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ELECTRON-TRANSFER ACTIVATION. PHOTOCYANATION OF TERTIARY AMINES.

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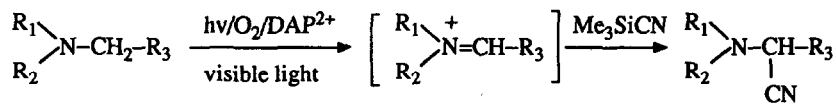
Abstract : *An efficient photoinduced cyanation of various alkaloids by Me_3SiCN in acetonitrile, sensitized by N,N'-dimethyl-2,7-diazapyrenium-bis-(tetrafluoroborate) (DAP^{2+}, 2 BF_4^-), is described.*

Selective N-demethylation of tertiary amines can be initiated by photoinduced single electron-transfer (SET) and recently we have reported [1a] an efficient procedure to apply this method in acetonitrile to several alkaloids, using DAP^{2+}, $2BF_4^-$ [2] or 9,10-dicyanoanthracene (DCA) with added salts [1b] as photosensitizers. It was assumed that the demethylation resulted from the hydrolysis of an intermediate iminium ion leading through an unstable α-hydroxy-amine to secondary amine and aldehyde [1b] (see also [3]).

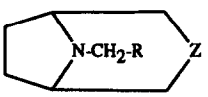
We thought worthwhile to check this point by trapping the postulated iminium ion with CN^- as nucleophile, especially as α-aminonitriles may be valuable synthetic intermediates.

Our first attempts have shown that cyanotrimethylsilane Me_3SiCN is a much better nucleophile source than the alkaline cyanides because it does not require addition of another solvent, water for example, which could modify the reaction medium. Its use led us to various α-aminonitriles in good to excellent yields (75-95 %), thus providing a novel strategy for a selective and mild synthesis of these compounds.

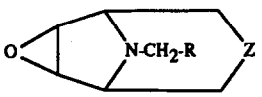


A typical procedure is as follows : a solution of the amine (2 mmol) and Me_3SiCN (4 mmol) in acetonitrile (50 ml) to which is added a catalytic amount of DAP^{2+}, 2 BF_4^- [2] (0.02 mmol) is irradiated under oxygen bubbling for 1-5 hours with a 500 W high-pressure Hg lamp through a U.V. cut-off glass filter ($\lambda \geq 400$ nm) at about 20 °C. After reaction (followed by t.l.c.) the products are separated by flash chromatography on alumina.

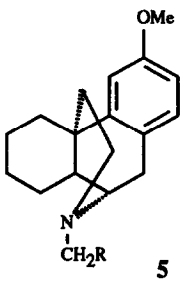
Table 1 summarizes the results obtained with various tertiary amines.



1 Z = C=O
2 Z = CHOH
3 Z = CHOCOCHPhCH$_2$OH



4 Z = CHOCOCHPhCH$_2$OH



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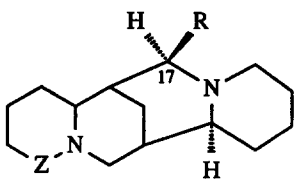
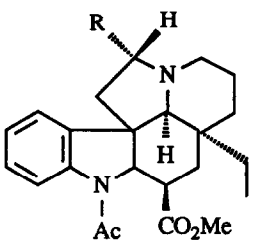


6 Z = CH$_2$
7 Z = C=O



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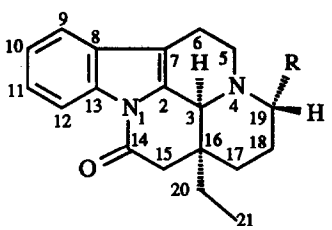

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a, R=H ; b, R=CN

Table 1. DAP^{2+} - sensitized photocyanation of various tertiary amines.

	Amine a R=H	α-Aminonitrile [a] b R=CN	Reaction time (h)	Yields (%)
Tropinone	**1a**	**1b**[4]	4	81
Tropine	**2a**	**2b**[5]	5	79
Atropine	**3a**	**3b**[6]	2.30	90
Scopolamine	**4a**	**4b**[7]	2.30	88
Dextromethorphan	**5a**	**5b**[8]	2	76
Sparteine	**6a**	**6b**[9]	1	90
Lupanine	**7a**	**7b**[9]	1	95
N-acetyl 2,16-dihydro-vincadifformine	**8a**	**8b**[10]	1	88
Eburnamonine	**9a**	**9b**[11]+ epimer[12]	4	79[b]

a. All products were characterized by IR, ^{1}H NMR and mass spectrometry.
b. α-aminonitriles epimeric on C-19 with **9b** (α-CN, 85 %) and its epimer (β-CN, 15 %) ; the ratio was determined by ^{13}C NMR data.

If examples **1a** to **5a** of amines previously submitted to the photo-demethylation procedure confirm the intermediate formation of iminium ions in the process, entries **6a** to **9a** of Table 1 illustrate the synthetic utility of the method.

Considering first photocyanation, the present conditions appear far superior to those applied earlier to **6a**, **7a** and **8a**, i.e. irradiations in methanol, with KCN and methylene blue or Bengal rose as sensitizers, which afforded the same α-aminonitriles but accompanied by the corresponding primary amides and furthermore in much lower yields : **6b** (20 %) [9], **7b** (70 %) [9] and **8b** (45 %) [10].

In the second place, as shown by the case of **9a**, the photochemical generation of iminium ions compares advantageously, as far as the yields are concerned, with the more general chemical methods : the classical or Potier-modified [13] Polonovski reaction on amine-oxides, or the mercuric acetate oxidation of amines [14]. At this point, it is to be stressed that the stereoselectivity, and possibly the regioselectivity of the photochemical process, may differ from those of the chemical methods. Thus **9a** affords by photocyanation a mixture of both epimers at C-19, with **9b** (α-CN, 85 %) predominating over its epimer (β-CN, 15 %) whereas oxidation of the corresponding N-oxide by the Potier-modified Polonovski protocole is reported as giving only the β-CN epimer (33,5 %) [12].

Further studies are underway to define on structurally-varied substrates the differences between both methods, which may be due to the opposite stereoselectivity of the attack by the nucleophile, or even to the very nature of the iminium ion generated intermediately .

References and Notes

1. - J. Santamaria, R. Ouchabane, and J. Rigaudy, *Tetrahedron Lett.* - **a. 30**, 2927 (1989) - **b. 30**, 3977 (1989).

2. - DAP^{2+}, 2 BF_4^-=N,N'-dimethyl-2,7-diazapyrenium-bis-(tetrafluoroborate) was obtained as described in S. Hünig, J. Gross, E.F. Lier, and H. Quast, *Liebigs Ann. Chem.*, 339 (1973).

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4. - **1b**. m.p. 70 °C ; M^+ 164 (5.7 %, $C_9H_{12}N_2O$), 106, 67, 55 ; *IR* (KBr, cm^{-1}) 1710 (C=O), 2240 (CN) ; *^1H NMR* ($CDCl_3$, δ) 3.56 (2H, *s*, CH_2CN), 3.63 (2H, *m*, $CH_2\underline{C}HN$).

5. - **2b**. m.p. 72 °C ; M^+ 166 (6 %, $C_9H_{14}N_2O$), 149, 121, 108, 82 (100 %), 67, 55 ; *IR* (KBr, cm^{-1}) 2260 (CN) ; *^1H NMR* ($CDCl_3$, δ) 3.20 (2H, *m*, $CH_2\underline{C}HN$), 3.33 (2H, *s*, CH_2CN), 4.0 (1H, *t*, $\underline{C}HOH$).

6. - **3b**. M^+ 314 (6 %, $C_{18}H_{22}N_2O_3$), 274, 268, 228, 149, 150 (100 %) ; *IR* ($CHCl_3$, cm^{-1}) 1730 (ester), 2250 (CN) ; *^1H NMR* ($CDCl_3$, δ) 3.16 and 3.20 (2H, *s*, CH_2CN), 3.80 (2H, *d*, CH_2OH), 4.11 (1H, *m*, CHOCO), 5.0 (1H, *t*, $\underline{C}HCH_2OH$), 7.3 (5H, *m*, H arom.).

7. - **4b**. M^+ 328 (8 %, $C_{18}H_{20}N_2O_4$), 180, 150, 121 ; *IR* ($CHCl_3$, cm^{-1}) 1740 (ester), 2255 (CN) ; *^1H NMR*

($CDCl_3$, δ) 3.58 (2H, *s*, CH_2CN), 3.71 (2H, *d*, $C\underline{H}_2OH$), 4.16 (1H, *m*, CHOCO), 5.0 (1H, *t*, $C\underline{H}CH_2OH$), 7.25 (5H, *m*, H arom.).

8. - **5b.** M^+ 296 (11 %, $C_{19}H_{24}N_2O$), 213 (100 %), 171 ; $[\alpha]_D$ = + 117 ° (c = 0.8, CH_3OH) ; *IR* ($CHCl_3$, cm^{-1}) 2220 (CN) ; *^1H NMR* ($CDCl_3$, δ) 3.51 and 3.53 (2H, *s*, NCH_2CN), 3.76 (3H, *s*, OCH_3), 6.96 (3H, *m*, H arom.).

9. - J. Santamaria and F. Khuong-Huu, *Tetrahedron*, **34**, 1523 (1978).

10. - J. Santamaria, D. Herlem, and F. Khuong-Huu, *Tetrahedron*, **33**, 2389 (1977).

11. - **9b.** m.p. 182 ° ; M^+ 319 (100 %, $C_{20}H_{21}N_3O$), 290, 262, 224, 209, 180, 167, 115, 84, 67 ; [α] = -168° (c = 0.5, $CHCl_3$) ; *IR* (KBr, cm^{-1}) 1720 (amide), 2240 (CN) ; *^1H NMR* (250 MHz, $CDCl_3$, δ) 0.93 (3H, *t*, 21-H_3), 1.08 (1H, *td*, 17-Ha, J_{gem} 13.8 Hz, $J_{17a,18a}$ 13.8 Hz, $J_{17a,18e}$ 14 Hz), 1.58 (1H, *m*, 17-He, J_{gem} 13.8 Hz, $J_{17e,18e}$ 4 Hz), 1.66 (1H, *m*, 20-Hx), 1.79 (1H, *dq*, 18-He, J_{gem} 13.5 Hz, $J_{18e,17e}$ 4 Hz, $J_{18e,19a}$ 3.4 Hz), 2.02 (1H, *m*, 18-Ha, $J_{18a\text{-}19a}$ 11.2 Hz), 2.07 (1H, *dq*, 20-Hy), 2.56 (1H, *dm*, 6-Ha, J_{gem} 17.5 Hz, $J_{6a,5a}$ 5.7 Hz, $J_{6a,5e}$ 0.5 Hz), 2.62 and 2.64 (2H, *s*, 15-H_2, J_{gem} 4.8 Hz), 2.89 (1H, *dm*, 6-He, $J_{6e,5a}$ 11.8 Hz, $J_{6e,5e}$ 6.0 Hz), 3.20 (1H, *dq*, 5-Ha, J_{gem} 14.5 Hz), 3.36 (1H, *dd*, 19-Ha, $J_{19a,18a}$ 11.2 Hz, $J_{19a,18e}$ 3.4 Hz), 3.80 (1H, *dq*, 5-He, J_{gem} 14.5 Hz), 4.04 (1H, *s*, 3-H), 7.30 (1H, *td*, 10-H), 7.34 (1H, *td*, 11-H), 7.43 (1H, *dd*, 9-H), 8.34 (1H, *dd*, 12-H) ; *^{13}C NMR* ($CDCl_3$, δ) 7.4 (C-21), 15.9 (C-6), 25.1 (C-17), 26.0 (C-18), 27.9 (C-20), 38.0 (C-16), 43.8 (C-15), 44.9 (C-19), 48.8 (C-5), 58.0 (C-3), 112.9 (C-7), 116.2 (C-12), 118.2 (C-9), 119.1 (CN), 124.1 (C-10), 124.9 (C-11), 129.5 (C-8), 130.3 (C-2), 134.3 (C-13), 166.6 (C-14).

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