General and Efficient Carbon Insertion Route to One-Carbon-Homologated α-Aryl, α-Alkenyl, α-Alkoxy, and α-Phenylthio Alkyl Ketones

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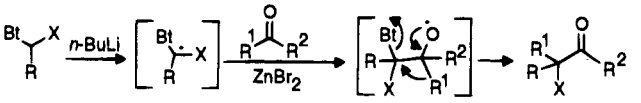
The importance of carbon-insertion methods for the homologation of aldehydes and ketones in organic synthesis and the limitations of the existing procedures are evidenced by the widespread and continuing interest in the development of new approaches.[1−12] Especially highly desired are methods which (i) are capable of introducing a variety of substituents at the carbon atom inserted; (ii) are of general applicability to diverse aldehydes and ketones; (iii) are highly regioselective; (iv) are one-step; and (v) avoid the use of diazo compounds.

In the course of our investigation on the use of benzotriazole derivatives in organic synthesis,[13] we found that the benzotriazolyl moiety is both a good anion-stabilizing group and a good leaving group. These properties, coupled with the ready availability of its derivatives, suggested its potential to provide general and efficient carbon-insertion methods. We herein report that a wide variety of benzotriazolyl-stabilized anions are excellent reagents for regioselective insertions into aliphatic and aromatic aldehydes and cyclic and acyclic ketones, which all furnish one-carbon-homologated α-aryl, α-alkenyl, α-alkoxy, and α-phenylthio alkyl ketones in simple one-pot operations (Scheme 1).

Our preliminary results are summarized in Table 1. The lithio derivatives of 1-(arylmethyl)benzotriazoles (entries 1−4), a 1-(alkenylmethyl)benzotriazole (entry 5), 1-(alkoxymethyl)-benzotriazoles (entries 6−9), and 1-[(phenylthio)methyl]benzotriazole (entries 10, 11), generated with *n*-butyllithium in THF at −78 °C, reacted with carbonyl compounds smoothly. The intermediates thus produced (Scheme 1) underwent *in situ* rearrangement, promoted by a *ca.* 3-fold molar excess of zinc bromide upon heating, to afford chain-extended or ring-expanded ketones with various α-functionalities in good to excellent yields. Each case, except for entry 4, afforded a single regioisomer by migration of the group which can best stabilize

Scheme 1[a]



[a] Bt = benzotriazol-1-yl; X = aryl, alkenyl, RO, PhS; R = H, aryl.

an electron deficiency in the transition state.[14] For 2-methylcyclohexanone (entry 4), two regioisomers were isolated, in yields of 81% and 3%, and the GC analysis of the crude reaction mixture indicated that they were formed in a ratio of 11:1, revealing a preferential migration of the most substituted alkyl group. The selectivity compares well with previous work: although ring expansion of 2-methylcyclohexanone with $^{-}CH(SPh)SO_2Ph$ was reported[2] to give a single isomer, it was isolated in a yield of 69%; no information regarding the other 31% was provided in the preliminary communication, and no full paper has yet appeared. When $^{-}CH(SPh)_2$ was used, both regioisomers were isolated[11b] in yields of 67 and 14%: again, no full experimental data are yet available.

The generality of our methodology is exemplified by the successful insertions of disubstituted methylene groups into carbonyl compounds (entries 8, 9): such insertions do not appear to have been previously reported. For vinyl-substituted methylene homologation, a stabilizing group such as phenyl (entry 5) at the vinylic terminal was found to be essential since the simple allyl analog 1-allylbenzotriazole failed to give homologation products.

In accordance with our previous observations,[13] zinc bromide played a vital role in assisting the departure of the benzotriazolyl group. The reaction temperatures necessary for the rearrangement vary as listed in Table 1. As expected, the more the X group (Scheme 1) stabilizes the transient cation, the lower is the temperature needed to complete the rearrangement. In those cases where the required temperature was higher than the boiling point of THF, the THF was distilled off and an appropriate solvent (or no solvent in the case of entry 1) was added in the rearrangement stage.

Aryl-substituted methylene homologations of aldehydes and ketones[5,15] and vinyl-substituted methylene homologations of ketones[7] have previously been accomplished by direct insertion of the corresponding diazo compounds, but this procedure is severely limited by low regioselectivity, multiple homologation, and handling difficulties. Another vinyl-substituted methylene homologation of cyclic ketones was achieved *via* a rather complex radical process.[8] The elegant insertions of alkoxymethylene and (phenylthio)methylene to form α-alkoxy and α-phenylthio alkyl ketones introduced by Trost *et al.*,[2] originally limited to cyclic ketones, were recently extended for alkoxymethylene insertion into monocyclic and acyclic ketones.[3] However, such insertions into aldehydes remain unreported.

In summary, we have shown that 1-(arylmethyl)-, 1-(heteroarylmethyl)-, 1-(alkenylmethyl)-, 1-(alkoxymethyl)-, and

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(14) Addition of the anion to an aldehyde or an unsymmetrical ketone gives a mixture of two diastereoisomers with almost equal amounts based on GC−MS, which reflects that the regioselectivity of subsequent rearrangement is not a function of the diastereoselectivity of addition. For reviews regarding migration aptitude in pinacol-type rearrangement, see: Hanson, J. R. (Section 3.1); Rickborn, B. (Section 3.2 and 3.3); Coveney, D. J. (Section 3.4). In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 3, p 705.

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(20) For the preparation of *N*-substituted benzotriazoles, see reviews quoted in refs 13.

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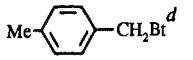
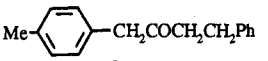
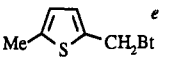
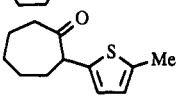
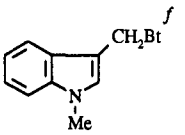
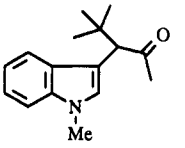
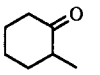
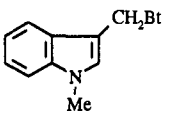
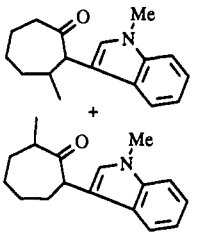
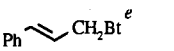
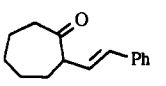
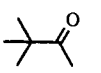
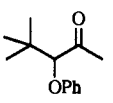
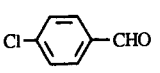
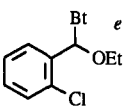
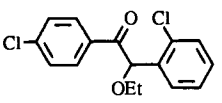
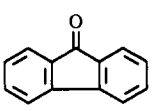
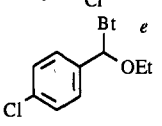
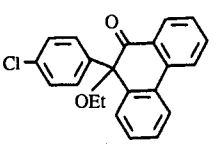
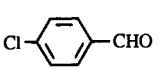
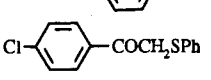
Table 1. Carbon Insertion into Aldehydes and Ketones

entry	carbonyl compound	Bt-reagent	temp, °C / time, h[a] / solvent	product[b]	yield[c] (%)
1	$PhCH_2CH_2CHO$	 [d]	210 / 0.5 / neat		65
2		 [e]	110 / 10 / $CH_2ClCHCl_2$		67
3		 [f]	65 / 3 / THF		87
4			65 / 10 / THF		81[g] 3
5		 [e]	110 / 12 / toluene		60
6	$PhCH_2CH_2CHO$	$BtCH_2OMe$ [h]	140 / 1 / $CHCl_2CHCl_2$	$PhCH_2CH_2COCH_2OMe$	50
7		$BtCH_2OPh$ [i]	140 / 10 / $CHCl_2CHCl_2$		47
8		 [e]	55 / 6 / THF		91
9		 [e]	66 / 24 / THF		51
10		$BtCH_2SPh$ [i]	140 / 1 / $CHCl_2CHCl_2$		86
11	PhCOMe	$BtCH_2SPh$	140 / 6 / $CHCl_2CHCl_2$	PhCH(SPh)COMe	65

[a] Conditions for the *in situ* rearrangement step. [b] All new compounds have been fully characterized by ^1H and ^{13}C NMR spectra and elemental analyses as recorded in the supporting information. [c] Overall yield of the isolated pure product from the carbonyl compound. [d] For preparation, see ref 16. [e] For preparation, see supporting information. [f] For preparation, see ref 17. [g] Total yield of *cis* and *trans* isomers. [h] For preparation, see ref 18. [i] For preparation, see ref 19.

1-[(phenylthio)methyl]benzotriazoles are excellent insertion reagents for the preparation of α-functionalized ketones. The significant features of the present benzotriazole-mediated methodology include its wide generality, its excellent regioselectivity, and the ready availability of starting materials.[20] More detailed studies of this methodology and its further extension to other functionalized benzotriazole derivatives are currently being pursued.

Supporting Information Available: Typical experimental procedures and characterization data for all new compounds (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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