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The Barbier Reaction of 1-(Chloromethyl)benzotriazole with Aldehydes and Ketones mediated by Samarium Diiodide†

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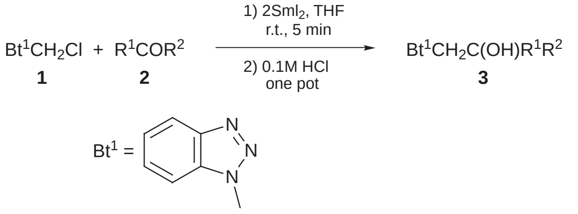
1-(Chloromethyl)benzotriazole can smoothly undergo the SmI_2–Barbier reaction with aldehydes and ketones to give 1-β-(hydroxyalkyl)benzotriazoles under very mild conditions.

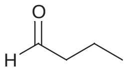
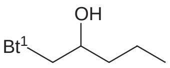
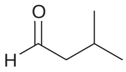
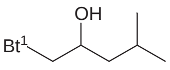
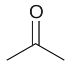
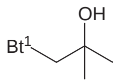
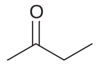
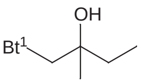
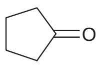
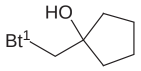
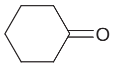
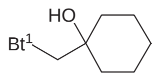
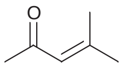
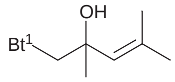
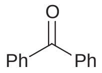
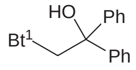
As a result of the prominent work of Katritzky's group, benzotriazole has become a versatile synthetic auxiliary.[1] Among numerous N-derivatives of benzotriazole, 1-(chloromethyl)benzotriazole (Bt^1CH_2Cl) has played an important role in the introduction of other heteroatom groups. Some related work mainly focused on halogen displacement of Bt^1CH_2Cl by a wide range of oxygen, sulfur, nitrogen, phosphorus and carbon nucleophiles.[2] Previous attempts to metallate Bt^1CH_2Cl with magnesium, zinc or BuLi were unsuccessful.[2] Fortunately, we find that with the SmI_2–Barbier protocol, Bt^1CH_2Cl can react smoothly with electrophiles such as aldehydes and ketones to conveniently introduce a hydroxy group in the β-position of benzotriazole (Scheme 1).



Scheme 1

Sequencing reactions with samarium diiodide has attracted increased attention.[3] Kagan and coworkers first found that a solution of SmI_2 in THF could efficently promote alkylations of ketones by alkyl halides and sulfonates.[4] However primary organic iodides and even organic tosylates required heating for 8–12 h in boiling THF while alkyl bromides were even less reactive and alkyl chlorides virtually inert. The SmI_2–Barbier reaction is, however, facile when a heteroatom such as oxygen[5] or sulfur[6] is introduced at the α-position of such alkyl halides. The activating ability of these functional groups to the adjacent carbon–halogen bond even activates alkyl chlorides. Herein, we report that benzotriazole, as a good activating group, can also efficiently promote Bt^1CH_2Cl to undergo SmI_2–Barbier type coupling with aldehydes and ketones. Alkyl aldehydes and many types of ketones lead to good results. Upon treatment of α,β-unsaturated ketones, only the 1,2-addition product is obtained. In alkylations of α,β-unsaturated aldehydes and aromatic aldehydes, Bt^1CH_2Cl remains almost intact owing to the rapid reaction of these aldehydes with SmI_2. Similarly the SmI_2–Grignard procedure[7] also fails, where even in the absence of a proton donor, Bt^1CH_2Cl is reduced to 1-methylbenzotriazole. While SmI_2 can initiate radical reactions *via* the reduction of α-aminosubstituted benzotriazoles,[8] the Bt^1 group is unaffected in the reduction of Bt^1CH_2Cl.

Table 1 The SmI_2-mediated reaction of Bt^1CH_2Cl with aldehydes and ketones

Entry	Substrate	Product	Yield[a](%)
a			73
b			86
c			72
d			70
e			70
f			80
g			72
h			60

[a]Yields of pure compounds.

Thus under very mild conditions we can conveniently obtain 1-(β-hydroxyalkyl)benzotriazoles, which show important utility in the synthesis of some oxygen-containing heterocyclic compounds.[9] Known synthetic strategies include the subsequent reactions of lithiated 1-alkyl benzotriazoles[10] or [1-(α-trimethylsilyl)alkyl]benzotriazoles[11] with aldehydes and ketones.

In conclusion, under SmI_2–Barbier conditions, 1-(chloromethyl)benzotriazole can react with many aldehydes and ketones and 1-(β-hydroxyalkyl)benzotriazoles can be conveniently prepared. Mild reaction conditions, readily available starting materials and simple operations make this method superior to previous routes.

Experimental

^1H NMR spectra were recorded in $CDCl_3$ on JEOL PMX 60si or Bruker AM-300 spectrometers using TMS as the internal standard. Chemical shifts (δ) are reported in ppm relative to TMS. IR spectra were obtained on a PE683 spectrometer and mass spectra (MS) were

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recorded on a HP5989A mass spectrometer. Elemental analyses were performed at Carlo-Erba 1106 instrument. THF was distilled from sodium/benzophenone, immediately before use. All reactions were performed under a nitrogen atmosphere.

Typical Procedure for the SmI_2*-mediated Reaction of* Bt^1CH_2Cl *with Aldehydes and Ketones.*—To a SmI_2 (2.0 mmol) solution of THF (20 ml) was added a mixture of Bt^1CH_2Cl (1.0 mmol) and butan-2-one (1.0 mmol) in 5 ml of THF. Reaction was performed under nitrogen at room temperature. After 5 min, the initial blue solution turned yellow, indicating the end of the reaction and the mixture was worked up with dilute HCl (0.1 M). The organic product was extracted twice with ethyl acetate and the organic layer washed with water, sodium thiosulfate, water and brine. After the solution was dried over $MgSO_4$, the solvent was removed. The product was separated from the residue by preparative TLC (silica gel) with hexane–ethyl acetate (5/1) as eluent to give 1-(benzotriazol-1-yl)-2-methylbutan-2-ol as white crystals (70%).

Compound **3a**: mp 60–61 °C, ν_{max}(KBr)/cm^{-1}: 3360, 3090, 2980, 1650, 1610, 1465, 1440, 1280, 1230, 1170, 1150, 1100, 780, 750. δ_H 0.9 (3H, t, $J = 6$ Hz), 1.2–1.7(4H, m), 2.3–2.4 (1H, d, $J = 4.2$ Hz), 4.1–4.2 (1H, m), 4.5 (2H, d, $J = 7.2$ Hz), 7.3–7.7 (3H, m), 7.9–8.1 (1H, m). MS:*m/z* 206 (M^++1) (Found: C, 64.0; H, 7.1; N, 20.2. $C_{11}H_{15}N_3O$ requires C, 64.4; H, 7.4; N, 20.5%).

Compound **3b**: mp 85 °C, ν_{max}(KBr)/cm^{-1}: 3300, 3090, 2960, 1650, 1610, 1465, 1440, 1390, 1280, 1230, 1150, 1090, 780, 750. δ_H 0.9 (6H, d, $J = 6$ Hz), 1.4–1.5 (2H, m), 1.8–1.85 (1H, m), 2.3 (1H, d, $J = 4.3$ Hz), 4.25–4.3(1H, m), 4.5 (2H, d, $J = 7.2$ Hz), 7.3–7.7 (3H, m), 7.9–8.1 (1H, m). MS:*m/z* 220(M^++1) (Found: C, 65.3; H, 7.6; N, 19.0. $C_{12}H_{17}N_3O$ requires C, 65.7; H, 7.8; N, 19.2%).

Compound **3c**: mp 114 °C, ν_{max}(KBr)/cm^{-1}: 3480, 3080, 3000, 1635, 1600, 1465, 1390, 1240, 1205, 1170, 1085, 930, 785, 765, 740. δ_H 1.3 (6H, s), 2.7 (1H, s), 4.6 (2H, s), 7.3–7.7 (3H, m), 7.9–8.1 (1H, m). MS:*m/z* 192 (M^++1) (Found: C, 63.0; H, 7.0; N, 22.2. $C_{10}H_{13}N_3O$ requires C, 62.8; H, 6.9; N, 22.0%).

Compound **3d**: mp 110 °C, ν_{max}(KBr)/cm^{-1}: 3460, 3080, 3000, 1645, 1620, 1465, 1395, 1350, 1240, 1200, 1095, 950, 780, 740. δ_H 1.0 (3H, t, $J = 7.5$ Hz), 1.2 (3H, s), 1.55 (2H, q, $J = 7$ Hz), 2.3 (1H, s), 4.6 (2H, s), 7.3–7.7 (3H, m), 7.9–8.1 (1H, m). MS:*m/z* 206 (M^++1) (Found: C, 64.2; H, 7.1; N, 20.2 $C_{11}H_{15}N_3O$ requires C, 64.4; H, 7.4; N, 20.5%).

Compound **3e**: mp 108 °C, ν_{max}(KBr)/cm^{-1}: 3450, 3100, 2990, 1625, 1605, 1465, 1445, 1330, 1240, 1170, 1080, 1030, 940, 900, 780, 750. δ_H 1.4–1.8 (8H, m), 2.4 (1H, s), 4.7 (2H, s), 7.3–7.7 (3H, m), 7.9–8.1 (1H, m). MS:*m/z* 218(M^++1) (Found: C, 66.6; H, 7.1; N, 19.7 $C_{12}H_{15}N_3O$ requires C, 66.3; H, 7.0; N, 19.3%).

Compound **3f**: mp 130 °C, ν_{max}(KBr)/cm^{-1} : 3460, 3090, 2960, 1650, 1620, 1465, 1360, 1235, 1185, 1125, 1080, 1040, 990, 890, 780, 740. δ_H 1.4–1.8 (10H, m), 2.4 (1H, s), 4.6 (2H, s), 7.3–7.7 (3H, m), 7.9–8.1 (1H, m). MS:*m/z* 232 (M^++1) (Found: C, 67.7; H, 7.7; N, 18.3. $C_{13}H_{17}N_3O$ requires C, 67.5; H, 7.4; N, 18.2%).

Compound **3g**: mp 82–83 °C, ν_{max}(KBr)/cm^{-1}: 3390, 3090, 2960, 2370, 1650, 1630, 1610, 1465, 1360, 1240, 1175, 1120, 945, 830, 780, 760. δ_H 1.4 (3H, s), 1.6 (3H, s), 1.7 (3H, s), 2.3 (1H, s), 4.6 (2H, s), 5.3 (1H, s), 7.3–7.7 (3H, m), 7.9–8.1 (1H, m). MS:*m/z* 232(M^++1) (Found: C, 67.8; H, 7.6; N, 18.4. $C_{13}H_{17}N_3O$ requires C, 67.5; H, 7.4; N, 18.2%).

Compound **3h**: mp 120 °C, ν_{max}(KBr)/cm^{-1}: 3300, 3080, 3030, 2960, 1650 ,1615, 1505, 1465, 1360, 1285, 1250, 1200, 1090, 1060, 945, 890, 780, 750, 700. δ_H 4.3 (2H, s), 5.2 (2H, s), 7.1–7.7 (13H, m), 7.9–8.1 (1H, m). MS:*m/z* 316 (M^++1) (Found: C, 76.4; H, 5.7; N, 13.6. $C_{20}H_{17}N_3O$ requires C, 76.2; H, 5.4; N, 13.3%).

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