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 Bu_4NCN 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

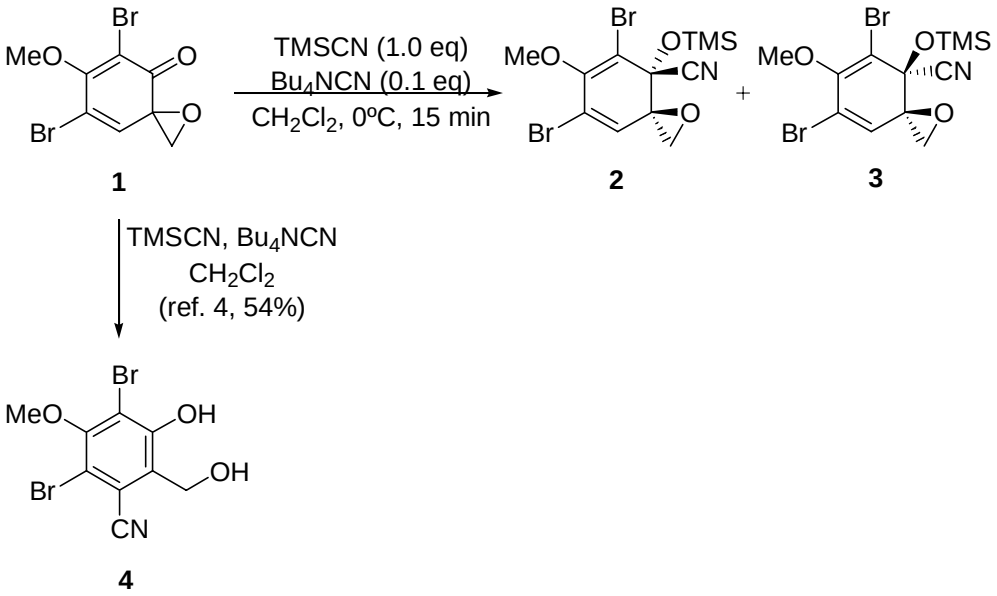
Introduction

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 spiroepoxycyclohexadienones[3] 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 Bu_4NCN (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 bezenic derivative **4** was observed when using a molar ratio **1**: TMS-CN: Bu_4NCN = 1: 18.4: 1 (Scheme 1).

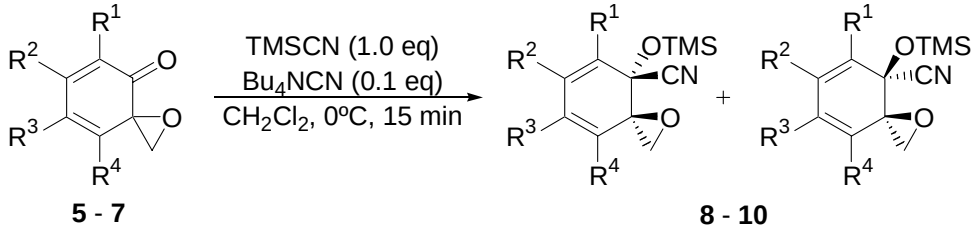


Scheme 1

In the context of these findings, two comments should be made: i) the reaction of **1** with TMSCN 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 Bu_4NCN 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 TMSCN/Bu_4NCN(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.

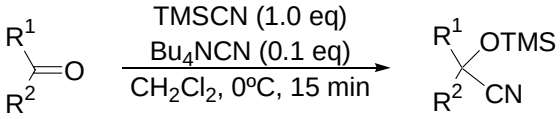


Scheme 2

Table 1. O-TMS cyanosilylation of spiroepoxycyclohexadienones

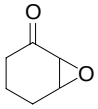
No.	Starting material	R^1	R^2	R^3	R^4	Product (%)[a]	Diastereomeric ratio
1	**5**	Br	MeO	Br	MeO	**8** (60)	1 : 1[b]
2	**6**	H	H	Br	H	**9** (50)	1 : 1.4[b]
3	**7**	H	MeO	H	H	**10** (45)	1 : 1.6[c]

[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 ^{1}H-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 ^{1}H-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 Et_2O.
[e] The reaction was achieved at room temperature for 1 h.

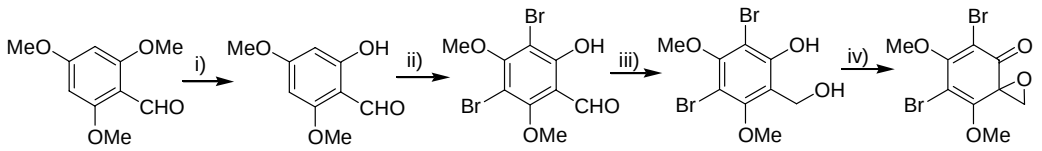
Conclusions

The formation of O-TMS cyanohydrins was possible for a variety of aldehydes and ketones using TMSCN as reagent and Bu_4NCN 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:



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i) BCl_3, CH_2Cl_2, 4 h., r. t., 91%; ii) Br_2.HBrPyridine, Pyridine, 2 h., 50 ºC, 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}H-NMR: ($CDCl_3$, 200 MHz) δ 3.27 (d, *J*=8.9 Hz, 1H, CH_2-O), 3.45 (d, *J*=8.9 Hz, 1H, CH_2-O), 3.83 (s, 3H, OCH_3), 4.07 (s, 3H, OCH_3) ppm; ^{13}C-NMR: ($CDCl_3$, 50 MHz) δ 57.47 (O-C-CH_2), 58.36 (CH_2-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) [$M^{+\cdot}$], 323/325/327 (51/100/61) [M-15], 322/324/326 (51/57/35) [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 ºC, 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 ºC 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}H NMR, ^{13}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 º-290 ºC. Mass spectrometer, HP 5890.

5,7-Dibromo-6-methoxy-4-trimethylsilanyloxy-1-oxa-spiro[2.5]octa-5,7-diene-4-carbonitrile (2) + (3). (a) ^{1}H NMR: ($CDCl_3$, 200 MHz) δ 0.41 (s, 9H, $3CH_3$-Si), 2.91 (d, *J*=5.0 Hz, 1H, CH_2-O), 3.44 (d, *J*=5.0 Hz, 1H, CH_2-O), 3.78 (s, 3H, OCH_3), 6.17 (s, 1H, CH) ppm; ^{13}C-NMR: ($CDCl_3$, 75 MHz) δ ($3CH_3$-Si), 50.16 (CH_2-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) [$M^{+\cdot}$], 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}H-NMR: ($CDCl_3$, 200 MHz) δ 0.28 (s, 9H, $3CH_3$-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}C-NMR: ($CDCl_3$, 75 MHz) δ ($3CH_3$-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) [$M^{+\cdot}$], 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-trimethylsilanyloxy-1-oxa-spiro[2.5]octa-5,7-diene-4-carbonitrile (8). (**a**) ^{1}H-NMR: ($CDCl_3$, 200 MHz) δ 0.14 (s, 9H, $3CH_3$-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) [$M^{+\cdot}$], 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}H-NMR: ($CDCl_3$, 200 MHz) δ 0.15 (s, 9H, $3CH_3$-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) [$M^{+\cdot}$], 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-trimethylsilanyloxy-1-oxa-spiro[2.5]octa-5,7-diene-4-carbonitrile (9). (**a**) ^{1}H-NMR**:** ($CDCl_3$, 200 MHz) δ 0.20 (s, 9H, $3CH_3$-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}H-NMR: ($CDCl_3$, 200 MHz) δ 0.19 (s, 9H, $3CH_3$-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-trimethylsilanyloxy-1-oxa-spiro[2.5]octa-5,7-diene-4-carbonitrile (10). (a) ^{1}H-NMR: ($CDCl_3$, 200 MHz) δ 0.02 (s, 9H, $3CH_3$-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}H-NMR: ($CDCl_3$, 200 MHz) δ 0.18 (s, 9H, $3CH_3$-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-Trimethylsilanyloxy-7-oxa-bicyclo[4.1.0]heptane-2-carbonitrile (11f). (a) ^{1}H-NMR: ($CDCl_3$, 500 MHz) δ 0.30 (s, 9H, $3CH_3$-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}C-NMR: ($CDCl_3$, 50 MHz) δ 1.18 ($3CH_3$-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}H-NMR: ($CDCl_3$, 500 MHz) δ 0.32 (s, 9H, $3CH_3$-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-Trimethylsilanyloxy-6-oxa-bicyclo[3.1.0]hexane-2-carbonitrile (11g). (a) ^{1}H-NMR: ($CDCl_3$, 500 MHz) δ 0.29 (s, 9H, $3CH_3$-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}C-NMR: ($CDCl_3$, 50 MHz) δ (3CH_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}H-NMR: (DMSO-d_6, 500 MHz) δ 0.22 (s, 9H, $3CH_3$-Si), 1.50-2.10 (m, 4H, $2CH_2$), 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).

Acknowledgements

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