt as a precursor to azaheterocycles [35,36] and many others.

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