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# Trimethylsilyl Cyanide as a Superior Trapping Agent for Iminium Ion Intermediates in the DCA-Sensitized Photooxygenation of Indole Derivatives and Analogues. Application to the Total Synthesis of Some Indoloquinolizidine Alkaloids

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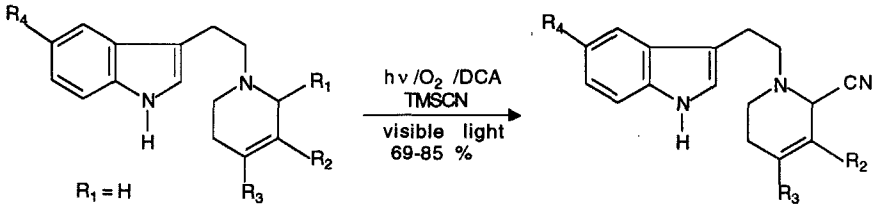
*Key words : Single Electron Transfer ; α-aminonitriles ; Pictet-Spengler cyclization ; indoloquinolizidines*

***Abstract :*** *A photoinduced electron transfer process sensitized by 9,10-dicyanoanthracene (DCA), using $Me_3SiCN$ (TMSCN) as cyanating agent, yields α-aminonitriles in the indole derivatives and analogues series. Efficient synthesis of indoloquinolizidine alkaloids through a Pictet-Spengler cyclization applied to these α-aminonitriles generated in situ is described.*

α-cyanoamines are stable versatile synthetic equivalents of the corresponding iminium species and are frequently used in indole alkaloid synthesis[1].

A selective procedure for generating an iminium cation can be initiated by photoinduced single electron transfer[2]. We have recently reported that this intermediate can be trapped with $Me_3SiCN$ (TMSCN) allowing the obtention of regioselective 2-cyano-3-piperideines[3] as well as α-aminonitriles from various alkaloids[4]. Unfortunately, electron-rich derivatives such as N-tryptophyl-3-piperideine or indolino-indolizidine alkaloids bearing an indole or enamine moiety are known to react readily under photooxygenation conditions. They yield unstable dioxetanes which subsequently undergo extensive decomposition leading to a complex mixture of products[5].

We report in this paper that in the 9,10-dicyanoanthracene (DCA)-sensitized photooxygenation of these indole derivatives, the TMSCN is a superior trapping agent for iminium ions and it also displays a suitable protection towards enamine moieties. TMSCN leads to α-cyanoamine derivatives in fair yields, this methodology is of general use. In addition, a mild and efficient synthesis of some indoloquinolizidine alkaloids through a Pictet-Spengler cyclization applied to these α-aminonitriles generated *in situ* is described.




**Typical procedure.** Irradiation of an acetonitrile solution (25 mL) of the indole derivative[1b,d] (2 mmol) and TMSCN (0.3 mL, 2.2 mmol) in the presence of catalytic amounts of DCA (0.02 mmol) is carried out with a 1800 W Xe lamp through a U.V. cut-off glass filter ($\lambda > 420$ nm) at 20 °C under oxygen bubbling. At the end of the reaction (TLC monitoring), the α-cyanoamines are separated by flash chromatography on alumina.

Table 1 summarizes the results obtained with various indole derivatives and analogues and illustrates the synthetic importance of the method. Considering the yields of α-cyanoamines, the photochemical process competes with the classical modified Polonovski reaction[6], *i.e.* TFAA treatment of the N-oxides followed by cyanide trapping, which affords the same α-aminonitriles: **1b** (protected with a phenylsulfonyl group, 31%)[1b], **3b** (85%)[1d], **6b** (41%)[7], **7b** (49%)[7]. Furthermore, the Polonovski protocole suffers from several drawbacks: the indole nitrogen has to be deactivated by a suitable electron-withdrawing group such as the *t*-butoxycarbonyl (Boc) or the phenylsulfonyl groups in order to avoid the formation of unwanted side products. Moreover, the acidity of the medium is a problem when considering *in situ* reactions with carbon nucleophiles and other organometallic reagents.

The role of TMSCN in the photochemical process is not totally elucidated. We have nevertheless established from photochemical experiments that:

- the use of other nucleophilic $CN^-$ sources such as alkaline cyanides or $Et_2AlCN$ leads to a rapid and extensive decomposition of indole derivatives.
- the trapping of a dipolar peroxide intermediate by TMSCN at low temperatures (-30 or -50 °C) is not observed; α-aminonitriles are obtained in all cases. This is not in agreement with the report of Saito[8] for the singlet oxygenation of N-methylindoles.

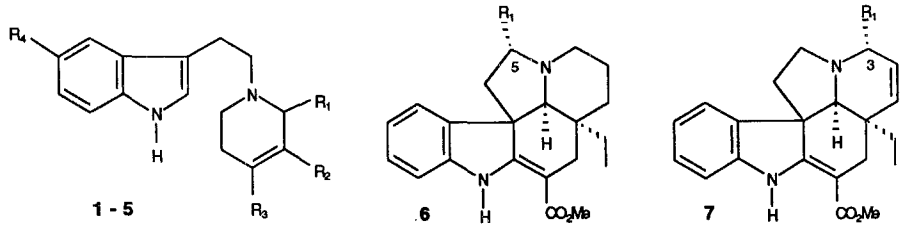


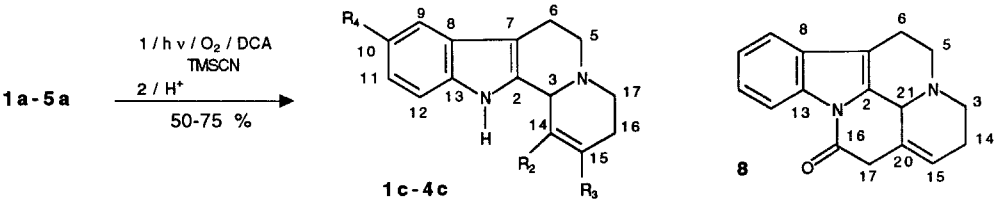

Table 1. α-aminonitriles resulting from DCA-sensitized photooxygenation of various indole alkaloids and analogues.

| Amine **a**, $R_1$=H | $R_2$ | $R_3$ | $R_4$ | α-aminonitrile[a] **b**, $R_1$=CN | Reaction time (h) | Yield[b] (%) |
|---|---|---|---|---|---|---|
| **1a** | Et | H | H | **1b*** | 4 | 85 (31)[c] |
| **2a** | Et | H | OMe | **2b*** | 2.5 | 70 |
| **3a** | OBn | H | H | **3b**[1d] | 4 | 65 (85)[c] |
| **4a** | Me | Me | H | **4b*** | 2.5 | 75 |
| **5a** | $CH_2CO_2Et$ | H | H | **5b*** | 2 | 55 |
| **6a** | Vincadifformine | | | **6b**[9] | 3 | 63 (41)[c] |
| **7a** | Tabersonine | | | **7b**[9] | 1 | 81 (49)[c] |

a. All new products (*) gave consistent spectroscopic data (exact MS, IR, $^1H$ and $^{13}C$NMR) ; b. Isolated yields ; c. Overall yields through the modified Polonovski procedure

These results clearly show that efficient deactivation of the indole nitrogen is obtained by using TMSCN to prevent side reactions during α-cyanoamine formation. The formation of α-aminonitriles indicates that the nucleophilic attack by the indole nitrogen on the silicon atom would give a hypervalent silicate which deposits directly the cyanide ion at the conjugated iminium site formed from the amine radical cation which is the primary intermediate in the single electron transfer process.

These 2-cyano-3-piperideines can be used as synthons for a general approach to the construction of complex alkaloids. So, a mild and efficient synthesis of some indoloquinolizidine alkaloids through a Pictet-Spengler reaction applied to these α-aminonitriles generated *in situ* has been carried out.




Following the preceding protocole, after complete disappearance of the starting amine, aqueous HCl 1N (10 mL) is added to the resulting reaction mixture which is stirred for 3 hours at 50-60 °C under argon atmosphere. After usual treatment, the tetracyclic indoloquinolizidine is separated by flash chromatography on alumina.

Table 2 summarizes the results obtained with various N-tryptophylpiperideines. It is noteworthy that an electron enrichment of the indole nucleus by a methoxy group (entry **2a**) accelerates the Pictet-Spengler cyclization. Lounasmaa[1d] has already obtained compound **3c** from compound **3a** through the same intramolecular acid cyclization applied to α-cyanoamine **3b** with an overall yield of 52 %. The lower yield obtained is probably due to the obtention of compound **3b** by the modified Polonovski protocole which thereby necessitates the deactivation of the indole nitrogen with a *t*-butoxycarbonyl protecting group (Boc).

The mild conditions of the straightforward electron transfer process compare advantageously with the cyclization through the modified Polonovski method, *i.e.* TFAA treatment of the N-oxides obtained from amines **1a,5a** followed by brief treatment with acid, which affords much lower yields of cyclized derivatives: **1c** (30%)[10a], **8** (30 %)[10].

Table 2. Indolizidine alkaloids[11] obtained with various N-tryptophyl-3-piperideines.

| Starting amine | | | | Cyclized product | Yield[a] (%) |
|---|---|---|---|---|---|
| | $R_2$ | $R_3$ | $R_4$ | | |
| **1a** | Et | H | H | **1c**[12] | 60 (30)[b] |
| **2a** | Et | H | OMe | **2c**[13] | 50 |
| **3a** | OBn | H | H | **3c**[1d] | 75 (52) |
| **4a** | Me | Me | H | **4c**[14] | 73 |
| **5a** | $CH_2CO_2Et$ | H | H | **8**[15] | 58 (30)[b] |

a. Isolated yields ; b. Overall yields through the modified Polonovski procedure.

The α-aminonitrile intermediate **5b** leads to the tetracyclic derivative **5c**, which spontaneously cyclizes to the pentacyclic eburnane type alkaloid **8.**

Further studies are carried out to elucidate the precise mechanistic role of TMSCN and the total synthesis of some complex indole alkaloids using these α-aminonitriles as intermediates is in progress.

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12 **1c.** mp. 115° (ether) ; $M^+$ 252 (100 %, $C_{17}H_{20}N_2$), 251, 223, 208, 180, 169, 151, 115, 83 ; IR (CHCl3, $cm^{-1}$) 3400, 2920, 1620, 1450 ; $^1H$ NMR (200 MHz, CDCl3, δ) 1.20 (3H, *t*, H-19, J=6.5 Hz), 2.33 (4H, *m*, H-16, H-18), 2.7 (1H, *m*, H-6), 2.93 (3H, *m*, H-6, H-17), 3.30 (2H, *m*, H-5), 4.6 (1H, *s*, H-3), 5.68 (1H, *m*, H-15), 7.12 (1H, *dt*, H-10, J=2.6 Hz, J=7.8 Hz), 7.17 (1H, *dt*, H-11, J=2.6 Hz, J=7.8 Hz), 7.35 (1H, *dd*, H-9, J=7.8 Hz, J=2.6 Hz), 7.54 (1H, *dd*, H-12, J=7.8 Hz, J=2.6 Hz), 7.90 (1H, *s*, NH) ; $^{13}C$ NMR (CDCl3) 12.7 (C-19), 18.0 (C-6), 24.7 (C-16), 28.6 (C-18), 44.1 (C-17), 49.7 (C-5), 56.6 (C-3), 107.2 (C-7), 110.7 (C-15), 118.0 (C-12), 119.3 (C-9), 120.8 (C-10), 121.4 (C-11), 127.0 (C-14), 133.6 (C-8), 135.5 (C-2), 137.1 (C-13).
13. **2c.** amorphous ; $M^+$ 282 (100 %, $C_{18}H_{22}N_2$), 190, 175, 143, 132, 117, 108, 85, 79 ; IR : 3400, 2920, 2830, 1710, 1620, 1450 ; $^1H$ NMR : δ 1.17 (3H, *t*, H-19, J=6.5 Hz), 2.06 (1H, *m*, H-16), 2.30 (3H, *m*, H-16, H-18) 2.69 (1H, *m*, He-6), 2.85 (1H, *m*, H-17), 2.95 (1H, *m*, Ha-6), 3.30 (1H, *m*, H-5), 3.85 (1H, s, H-20), 4.60 (1H, *s*, H-3), 5.64 (1H, *m* H-15), 6.80 (1H, *dd*, H-11, J=8.8 Hz, J=2.4 Hz), 6.93 (1H, *d*, H-9, J=2.4 Hz), 7.21 (1H, *d*, H-12, J=8.8 Hz), 7.90 (1H, *s*, NH) ; $^{13}C$ NMR : δ 12.6 (C-19), 18.0 (C-6), 24.5 (C-16), 28.5 (C-18), 44.1 (C-17), 49.5 (C-5), 55.8 (C-20), 56.6 (C-3), 100.2 (C-15), 106.9 (C-7), 111.2 (C-12), 111.4 (C-9), 120.6 (C-11), 127.4 (C-14), 130.7 (C-8), 134.2 (C-2), 137.0 (C-13), 153.9 (C-10).
14. **4c.** amorphous ; $M^+$ 252 (100 %, $C_{17}H_{20}N_2$), 237, 223, 194, 180, 169, 156, 143, 92 ; IR : 3470, 2910, 1450 ; $^1H$ NMR : δ 1.72 (1H, *s*, H-19), 1.9 (1H, *m*, Ha-16), 2.05 (1H, *s*, H-18), 2.35 (1H, *m*, He-16), 2.70 (2H, *m*, He-6, H-17), 2.95 (2H, m, Ha-6, H-17), 3.34 (2H, *m*, H-5), 4.53 (1H, *s*, H-3), 7.12 (1H, *dt*, H-10, J=2.6 Hz, J=6.6 Hz), 7.18 (1H, *dt*, H-11, J=2.6 Hz, J=6.6 Hz), 7.34 (1H, *dd*, H-9, J=6.6 Hz, J=2.6 Hz), 7.50 (1H, dd, H-12, J=6.6 Hz, J=2.6 Hz), 7.91 (1H, *s*, N) ; $^{13}C$ NMR : δ 17.4 (C-6), 18.7 (C-18), 31.5 (C-16), 43.6 (C-17), 50.3 (C-5), 58.8 (C-3), 106.6 (C-7), 110.7 (C-12), 118.0 (C-9), 119.3 (C-10), 121.4 (C-11), 123.2 (C-8), 127.1 (C-15), 128.4 (C-14), 134 (C-2), 135.5 (C-13).
15. **8.** amorphous ; $M^+$ 264 (100 %, $C_{17}H_{16}N_2O$), 235, 223, 205, 180, 167, 149, 118, 85, 70 ; IR : 2910, 1710, 1640, 1450 ; $^1H$ NMR : δ 2.25 (1H, *m*, He-14), 2.38 (1H, *m*, Ha-14), 2.70 (2H, *m*, H-6), 2.95 (3H, *m*, H-3, H-5), 3.30 (2H, *m*, H-3, Ha-17), 3.51 (1H, *m*, He-17), 4.05 (1H, *s*, H-21), 5.67 (1H, *m*, H-15), 7.25 (1H, *m*, H-10), 7.30 (1H, *m*, H-11), 7.40 (1H, *m*, H-9), 8.34 (1H, *m*, H-12) ; $^{13}C$ NMR : δ 20.3 (C-6), 26.2 (C-14), 40.2 (C-17), 48.0 (C-3), 51.3 (C-5), 55.8 (C-21), 112.2 (C-7), 116.1 (C-15), 118.0 (C-12), 121.6 (C-9), 123.9 (C-10), 124.2 (C-11), 128.3 (C-8), 130.1 (C-20), 132.9 (C-2)), 134.9 (C-13), 166.4 (C-16).

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