α-Alkylation of Amines *via* a 1,5-Hydrogen Shift

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Radicals derived from *N*-(2-iodobenzyl) 'protected' amines undergo a 1,5-hydrogen shift to give more stable α-amino radicals, which can be subsequently trapped by electron deficient alkenes.

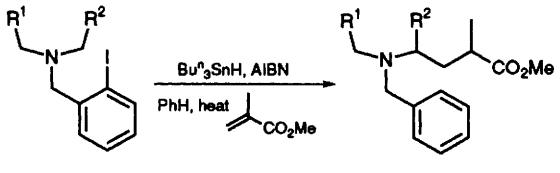
Substitution at a carbon adjacent to nitrogen usually requires indirect activation. There are many examples involving the use of α-metallo amine synthetic equivalents.[1] However, these have proved quite ineffective in more complex systems.[2] We have therefore adopted an approach based on radical chemistry since this negates the use of charged intermediates and hence should be immune to the nature and polarity of surrounding functionality.

Curran *et al.* have recently shown quite effectively that α-benzamidoyl radicals can be generated from *o*-halobenzamides by a 1,5-hydrogen atom transfer. The α-amino radical is subsequently trapped by intra- /inter-molecular reaction/ addition.[3] We decided to adopt this methodology towards the alkylation of heterocyclic systems, whereby the initial radical is generated at a remote site followed by translocation to the desired site of reaction.

The 2-iodobenzyl moiety was selected to generate the initial radical in a series of heterocycles, as facile removal of the subsequent benzyl group can be effected by hydrogenolysis to yield the α-alkylated amine. The radical precursors **1–7** were synthesised in good yield (66–98%) by heating 2-iodobenzyl chloride either with an excess of the respective amine in toluene, or with the amine and an excess of potassium carbonate in acetone.

Results for the reaction of the radical precursors **1–7** with methyl methacrylate using the tin hydride method for the generation of radicals are shown in Table 1.†‡ Optimum yields were obtained by syringe pump addition of tri-*n*-butyltin hydride (2 equiv.) and AIBN (0.1 equiv.) over a period of 9 h, to the radical precursor and a threefold excess of the electrophile in refluxing benzene.

In the case of the acyclic precursor **1**, the reaction proceeded very cleanly in high yield. However, with the heterocyclic precursors **2–6** competing reduction and telomerisation side reactions gave the products in a moderate yield. The product from the reaction of **7** was isolated in low yield with some difficulty due to a vast increase in the reduction of **7**, indicating that the 1,5-hydrogen translocation is not favoured due to destabilisation of the α-amino radical by the methyl group in the 4-position.



In summary, this methodology provides an accessible route to a range of α-substituted amines in good to moderate yields.

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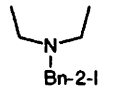
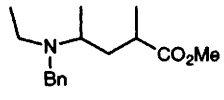
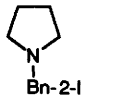
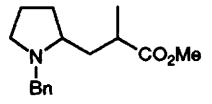
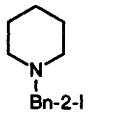
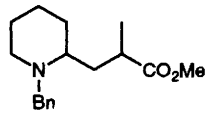
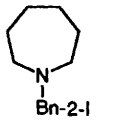
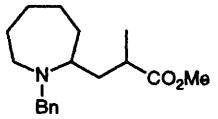
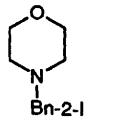
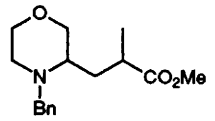
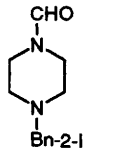
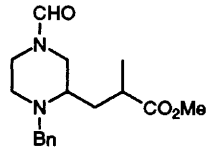
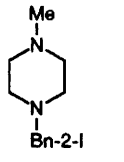
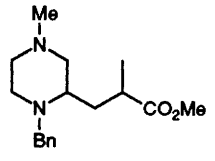
Table 1 Radical reaction of **1–7** with methyl methacrylate using the tin hydride method

Precursor	Product	Yield (%)
 **1**	 **8**	95
 **2**	 **9**	66
 **3**	 **10**	65
 **4**	 **11**	55
 **5**	 **12**	55
 **6**	 **13**	41
 **7**	 **14**	29

Footnotes

† All products were obtained as a mixture of diastereoisomers. All new compounds have satisfactory spectral and analytical data.

‡ *Typical procedure*: Tri-*n*-butyltin hydride (0.28 ml, 1.05 mmol) and AIBN (9 mg, 0.05 mmol) in dry, degassed benzene (5 ml) were added over a period of 9 h *via* syringe pump to **2** (1.5 g, 0.52 mmol) and methyl methacrylate (0.17 ml, 1.57 mmol) in dry, degassed benzene (20 ml) at reflux under argon. After cooling, the solvent was removed under reduced pressure and the crude product diluted with wet diethyl ether (25 ml). 1,8-Diazabicyclo[5.4.0]undec-7-ene[4] (0.22 ml, 1.5 mmol) was then added and the mixture stirred for 30 min before being

filtered through a silica plug and concentrated to afford the crude product. Purification by flash chromatography on silica gel yielded **9** as a pale-yellow oil (90 mg, 66%); R_f 0.17 (ethyl acetate–hexanes, 1:2, v/v); δ_H ($CDCl_3$, 200 MHz) 7.33 (5 H, s, Ar*H*), 4.03 (1 H, d, *J* 12.9 Hz, C*H*$_a$H$_b$Ph), 3.66 (3 H, s, CO_2CH_3), 3.20 (1 H, d, *J* 12.9 Hz, CH$_a$*H*$_b$Ph), 2.80 (1 H, m, CHN), 2.53 (2 H, m, CH_2N), 2.15 (1 H, m, $CHCO_2$), 2.04–1.40 (6 H, m, 3 × CH_2), 1.20 (3 H, d, *J* 6.0 Hz, CH_3); δ_C ($CDCl_3$, 50 MHz) 176.9 (CO_2), 141.6 (Ar*C*), 129.7 (2 × Ar*C*), 128.7 (2 × Ar*C*), 127.5 (Ar*C*), 62.9 (CHN), 59.1 (*C*H$_2$Ar), (CH_2N), 52.1 (CO_2CH_3), 37.6 (*C*HCO$_2$), 30.8 (CH_2), 22.7 (CH_2), 18.0 (CH_3), 17.9 (CH_2); ν_{max}/cm^{-1} ($CDCl_3$) 3064, 3033, 2952, 2871, 2795, 1740; *m/z* (EI, % rel intensity) 261 M^+ (2), 161 (12), 160 (100). Found 260.1637. $C_{16}H_{22}NO_2$ requires 260.1651.

References

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4 D. P. Curran and C.-T. Chang, *J. Org. Chem.*, 1989, **54**, 3140.