Facile α-deprotonation–electrophilic substitution of quinuclidine and DABCO

Satinder V. Kessar,* Paramjit Singh, Kamal N. Singh and Sandeep K. Singh

Department of Chemistry, Panjab University, Chandigarh-160014, India. E-mail: svkessar@panjabuniv.chd.nic.in

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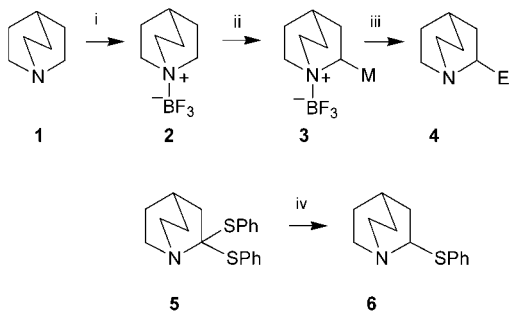
Deprotonation of BF_3 complexes of quinuclidine or DABCO by Schlosser base and subsequent reaction with electrophiles affords α-substituted products in moderate to good yields.

A number of drugs and molecules acting as chiral catalysts have a quinuclidine (**1**) framework with an appendage at a carbon atom α to the bridgehead nitrogen.[1] We envisaged a direct access to such compounds from the basic system *via* a Lewis acid promoted amine deprotonation procedure,[2] even though removal of a secondary α-proton from a piperidine ring is often problematic.[3] In the event, strong BF_3 activation in conjunction with the use of a superbase (Bu^sLi/Bu^tOK) proved to be effective for deprotonation of **1** (Scheme 1).[4,5] Subsequent reaction with electrophiles proceeded smoothly to afford a variety of products **4** in moderate to good yields (Table 1).† Barton's *N*-oxide approach is the only other route available for similar elaboration of the quinuclidine framework.[6] Our method

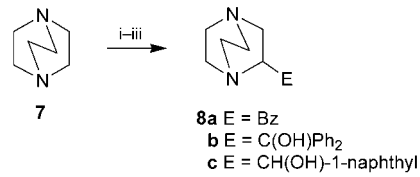


Scheme 1 *Reagents and conditions:* i, $BF_3.Et_2O$ (1.1 equiv.), 0 °C, 0.25 h, THF; ii, Bu^sLi/Bu^tOK (2.2 equiv.). −78 °C, 2 h; iii, electrophile (2.2 equiv.), −78 °C, 30 min, 30 min, −30 °C, then HCl (10%); iv, lithium naphthalenide, THF, −78 °C AcOH.

Table 1 Reaction of deprotonated BF_3-complexed bridgehead amines

Entry	Amine	Electrophile	Product	Yield (%)[a]
1	**1**	BnBr	**4a** E = Bn	34
2	**1**	BzOEt	**4b** E = Bz	74
3	**1**	$(p\text{-}MeOC_6H_4)_2C{=}O$	**4c** E = $C(OH)(p\text{-}MeOC_6H_4)_2$	68
4	**1**	PhCH=O	**4d** E = CH(OH)Ph	
			threo[b]	72
			erythro	< 6[c]
5	**1**	1-Naphthaldehyde	**4e** E = CH(OH)-1-naphthyl	
			threo	41
			erythro	15
6	**1**	2-Naphthaldehyde	**4f** E = CH(OH)-2-naphthyl	
			threo	40
			erythro	24
7	**1**	PhSSPh	**5**	52
			6	4
8	**7**	BzOEt	**8a** E = Bz	51
9	**7**	$Ph_2C{=}O$	**8b** E = $C(OH)Ph_2$	72
10	**7**	1-Naphthaldehyde	**8c** E = CH(OH)-1-naphthyl	
			threo	36
			erythro	40

[a] Yields are for pure products isolated after chromatography or crystallisation. [b] Ref. 7. [c] Could not be obtained in pure form.



Scheme 2 *Reagents and conditions:* i–iii as in Scheme 1.

avoids separate *N*-oxide formation–deoxygenation steps and the overall yields for the two procedures are comparable.

The Lewis acid activation method was also explored to obtain a quinuclidine with an α-attached sulfur atom, which with its various oxidation states can provide novel bidentate ligands. On reaction of **1** with diphenyl disulfide under standard conditions the disubstituted compound **5** was obtained as the major product (52%). However, it could be cleanly reduced to the desired monosubstituted compound **6** with lithium naphthalenide in THF.[8] Finally, this methodology was extended to α-deprotonation–electrophilic substitution of DABCO (**7**) (Scheme 2).‡ This readily available diazabicyclooctane has also been used extensively to modify organic reactions.[9] However, few reports of the synthesis and use of DABCO analogs of natural and synthetic quinuclidine compounds have appeared in the literature and their potential, as ligands and drugs, has remained largely unexplored.[10]

Notes and references

† All compounds were characterised by ^1H NMR and ^{13}C NMR spectroscopy and mass spectrometry. Mps of known compounds corresponded with literature values. *Selected data* for **4f** (*threo*): mp 104–105 °C (hexane); $\delta_H(CDCl_3$, 300 MHz) 1.13–1.33 (m, 2H), 1.38–1.55 (m, 4H) (C-3H, C-5H, C-7H), 1.75 (br s, 1H, C-4H), 2.73–2.89 (m, 2H), 2.93–2.99 (m, 2H), 3.05–3.15 (m, 1H) (C-2H, C-6H, C-8H), 4.52–4.55 (d, *J* 9.7, 1H, C-9H), 7.43–7.49 (m, 2H, ArH), 7.54–7.57 (d, *J* 8.6, 1H, ArH), 7.81–7.84 (m, 4H, ArH); $\delta_C(CDCl_3)$ 21.5 (CH), 25.8 (CH_2), 26.8 (CH_2), 29.4 (CH_2), 41.4 (CH_2), 49.6 (CH_2), 62.6 (CH), 74.7 (CH), 125.0 (CH), 125.7 (CH), 125.9 (CH), 126.5 (CH), 127.7 (CH), 127.9 (CH), 128.0 (CH and Cq), 133.2 (Cq), 138.7 (Cq); *m*/*z* 268 (M^+ + 1, 11.9%), 267 (M^+, 54.7), 250 (11.2), 158 (12.0), 141 (14.4), 129 (28.9), 111 (57.2), 82 (100) (Calc. for $C_{18}H_{21}NO$, 267.1623. Found 267.1628). For **6**: mp 65–66 °C (hexane); $\delta_H(CDCl_3$, 300 MHz) 1.25 (br s, 1H), 1.31–1.38 (m, 1H), 1.51–1.54 (m, 3H), 1.82 (br s, 1H), 2.02–2.10 (m, 1H) (C-3H, C-4H, C-5H, C-7H), 2.69–2.78 (m, 1H), 2.99–3.11 (m, 2H), 3.49–3.59 (m, 1H) (C-6H, C-8H), 4.50–4.56 (t, *J* 8.6, 1H, C-2H), 7.14–7.17 (d, *J* 7.1, 1H, ArH), 7.22–7.27 (t, *J* 7 Hz, 2H, ArH), 7.41–7.44 (d, *J* 7.4, 2H, ArH); $\delta_C(CDCl_3)$ 22.7 (CH), 25.5 (CH_2), 26.8 (CH_2), 34.5 (CH_2), 40.8 (CH_2), 48.6 (CH_2), 65.8 (CH), 126.0 (CH), 128.7 (2CH), 129.2 (2CH), 136.9 (Cq); *m*/*z* 220 (M^+ + 1, 14.8%), 219 (M^+, 100), 218 (17.9), 186 (30.7), 142 (31.5), 110 (80.0), 98 (79.0), 82 (25.8) (Calc. for $C_{13}H_{17}NS$, 219.1081. Found 219.1083).

‡ *Conditions* for α-deprotonation–electrophile reaction of DABCO: To a solution of Bu^tOK (2.2 mmol) and Bu^sLi (2.2 mmol) in THF (6 ml) at −78 °C was added slowly *via* a cannula a solution of DABCO–BF_3 complex (1.0 mmol) in THF (4 ml) under a nitrogen atmosphere. After stirring for 2 h, a solution of the electrophile (2.2 mmol) in THF (2 ml) was added dropwise. The temperature was maintained at −78 °C for 30 min and then allowed to rise to −30 °C over a period of 30 min. The reaction mixture was quenched with 10% HCl (5 ml) and worked up.

1 R. Verpoorte, J. Shripsema and T. van der Leer, *The Alkaloids*, ed. A. Brossi, Academic Press, New York, 1988, vol. 34, p 332; M. S. Ashwood, A. W. Gibson, P. G. Houghton, G. R. Humphrey, D. C.

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Roberts and S. H. B. Wright, *J. Chem. Soc., Perkin. Trans. 1*, 1995, 641; K. B. Sharpless, W. Amberg, Y. L. Bennani, G. A. Crispino, J. Hartung, K.-S. Jeong, H.-L. Kwong, K. Morikawa, Z.-M. Wang, D. Xu and X.-L. Zhang, *J. Org. Chem.*, 1992, **57**, 2768; K. E. Simons, A. Ibbotson, P. Johnston, H. Plum and P. B. Wells, *J. Catal.*, 1994, **150**, 321; M. J. O'Donnell, *Catalytic Asymmetric Synthesis*, ed. I. Ojima, VCH, Weinheim, 1993, p. 389.

2 S. V. Kessar, P. Singh, R. Vohra, N. P. Kaur and K. N. Singh, *J. Chem. Soc., Chem. Commun.*, 1991, 568; S. V. Kessar, P. Singh, K. N. Singh and M. Dutt, *J. Chem. Soc., Chem. Commun.*, 1991, 570; S. V. Kessar and P. Singh, *Chem. Rev.*, 1997, **97**, 721.

3 R. E. Gawley and K. Rein, *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon, New York, 1991, vol. 1, p 459 and vol. 3, p. 65.

4 M. Schlosser and J. Hartmann, *Angew. Chem., Int. Ed. Engl.*, 1973, **12**, 508; W. Bauer and L. Lochmann, *J. Am. Chem. Soc.*, 1992, **114**, 7482; P. Caubere, *Chem. Rev.*, 1993, **93**, 2317.

5 Attempted deprotonation with alkyllithiums was unsuccessful and use of 2 equiv. of Schlosser base seems necessary. BH_3 activation is ineffective in this case although it is very useful for removal of more acidic α-protons. M. R. Ebden, N. S. Simpkins and D. N. A. Fox, *Tetrahedron Lett.*, 1995, **36**, 8697; E. Vedejs and J. T. Kendall, *J. Am. Chem. Soc.*, 1997, **119**, 6941.

6 D. H. R. Barton, R. Beugelmans and R. N. Young, *Nouv. J. Chim.*, 1978, **2**, 363. For $TiCl_3$ reduction modification of this procedure see: K. B. Sharpless, H. C. Kolb and P. G. Andersson, *J. Am. Chem. Soc.*, 1994, **116**, 1278.

7 The *threo* and *erythro* configurations were assigned on the basis of coupling constants between C-2 and C-9 methine protons in the NMR spectrum. T. Kametani, H. Matsumoto, Y. Satoh, H. Nemoto and K. Fukumoto, *J. Chem. Soc., Perkin Trans. 1*, 1977, 376.

8 T. Cohen, W. M. Daniewski and R. B. Weisenfeld, *Tetrahedron Lett.*, 1978, 4665.

9 K. B. Sharpless and R. Oi, *Tetrahedron Lett.*, 1991, **32**, 4853.

10 K. Soai, A. Oshio and H. Yoneyama, *Tetrahedron: Asymmetry*, 1992, **3**, 359.

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