

Tetrabutylammonium cyanide catalyzes the addition of TMSCN to aldehydes and ketones

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Dedicated to Prof. Enrique Meléndez

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Abstract

The catalytic effect of Bu₄NCN on the addition of TMSCN to the carbonyl group of spiroepoxycyclohexadienones and to some other representative carbonyl compounds has been considered.

Keywords: Ammonium salts, catalysis, trimethylsilyl cyanide, cyanohydrins

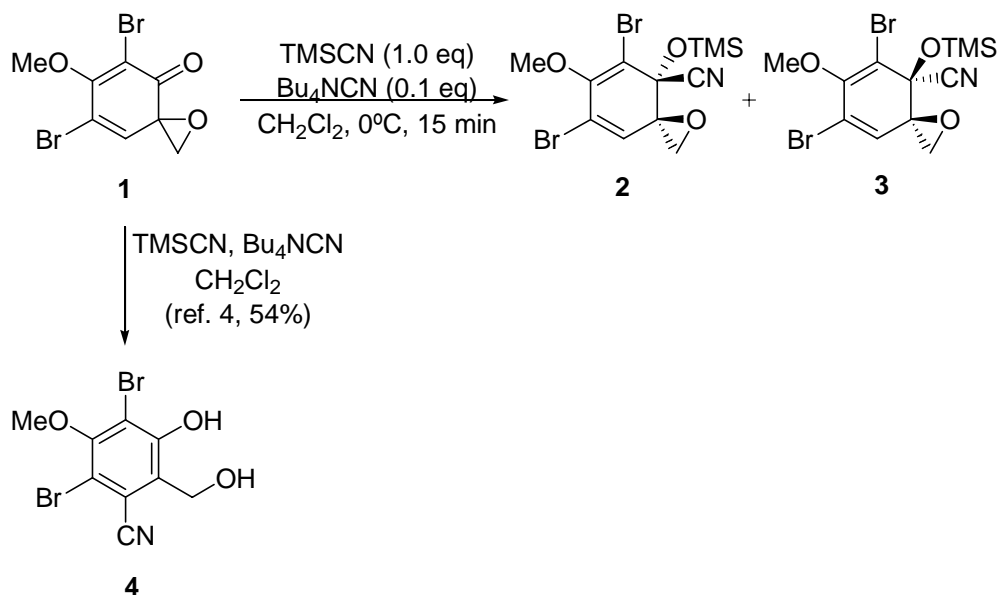
Introduction

Cyanohydrin trimethylsilyl ethers are useful synthetic intermediates for the preparation of elaborated targets.¹ For this reason, a large array of catalytic species has been used for the synthesis of this kind of compounds.² Among them, particular attention has been devoted to metal-catalyzed processes. However, the use of non-metal catalysts to carry out organic transformations is important from an environmental standpoint. In this paper we describe the results of the TMSCN addition to the carbonyl group of spiroepoxycyclohexadienones³ and certain representative carbonyl compounds catalyzed by ammonium salts.

Results and Discussion

In the context of the synthesis of cyanohydrins derived from spiroepoxycyclohexadienones,³ we have observed that the reaction of compound **1** with TMSCN (1.0 eq) in the presence of Bu₄NCN (0.1 eq) afforded an inseparable mixture of diastereomeric cyanohydrin derivatives **2** and **3** in ratio 1:1.3 (71% isolated yield). However, at this stage the stereochemical assignment of compounds **2** and **3** was not possible. This result contrasts with those reported by Waldmann *et*

*al.*⁴ where the formation of benzenic derivative **4** was observed when using a molar ratio 1: TMS-CN: Bu₄NCN = 1: 18.4: 1 (Scheme 1).

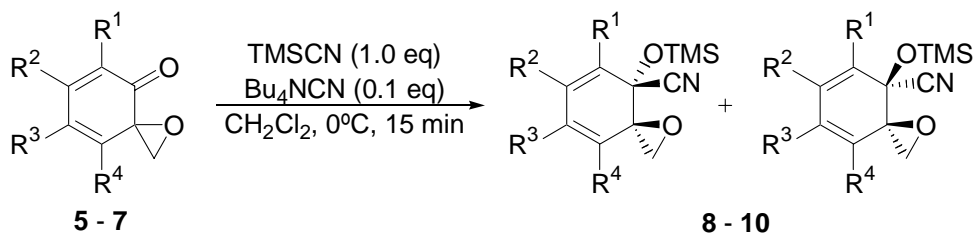


Scheme 1

In the context of these findings, two comments should be made: i) the reaction of **1** with TMS-CN in the absence of the ammonium salt resulted in the recovering of unaltered starting material; and ii) to the best of our knowledge, only an isolated report describing the use of Bu₄NCN as catalytic agent for the O-TMS-cyanosilylation of 3-pentanone (84% isolated yield) has been previously reported.⁵

On the basis of these considerations, we decided to explore the scope and limitations of the use of the system TMS-CN/Bu₄NCN(cat.) for the O-TMS-cyanosilylation of other spiroepoxycyclohexadienones and also for the same reaction using some representative carbonyl derivatives as starting materials.

The results of the OTMS-cyanosilylation of a variety of spiroepoxycyclohexadienones (Scheme 2) and some other representative carbonyl compounds (Scheme 3) are quoted in Tables 1 and 2 respectively.



Scheme 2

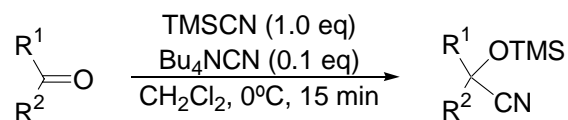
Table 1. O-TMS cyanosilylation of spiroepoxycyclohexadienones

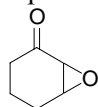

No.	Starting material	R ¹	R ²	R ³	R ⁴	Product (%) ^a	Diastereomeric ratio
1	5	Br	MeO	Br	MeO	8 (60)	1 : 1 ^b
2	6	H	H	Br	H	9 (50)	1 : 1.4 ^b
3	7	H	MeO	H	H	10 (45)	1 : 1.6 ^c

^a Isolated yield of the diastereomeric O-TMS cyanohydrins.

^b Determined by GC/MS on the purified mixture of diastereomeric O-TMS cyanohydrins.

^c Determined by ¹H-NMR on the purified mixture of diastereomeric O-TMS cyanohydrins.

**Scheme 3****Table 2.** O-TMS cyanosilylation of representative carbonyl compounds

No		Product (%) ^a	Diastereomeric ratio
1	Benzaldehyde	11a (88)	---
2 ^d	p-Methoxybenzaldehyde	11b (86)	---
3 ^e	2-Furaldehyde	11c (86)	---
4	Cyclohexanone	11d (89)	---
5	Cyclopentanone	11e (92)	---
6		11f (95)	3.3 : 1 ^b
7		11g (97)	4.0 : 1 ^c

^a Isolated yield of the diastereomeric O-TMS cyanohydrins.

^b Determined by ¹H-NMR on the purified mixture of diastereomeric O-TMS cyanohydrins.

^c Determined by GC/MS on the purified mixture of diastereomeric O-TMS cyanohydrins.

^d The reaction was carried out in dry Et₂O.

^e The reaction was achieved at room temperature for 1 h.

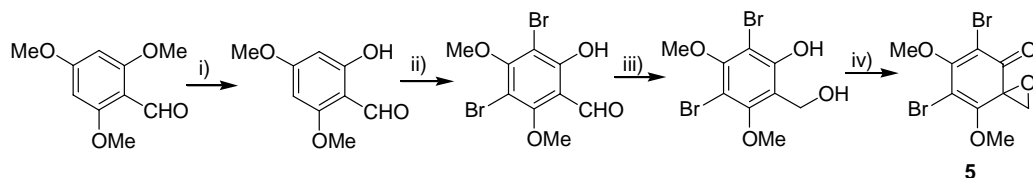
Conclusions

The formation of O-TMS cyanohydrins was possible for a variety of aldehydes and ketones using TMSCN as reagent and Bu₄NCN as catalyst. The method is characterized by mild reaction conditions, short reaction times and good yields of the final O-TMS cyanohydrins. In those cases

where the formation of stereoisomers is possible, an excess of one of the diastereomers was observed.

Experimental Section

Synthesis of 2,4-dibromo-3,5-dimethoxy-cyclohexa-2,4-diene-1-one-5-spirooxirane (5). Following the analogous synthetic route used by K. Hinterding *et al.*⁴ to obtain the spiroepoxycyclohexadienone **1**, 2,4,6-trimethoxybenzaldehyde was submitted to a four-step sequence:



i) BCl_3 , CH_2Cl_2 , 4 h., r. t., 91%; ii) $\text{Br}_2 \cdot \text{HBr}$ Pyridine, Pyridine, 2 h., 50 °C, 76%; iii) NaBH_4 , THF, 1 h., r. t., 80%; iv) NaIO_4 , HCl, H_2O , THF, r. t., 70 %.

Spectroscopic data for 5. $^1\text{H-NMR}$: (CDCl_3 , 200 MHz) δ 3.27 (d, $J=8.9$ Hz, 1H, $\text{CH}_2\text{-O}$), 3.45 (d, $J=8.9$ Hz, 1H, $\text{CH}_2\text{-O}$), 3.83 (s, 3H, OCH_3), 4.07 (s, 3H, OCH_3) ppm; $^{13}\text{C-NMR}$: (CDCl_3 , 50 MHz) δ 57.47 (O-C- CH_2), 58.36 ($\text{CH}_2\text{-O}$), 61.72 (OCH_3), 61.81 (OCH_3), 107.17 (CBr), 107.37 (CBr), 159.11 (C- OCH_3), 166.10 (C- OCH_3), 185.48 (C=O) ppm; MS (70 eV, EI) m/z (%): 338/340/342 (52/94/44) [M^+], 323/325/327 (51/100/61) [$\text{M}-15$], 322/324/326 (51/57/35) [$\text{M}-16$], 241/243 (47/47), 59 (14).

Typical procedure for the cyanosilylation of carbonyl compounds

To a solution of the carbonyl compound (0.367 mmol) in dry CH_2Cl_2 (0.5 mL) was added, under Argon an at 0 °C, TMSCN (0.046 mL, 0.367 mmol) followed by a solution of the ammonium salt (10 mg, 0.037 mmol) in dry CH_2Cl_2 (0.5 mL). The mixture was stirred at 0 °C for 15 minutes. A solution of NaHCO_3 sat. (3 mL) was added and the mixture was extracted with CH_2Cl_2 . Drying of the combined organic phases with MgSO_4 was followed by evaporation of the solvent in vacuo. The products were purified by chromatography on silica gel (ethyl acetate/hexane) and characterized by $^1\text{H NMR}$, $^{13}\text{C NMR}$ and mass spectrometry. For compounds **2+3**, **8**, **9** and **11g** the diastereomeric ratio was determined by GC/MS. Conditions: Capillary column 95 % dimethyl 5 % diphenylpolysiloxilane. Gradient of temperature 45 °-290 °C. Mass spectrometer, HP 5890.

5,7-Dibromo-6-methoxy-4-trimethylsilyloxy-1-oxa-spiro[2.5]octa-5,7-diene-4-carbonitrile (2) + (3). (a) $^1\text{H NMR}$: (CDCl_3 , 200 MHz) δ 0.41 (s, 9H, $3\text{CH}_3\text{-Si}$), 2.91 (d, $J=5.0$ Hz, 1H, $\text{CH}_2\text{-O}$), 3.44 (d, $J=5.0$ Hz, 1H, $\text{CH}_2\text{-O}$), 3.78 (s, 3H, OCH_3), 6.17 (s, 1H, CH) ppm; $^{13}\text{C-NMR}$: (CDCl_3 , 75 MHz) δ ($3\text{CH}_3\text{-Si}$), 50.16 ($\text{CH}_2\text{-CN}$), 58.87 (OCH_3), 59.46 (O-C- CH_2), 73.70 (O-C- CN), 109.10 (CBr), 114.68 (CN), 119.27 (CBr), 129.01 (CH), 148.87 (C- OCH_3) ppm; MS (70

eV, EI) m/z (%): 407/409/411 (5/10/5) [M^+], 362/364/366 (11/22/11) [M-45], 352/354/356 (5/8/4) [M-55], 347/349/351 (3/7/4) [M-60], 337/339/341 (4/6/3) [M-70], 229/231 (18/18), 201/203 (7/7), 137/139 (5/5), 122 (5), 103 (6), 89 (8), 75(34), 74 (10), 73 (100), 59 (9), 45 (30), 44 (5), 43 (10). **b**) $^1\text{H-NMR}$: (CDCl_3 , 200 MHz) δ 0.28 (s, 9H, 3 CH_3 -Si), 3.03 (d, $J=5.0$ Hz, 1H, CH_2 -O), 3.42 (d, $J=5.0$ Hz, 1H, CH_2 -O), 3.78 (s, 3H, OCH_3), 6.09 (s, 1H, CH) ppm; $^{13}\text{C-NMR}$: (CDCl_3 , 75 MHz) δ (3 CH_3 -Si), 51.75 (CH_2 -CN), 58.00 (O-C- CH_2), 58.87 (OCH_3), 74.28 (O-C-CN), 108.50 (CBr), 115.27 (CN), 118.93 (CBr), 128.72 (CH), 148.87 (C- OCH_3) ppm; MS (70 eV, EI) m/z (%): 407/409/411 (7/15/8) [M^+], 363/365/367 (11/15/9) [M-44], 362/364/366 (39/78/40) [M-45], 352/354/356 (7/12/6) [M-55], 347/349/351 (6/13/8) [M-60], 229/231 (14/14), 201/203 (7/8), 137/139 (10/9), 103 (13), 89 (8), 75(32), 74 (11), 73 (100), 59 (14), 47 (11), 45 (32), 43 (12).

5,7-Dibromo-6,8-dimethoxy-4-trimethylsilyloxy-1-oxa-spiro[2.5]octa-5,7-diene-4-

carbonitrile (8). **(a)** $^1\text{H-NMR}$: (CDCl_3 , 200 MHz) δ 0.14 (s, 9H, 3 CH_3 -Si), 3.09 (d, 1H, $J=5.4$ Hz, CH_2 -O), 3.22 (d, 1H, $J=5.4$ Hz, CH_2 -O), 3.61 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3) ppm. MS (70 eV, EI) m/z (%): 437/439/481 (20/40/21) [M^+], 392/394/396 (10/18/11) [M-45], 377/379/381 (10/21/12) [M-60], 358/360 (47/47) [M-Br], 335/337/339 (12/20/12) [M-104], 259/261 (49/50) [M-Br-TMSCN], 231/233 (22/21), 75 (46), 73 (100), 59 (27), 45 (25), 43 (26). **(b)** $^1\text{H-NMR}$: (CDCl_3 , 200 MHz) δ 0.15 (s, 9H, 3 CH_3 -Si), 3.05 (d, 1H, $J=5.6$ Hz, CH_2 -O), 3.22 (d, 1H, $J=5.6$ Hz, CH_2 -O), 3.61 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3) ppm. MS (70 eV, EI) m/z (%): 437/439/481 (22/47/23) [M^+], 392/394/396 (24/48/96) [M-45], 377/379/381 (17/34/16) [M-60], 358/360 (34/34) [M-Br], 335/337/339 (16/32/15) [M-104], 259/261 (52/50) [M-Br-TMSCN], 231/233 (21/19), 75 (28), 73 (100), 59 (28), 45 (32).

7-Bromo-4-trimethylsilyloxy-1-oxa-spiro[2.5]octa-5,7-diene-4-carbonitrile (9). **(a)** $^1\text{H-NMR}$: (CDCl_3 , 200 MHz) δ 0.20 (s, 9H, 3 CH_3 -Si), 2.83 (d, 1H, $J=4.9$ Hz, CH_2 -O), 3.28 (d, 1H, $J=4.9$ Hz, CH_2 -O), 5.70-5.90 (m, 2H, H-5, H-8), 6.21 (dd, 1H, $J=9.8$ Hz, $J=1.5$ Hz, H-6) ppm. MS (70 eV, EI) m/z (%): 254/256 (18/19) [M-45], 244/246 (10/10) [M-55], 103 (17), 75 (20), 73 (100), 45 (66). **(b)** $^1\text{H-NMR}$: (CDCl_3 , 200 MHz) δ 0.19 (s, 9H, 3 CH_3 -Si), 2.89 (d, 1H, $J=5.0$ Hz, CH_2 -O), 3.25 (d, 1H, $J=4.9$ Hz, CH_2 -O), 5.70-5.90 (m, 2H, H-5, H-8), 6.21 (dd, 1H, $J=9.8$ Hz, $J=1.5$ Hz, H-6) ppm. MS (70 eV, EI) m/z (%): 254/256 (79/81) [M-45], 103 (25), 75 (26), 73 (100), 45 (32).

6-Methoxy-4-trimethylsilyloxy-1-oxa-spiro[2.5]octa-5,7-diene-4-carbonitrile (10). **(a)** $^1\text{H-NMR}$: (CDCl_3 , 200 MHz) δ 0.02 (s, 9H, 3 CH_3 -Si), 2.94 (d, 1H, $J=4.9$ Hz, CH_2 -O), 3.45 (d, 1H, $J=4.9$ Hz, CH_2 -O), 4.87 (d, 1H, $J=2.5$ Hz, H-5), 5.55 (d, 1H, $J=10.1$ Hz, H-8), 6.05 (dd, 1H, $J=10.1$ Hz, $J=2.5$ Hz, H-7) ppm. **(b)** $^1\text{H-NMR}$: (CDCl_3 , 200 MHz) δ 0.18 (s, 9H, 3 CH_3 -Si), 2.93 (d, 1H, $J=4.9$ Hz, CH_2 -O), 3.50 (d, 1H, $J=4.9$ Hz, CH_2 -O), 4.81 (d, 1H, $J=2.5$ Hz, H-2), 5.55 (d, 1H, $J=10.1$ Hz, H-5), 6.08 (dd, 1H, $J=10.1$ Hz, $J=2.5$ Hz, H-4) ppm.

2-Trimethylsilyloxy-7-oxa-bicyclo[4.1.0]heptane-2-carbonitrile (11f). **(a)** $^1\text{H-NMR}$: (CDCl_3 , 500 MHz) δ 0.30 (s, 9H, 3 CH_3 -Si), 1.40-2.10 (m, 6H, 3 CH_2), 3.38 (t, 1H, $J=4.0$ Hz, CH-O, H-6), 3.40 (d, 1H, $J=4.0$ Hz, CH-O, H-1) ppm; $^{13}\text{C-NMR}$: (CDCl_3 , 50 MHz) δ 1.18 (3 CH_3 -Si), 18.82 (CH_2), 21.16 (CH_2), 32.03 (CH_2 , C-3), 55.09 (CH), 56.71 (CH), 70.65 (C), 119.72 (CN)

ppm. **b**) $^1\text{H-NMR}$: (CDCl_3 , 500 MHz) δ 0.32 (s, 9H, 3 CH_3 -Si), 1.40-2.10 (m, 6H, 3 CH_2), 3.20 (d, 1H, $J=3.5$ Hz, CH-O, H-1), 3.34 (t, 1H, $J=3.5$ Hz, CH-O, H-6) ppm.

2-Trimethylsilyloxy-6-oxa-bicyclo[3.1.0]hexane-2-carbonitrile (11g). **(a)** $^1\text{H-NMR}$: (CDCl_3 , 500 MHz) δ 0.29 (s, 9H, 3 CH_3 -Si), 1.75 (dd, 1H, $J=11.7$ Hz, $J=8.5$ Hz, H-4), 1.83 (dd, 1H, $J=11.7$ Hz, $J=9.0$ Hz, H-3), 2.12 (dd, 1H, $J=13.3$ Hz, $J=9.0$ Hz, H-3), 2.21 (dd, 1H, $J=13.3$ Hz, $J=8.5$ Hz, H-3), 3.56 (d, 1H, $J=2.6$ Hz, H-5), 3.66 (d, 1H, $J=2.6$ Hz, H-1) ppm; $^{13}\text{C-NMR}$: (CDCl_3 , 50 MHz) δ (3 CH_3 -Si), 24.91 (CH_2 , C-4), 32.62 (CH_2 , C-3), 55.17 (CH), 59.64 (CH), 74.91 (C), 119.61 (CN) ppm; MS (70 eV, EI) m/z (%): 182 (49) [M- CH_3], 155 (34) [M- CH_3 -HCN], 127 (81), 84 (28), 81 (33), 75 (55), 73 (100), 45 (44), 43 (22), 41 (75). **(b)** $^1\text{H-NMR}$: (DMSO-d_6 , 500 MHz) δ 0.22 (s, 9H, 3 CH_3 -Si), 1.50-2.10 (m, 4H, 2 CH_2), 3.73 (d, 1H, $J=2.5$ Hz, H-5), 3.82 (d, 1H, $J=2.5$ Hz, H-1) ppm; MS (70 eV, EI) m/z (%): 182 (21) [M- CH_3], 155 (69) [M- CH_3 -HCN], 126 (12), 113 (14), 101 (13), 84 (16), 81 (35), 75 (28), 73 (100), 47 (13), 45 (35), 43 (16).

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