A Tandem Aminoalkylation of Aldehydes; Application to the Synthesis of Substituted Phenols and Naphthols†

J. Chem. Research (S), 1997, 340–341†

Mohammad R. Saidi* and Hamid R. Khalaji

Department of Chemistry, Sharif University of Technology, P.O. Box 11365-9516, Tehran, Iran

Treatment of a protected salicylic aldehyde (**2**) and 2-hydroxy-1-naphthaldehyde (**6**) with (trimethylsilyl)dialkylamines and various nucleophiles in a 5 M diethyl ether solution of lithium perchlorate gives a variety of *N*,*N*-dialkylaminophenols (**4**) and 1-(*N*,*N*-dialkylamino)-2-naphthols (**8**) in short reaction times and in good yields.

Recently we reported the lithium perchlorate-mediated aminoalkylation of aldehydes with (trimethylsilyl)dialkyl amines and various nucleophiles.[1,2] We now describe an efficient synthesis of functionalized aminophenols (**4a–i**) and aminonaphthols (**8a–i**) (Scheme 1). Good yields were obtained with the trimethylsiloxy aldehydes **2** and **6**.

Iminium salts are important intermediates in organic synthesis.[3] These salts may be produced in the reaction of (trimethylsilyl)dialkylamines promoted by 5 M lithium perchlorate in diethyl ether, *in situ.* The nucleophiles and the functionalized organozinc reagents were produced according to the literature procedures.[4–6] Cyanotrimethylsilane (TMSCN), organolithium and functionalized organozinc Grignard reagents can react as nucleophiles with the preformed iminium salt at room temperature, to provide a useful route to large numbers of structurally distinct compounds in good yields. The yield was low (58%) when $LiCH_2CN$ was used,[7,8] (Scheme 1). Yields and the nucleophiles are shown in Tables 1 and 2. A comparison of the results in Tables 1 and 2 shows that in general the yields for substituted phenols are higher than for naphthols, which is maybe due to steric electronic effects in the naphthalene ring. When unprotected phenols or naphthols were used, the products **4** and **8** were formed in only low yields.

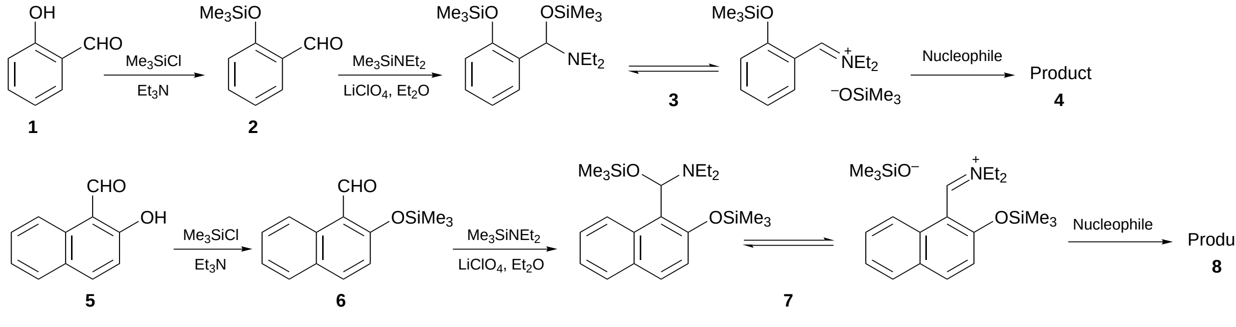
Experimental

$LiClO_4$ (Fluka) was dried at 160 °C and 10^{-1} Torr for 48 h. Diethyl ether was dried over sodium diphenylketyl. IR spectra were taken on a Matt Son 1000 Unicam FTIR spectrophotometer, ^1H and ^{13}C NMR spectra on a Bruker AC 80 spectrometer and mass spectra on Varian MAT 311A and Varian CH 5 spectrometers.

General Procedure for the Preparation of Bromozinc Esters.—Zn–Cu (3.3 mmol, 0.22 g) (prepared according to ref. 9) was placed in a two-necked flask fitted with a condenser and a stirring bar under argon. Dry diethyl ether or dry THF (3 mL) and TMSCl (0.05 mL) were added, and the mixture was sitrred for *ca.* 5 min. Then bromoester (4 mmol) was added *via* a syringe. After stirring had continued for an additional 30 to 60 min, the solvent was taken off under vacuum to leave $BrZnCH_2CO_2Et$ reagent ready for the next step.

General Procedure for the Three-component Aminoalkylation of Aldehydes **2** *and* **6**.—The aldehyde (2.0 mmol) was placed in a two-necked flask fitted with a stirring bar under argon. A 5 M $LiClO_4$ solution in diethyl ether (3 mL) was added, and the mixture was stirred for *ca.* 10 min. (Trimethylsilyl)dialkylamine (3.5 mmol) was added and the mixture was stirred for an additional 30 min. The nucleophile was added to the mixture and, after stirring had continued for *ca.* 1 h at room temperature, water (20 mL) and ether (20 mL) were added. After filtration, the organic layer was separated off and extracted with cold 0.2 M HCl solution. Neutralization with 2.0 M aqueous KOH gave the desired product.[10] Further purification was done by preparative GC if needed. The structures of the new compounds were determined by their ^1H NMR, ^{13}C NMR and mass spectra and by elemental analysis.

Selected Spectroscopic Data.—3-(Diethylamino)-3-(2-hydroxyphenyl)propanenitrile (**4c**): δ_H ($CDCl_3$) 1.10 (6 H, t, *J* 7.1 Hz), 2.51–2.80 (6 H, m), 4.01–4.30 (1 H, dd, *J* 7.4 and 5.7 Hz), 6.80–7.32 (5 H, m). 2-(*Diethylamino*)-2-(2-*hydroxyphenyl*)*acetonitrile* (**4d**): δ_H ($CDCl_3$) 1.20 (6 H, t, *J* 8.4 Hz), 2.60–2.91 (4 H, m), 4.91 (1 H, s), 6.60–7.62 (5 H, m) (Found: C, 70.34; H, 8.01. $C_{10}H_{16}N_2O$ requires C, 70.56; H, 7.89%). *N*,*N*-Diethyl-1-(2-hydroxyphenyl)but-3-enamine (**4e**): δ_H ($CDCl_3$) 1.01 (6 H, t, *J* 7.2 Hz), 2.61 (6 H, m), 3.81 (1 H, dd, *J* 7.8 and 5.3 Hz), 4.80–5.12 (2 H, m), 5.41–5.80 (1 H, m), 6.63–7.31 (5 H, m); δ_C ($CDCl_3$) 11.22, (CH_3), 33.64 (CH_2), 42.51 (CH_2), 64.31 (CH), 116.37 (CH_2), 118.36 (CH), 120.10 (CH), 126.12 (C), 128.27 (CH), 128.51 (CH), 135.54 (CH), 159.10 (C). N,N-*Diethyl*-1-(2-*hydroxyphenyl*)-2-*phenylethanamine* (**4g**): δ_H ($CDCl_3$) 1.22 (6 H, t, *J* 7.3 Hz), 2.81 (4 H, m), 3.11–3.50 (2 H, dd, *J* 14.1 and 5.6 Hz), 3.78–4.17 (1 H, dd, *J* 14.1 and 5.6 Hz), 6.37–7.52 (10 H, m) (Found: C, 80.95; H, 8.93. $C_{18}H_{23}NO$ requires C, 80.27; H, 8.61%). N,N,-*Diethyl*-1-(2-*hydroxyphenyl*)*ethanamine* (**4i**): δ_H ($CDCl_3$) 0.91 (6 H, t, *J* 7.2 Hz), 1.25 (3 H, d, *J* 5.8 Hz), 2.29–2.70 (4 H, m), 3.95 (1 H, q, *J* 5.8 Hz), 6.39–7.17 (5 H, m) (Found: C, 74.60; H, 9.99. $C_{12}H_{19}NO$ requires C, 74.57; H, 9.91%). *Ethyl* 3-(*diethylamino*)-3-(2-*hydroxy*-1-*naphthyl*)*propionate* (**8a**): δ_H ($CDCl_3$) 1.01–1.39 (9 H, m), 2.52–2.90 (6 H, m), 3.65 (1 H, dd, *J* 14.3 and 7.2 Hz), 4.21 (2 H, q, *J* 7.2 Hz), 6.82–8.40 (7 H, m) (Found: C, 72.10; H, 8.06. $C_{19}H_{25}O_3N$ requires C, 72.35; H, 7.99%). *N*,*N*-Diethyl-1-(2-hydroxy-1-naphthyl)ethanamine (**8c**): δ_H ($CDCl_3$) 1.00 (6 H, t, *J* 7.2 Hz), 1.42 (3 H, d, *J* 5.7 Hz), 2.49–3.00 (4 H, m), 4.64 (1 H, q, *J* 5.7 Hz), 6.79–7.81 (7 H, m). N-*Morpholino*-1-(2-*hydroxy*-1-*naphthyl*)-2-*phenylethanamine* (**8g**): δ_H ($CDCl_3$) 2.40–3.78 (10 H, m), 4.26 (1 H, dd, *J* 8.9 and 5.3 Hz), 6.48–7.81 (12 H, m) (Found: C, 79.08; H, 6.71. $C_{22}H_{23}O_2$ requires C, 79.25; H, 6.95%). 1-*Piperidino*-1-(2-*hydroxy*-1-*naphthyl*)*but*-3-*ene* (**8h**): δ_H ($CDCl_3$) 1.01 (6 H, t, *J* 7.2 Hz), 2.61 (6 H, m), 3.81 (1 H, dd, *J* 7.8 and 5.3 Hz), 4.80–5.12 (2 H, m), 5.41–5.80 (1 H, m), 6.63–7.31 (5 H, m) (Found: C, 81.08; H, 8.56. $C_{19}H_{23}ON$ requires C, 81.10; H, 8.24%).



Scheme 1

---

*To receive any correspondence.

†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1997, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

Table 1 Products obtained from reaction of aldehyde **2** with various nucleophiles

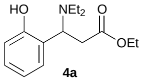
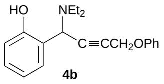
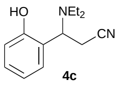
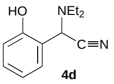
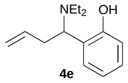
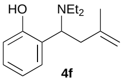
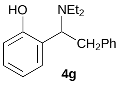
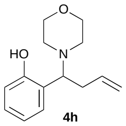
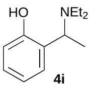
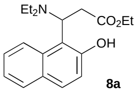
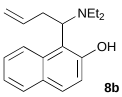
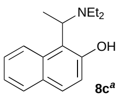
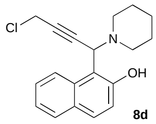
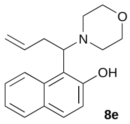
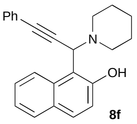
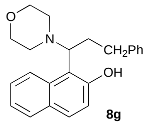
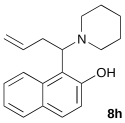
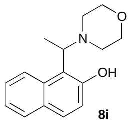
Nucleophile	Product	ν_{max}/cm^{-1}	Yield (%)
$BrZnCH_2CO_2Et$	 **4a**	3369.2, 1653.8	81
$LiC\equiv CCH_2OPh$	 **4b**	3407.7, 2484.6	80
$LiCH_2CN$	 **4c**	3053.8, 2192.3	58
$N\equiv CSiMe_3$	 **4d**	3061.5, 1600.1	83
$BrMgCH_2CH{=}CH_2$	 **4e**	3270.1, 1605.6	86
$BrMgCH_2Me{=}CH_2$	 **4f**	3300.0, 1576.9	73
$BrMgCH_2Ph$	 **4g**	3030.8, 1600.3	82
$BrMgCH_2CH{=}CH_2$	 **4h**	3276.9, 1607.9	89
LiMe	 **4i**	3150.0, 1600.2	89

Table 2 Products obtained from reaction of aldehyde **6** with various nucleophiles

Nucleophile	Product	ν_{max}/cm^{-1}	Yield (%)
$BrZnCH_2CO_2Et$	 **8a**	3340.0, 1707.7	63
$BrMgCH_2CH{=}CH_2$	 **8b**	3385.7, 1623.0	73
LiMe	 **8c**[a]	3300.0, 1623.1	71
$LiC\equiv CCH_2Cl$	 **8d**	3300.0, 2523.1	75
$BrMgCH_2CH{=}CH_2$	 **8e**	3384.6, 1600.6	62
LiC≡CPh	 **8f**	3400.0, 2123.1	71
$BrMgCH_2Ph$	 **8g**	3284.6, 1592.3	69
$BrMgCH_2CH{=}CH_2$	 **8h**	3061.5, 1623.1	67
LiMe	 **8i**	3300.0, 1623.1	71

[a] When unprotected aldehyde was used the yield was 18%.

We acknowledge 'Volkswagen-Stiftung, Federal Republic of Germany' for partial support of this work.

Received, 8th January 1997; Accepted, 3rd June 1997
Paper E/7/00193B

References cited in this synopsis

1 K. J. Henry, Jr., and P. A. Grieco, *J. Chem. Soc.*, *Chem. Commun.*, 1993, 510; P. A. Grieco and E. D. Moher, *Tetrahedron Lett.*, 1993, **34**, 5567.
2 M. R. Saidi, A. Heydari and J. Ipaktschi, *Chem. Ber.*, 1994, **127**, 1761.
3 M. E. Jung, in *Comprehensive Organic Synthesis*, ed. B. Trost and I. Fleming, Pergamon Press, Oxford, 1991, vol. 2, p. 893.
4 P. Knochel and R. D. Singer, *Chem. Rev.*, 1993, **93**, 2117.
5 A. Devasagayaraj, L. Schwink and P. Knochel, *J. Org. Chem.*, 1995, **60**, 3311.
6 Y. Tamaru, T. Nakamura, M. Salkaguchi, H. Ochiai and Z. Yoshida, *J. Chem. Soc.*, *Chem. Commun.*, 1988, 610; H. Ochiai, T. Nishihara, Y. Tamaru and Z. Yoshida, *J. Org. Chem.*, 1988, **53**, 1343.
7 J. O. Karlsson, A. Svensson and S. Gronowitz, *J. Org. Chem.*, 1984, **49**, 2018.
8 S. Kobayashi, S. Nagayama and T. Busujima, *Tetrahedron Lett.*, 1996, **37**, 9221.
9 R. D. Smith and H. E. Simmons, *Org. Synth.*, 1973, Coll. Vol. V, 855.
10 D. Seebach, C. Bestschuart and M. Schiess, *Helv. Chem. Acta.*, 1984, ***67***, 1593.