This article was downloaded by: [Kungliga Tekniska Hogskola]
On: 07 October 2014, At: 02:21
Publisher: Taylor & Francis
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Novel Uncatalyzed Hydrocyanation of Ketones utlizing Tetrachlorosilane-Potassium Cyanide Reagent

Tarek A. Salama [a] , Saad S. Elmorsy [a] , Abdel-Galel M. Khalil [a] , Margret M. Girges [a] & Abdel-Aziz S. El-Ahl [a]

[a] Department of Chemistry, Faculty of Science , Mansoura University , Mansoura, Egypt

Published online: 12 Apr 2007.

To cite this article: Tarek A. Salama , Saad S. Elmorsy , Abdel-Galel M. Khalil , Margret M. Girges & Abdel-Aziz S. El-Ahl (2007) Novel Uncatalyzed Hydrocyanation of Ketones utlizing Tetrachlorosilane-Potassium Cyanide Reagent, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 37:8, 1313-1319, DOI: 10.1080/00397910701226897

To link to this article: http://dx.doi.org/10.1080/00397910701226897

PLEASE SCROLL DOWN FOR ARTICLE

Taylor & Francis makes every effort to ensure the accuracy of all the information (the “Content”) contained in the publications on our platform. However, Taylor & Francis, our agents, and our licensors make no representations or warranties whatsoever as to the accuracy, completeness, or suitability for any purpose of the Content. Any opinions and views expressed in this publication are the opinions and views of the authors, and are not the views of or endorsed by Taylor & Francis. The accuracy of the Content should not be relied upon and should be independently verified with primary sources of information. Taylor and Francis shall not be liable for any losses, actions, claims, proceedings, demands, costs, expenses, damages, and other liabilities whatsoever or howsoever caused arising directly or indirectly in connection with, in relation to or arising out of the use of the Content.

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden. Terms & Conditions of access and use can be found at http://www.tandfonline.com/page/terms-and-conditions

Synthetic Communications®, 37: 1313–1319, 2007
Copyright © Taylor & Francis Group, LLC
ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910701226897

Novel Uncatalyzed Hydrocyanation of Ketones utlizing Tetrachlorosilane–Potassium Cyanide Reagent

Tarek A. Salama, Saad S. Elmorsy, Abdel-Galel M. Khalil,
Margret M. Girges, and Abdel-Aziz S. El-Ahl
Department of Chemistry, Faculty of Science, Mansoura University,
Mansoura, Egypt

Abstract: A combination of tetrachlorosilane and potassium cyanide (in situ trichlorosilyl cyanide) was found to work efficiently for hydrocyanation of ketones to afford the corresponding cyanohydrins in high yield under mild conditions.

INTRODUCTION

Cyanohydrins are key building blocks for the one-step synthesis of many biologically active compounds that are otherwise obtained only with difficulty, such as α-hydroxy aldehydes, α-aminoalcohols, α-azidonitriles, β-hydroxy-α-aminoacids, and α-hydroxyacids.[1] The formation of cyanohydrins is generally considered to be a reaction that is achieved under equilibrating conditions.[2] One of the most convenient preparative methods for cyanohydrins is the addition reaction of trimethylsilyl cyanide (TMSCN) to carbonyl compounds under catalysis by a plethora of reagents including Lewis acids,[3] Lewis bases,[4] inorganic/organic salts,[5] metal complexes,[6] and organic catalysts[7] followed by acid hydrolysis in a subsequent step. Only a few reports for uncatalyzed cyanation reaction of aldehydes have appeared,[8] but cyanation of keto compounds has not been hitherto

Received in Poland June 12, 2006

Address correspondence to Tarek A. Salama, Natural Products Synthesis and Bioorganic Chemistry Laboratory, National Center for Scientific Research “NCSR Demokritos,” 15310 Ag. Paraskevi, P. O. Box 60228, Athenes, Greece. E-mail: tasalama@yahoo.com

observed in the absence of catalyst. In conjunction with our interest[9] in exploring the utility of in situ reagents based on tetrachlorosilane (TCS)[10] in organic synthesis, we report here a facile and comparably safe practical route for cyanation of ketones using the inexpensive and readily available TCS and potassium cyanide (in situ trichlorosilyl cyanide)[9c] without further addition of any catalyst.

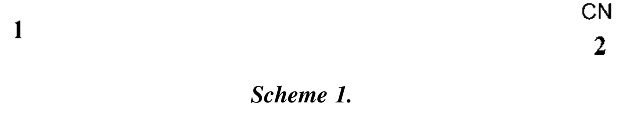
RESULTS

Stirring a mixture of ketone (1 equiv) with a combination of TCS (2 equiv) and potassium cyanide (2 equiv) at 60–70°C in acetonitrile affords the corresponding cyanohydrins in high yields in one-pot process after a simple aqueous workup (Scheme 1, Table 1).

The results summarized in Table 1 show that the cyanohydrin formation was applied for aryl methyl ketones and tolerated a variety of functional groups on the phenyl ring regardless of whether they had electron-donating or electron-withdrawing character. Thus, chloro-, bromo-, methyl-, and nitro-containing aromatic ketones underwent this transformation in good to excellent yields (entries 2, 3, 4, 6).

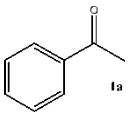
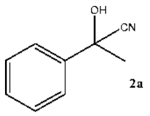
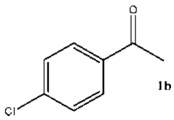
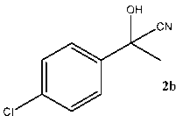
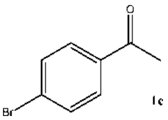
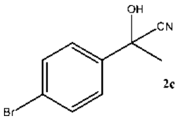
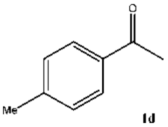
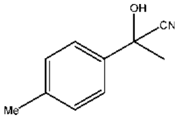
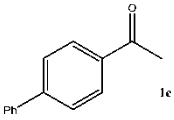
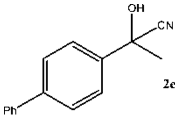
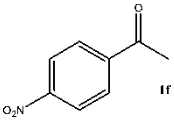
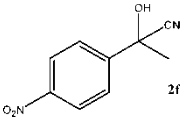
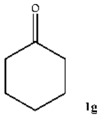
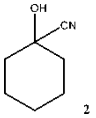
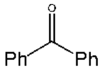
Identification of cyanohydrins was carried out by their spectroscopic analyses as well as by comparing their properties to those reported. Each product exhibited the characteristic IR signals at 2237–2247 and 3375–3442 cm^{-1} for the -CN and -OH groups respectively. Absence of the -CO-stretching bands indicate that the starting material was consumed in each case. The ^{1}H NMR spectra showed broad singlet peaks at 2.96–3.5 ppm attributed to the OH group which disappeared with D_2O exchange, as well as the characteristic singlet peaks at 1.87–1.93 ppm for the methyl group. In addition, ^{13}CNMR of **2f**, for example, showed two characteristic peaks at 120.5 and 69.97, corresponding to CN and C-2 respectively.[11]

In contrast to the electronic factor, which seems to have no observable effect on the reaction path, it seems that the steric factor is so important in this reaction that actually no reaction was observed with the sterically hindered ketones. Stirring a mixture of benzophenone in acetonitrile even in the presence of an excess of TCS/KCN under gentle reflux conditions for a relatively long time led to the recovery of the starting material after usual



Scheme 1.

Table 1. Cyanation of ketones with $SiCl_4$/KCN

Entry	Substrate	Time (h)	Product	Yield[a] (%)
1	 1a	5	 2a	82
2	 1b	6	 2b	79
3	 1c	7	 2c	77
4	 1d	5		86
5	 1e	6	 2e	95
6	 1f	14	 2f	91
7	 1g	6	 2	68
8	 1h	22	none	—

[a]Isolated yield.

aqueous workup (entry 8). On the other hand, the TCS/KCN system is highly reactive toward alicyclic ketones. For example, the reaction of TCS/KCN with cyclohexanone under the same conditions led to the formation of respective cyanohydrin in relatively good yield (entry 7, Table 1).

In contrast to the substrate sensitivity of HCN–carbonyl addition reactions, the addition of the present reagent to ketones is a general and high-yield process. Apparently this is a consequence of the alteration in the ΔH for the carbonyl addition reaction when changing from proton to silicon. From thermodynamic calculations of the bond energy values of Si-CN and H-C, it was suggested that the addition of silyl cyanides to carbonyl groups should be energetically more favorable than the corresponding addition reactions of HCN ($\Delta H_{Si}-\Delta H_H$ value of −31 to −41 Kcal/mol).[12] A plausible mechanism for the present reaction may agree with that depicted in Scheme 2.

In conclusion, we have developed TCS/KCN (in situ trichlorosilyl cyanide) as a new reagent for the cyanation of ketones in high yields without the need for further catalyst. It is relatively cheap compared with TMSCN, and it is safer comparable to the volatile and highly toxic HCN. Moreover, it does not involve equilibrating conditions.

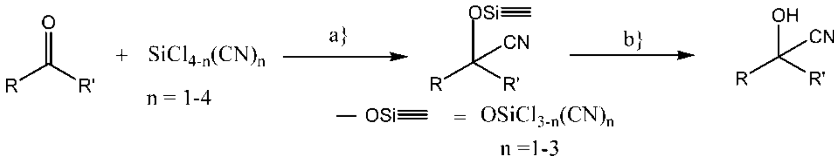
EXPERIMENTAL

General

Melting points were recorded using a Griffin capillary Melt-Temp apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Varian +300 spectrometer; chemical shifts (δ) are in ppm relative to TMS, and coupling constants (J) are in Hertz. TCS was used as obtained from Aldrich. Acetonitrile was dried by refluxing over P_2O_5 followed by distillation. All reactions were monitored by thin-layer chromatography (TLC) carried out on 0.2-mm silica-gel aluminum sheets Merck, (60 F-254) using UV light and heat for visualization. Merck silica gel 60 F-245 (230–400 mesh) was used for column chromatography.

General Procedure for Synthesis of Cyanohydrins

TCS (1.2 mL, 10 mmol) was added under anhydrous conditions to a mixture of ketone (5 mmol) and KCN (1.3 g, 10 mmol) in 15 mL of acetonitrile. The



Scheme 2. Regents and conditions: a) MeCN, 60–70°C and b) aq. $NAHCO_3$.

mixture was stirred under gentle heating (60–70°C) until TLC showed the disappearance of the starting material. The reaction mixture was allowed to cool to room temperature, quenched with a cold $NaHCO_3$ solution, and extracted with 2 × 50 mL of diethyl ether. The combined ether was washed with water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure. The crude products were purified either by recrystallization from pet. ether (**2b–d**) or from pet. ether–diethyl ether (3:1) (**2e**,**f**) or by column chromatography using a mixture of pet. ether–ethyl acetate (10:1) for **2a**,**g**.

Data

Acetophenone cyanohydrin (2a): Yield 82%; TLC; $R_f = 0.34$ (pet. ether–ethyl acetate = 6:1); IR (neat) $\upsilon = 3420$ (-OH), 2243 (CN); ^1H NMR ($CDCl_3$) δ 7.86 (d, $J = 8$ Hz, 2H, Ar-H,), 7.55 (t, 2H, Ar-H), 7.44 (t, 1H, Ar-H), 3.22 (br s, 1H, -OH), 1.89 (s, 3H, CH_3).

4-Chloroacetophenone cyanohydrin (2b): Yield 79%; mp 90–91°C (lit.[3b] 91.5–92.5°C); TLC; $R_f = 0.35$ (pet. ether–ethyl acetate = 6:1); IR (KBr, cm^{-1}) 3381 (-OH), 2247 (CN); ^1H NMR ($CDCl_3$) δ 7.51 (d, $J = 8.4$ Hz, 2H, Ar-H), 7.39 (d, $J = 8.4$ Hz, 2H, Ar-H), 3.26 (br s, 1H, -OH), 1.87 (s, 3H, CH_3).

4-Bromoacetophenone cyanohydrin (2c): Yield 77%; mp 96–98°C (the compound is mentioned in the literature[13] but no data are available); TLC; $R_f = 0.34$ (pet. ether–ethyl acetate = 6:1); IR (KBr, cm^{-1}) 3383 (-OH), 2249 (CN); ^1H NMR ($CDCl_3$) δ 7.65 (d, $J = 8.2$ Hz, 2H, Ar-H), 7.32 (d, $J = 8.2$ Hz, 2H, Ar-H), 3.22 (br s, 1H, -OH), 1.90 (s, 3H, CH_3).

4-Methylacetophenone cyanohydrin (2d): Yield 86%; mp 78–80°C (lit.[3b] 79.5–80°C); TLC; $R_f = 0.38$ (pet. ether–ethyl acetate = 6:1); IR (KBr, cm^{-1}) 3383 (-OH), 2249 (CN); ^1H NMR ($CDCl_3$) δ 7.47 (d, $J = 7.8$ Hz, 2H, Ar-H), 7.23 (d, $J = 7.8$ Hz, 2H, Ar-H), 2.96 (s, 1H, -OH), 2.39 (s, 3H, Ar-CH_3), 1.91 (s, 3H, CH_3).

4-Acetylbiphenyl cyanohydrin (2e): Yield 95%; mp 136°C (the compound is mentioned in the literature[2b] but no data are available); TLC; $R_f = 0.35$ (pet. ether–ethyl acetate = 6:1); IR (KBr, cm^{-1}) 3408 (-OH), 2242 (CN); ^1H NMR ($CDCl_3$) δ 7.55–7.52 (m, 4H, Ar-H), 7.41–7.23 (m, 5H, Ar-H), 3.17 (br s, 1H, -OH), 1.92 (s, 3H, CH_3).

4-Nitroacetophenone cyanohydrin (2f): Yield 91%; mp 114°C (lit.[3b] 112–113°C); TLC; $R_f = 0.33$ (pet. ether–ethyl acetate = 3:1); IR (KBr, cm^{-1}) 3375 (-OH), 2247 (CN), 1522, 1347 (-NO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.29

(d, $J = 9$ Hz, 2H, Ar-H), 7.79 (d, $J = 9.3$ Hz, 2H, Ar-H), 3.5 (brs, 1H, -OH) exchanged with D_2O, 1.93 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 148.23, 147.16, 125.74, 124.19, 120.5 (CN), 69.97 (C-2), 31.43 (CH_3).

Cyclohexanone cyanohydrin (2g): Yield 68%; mp 32–33°C (lit.[14] 35°C); IR (neat, cm^{-1}) 3590 (-OH), 2943, 2864 (CH), 2240 (-CN), 1450, 1345, 1158, 1094, 977, 932.

ACKNOWLEDGMENT

We are indebted to M. A. Ismail for NMR spectroscopic assistance.

REFERENCES

1. (a) Gregory, R. J. H. Cyanohydrins in nature and the laboratory: Biology, preparations, and synthetic applications. *Chem. Rev.* **1999**, *99*, 3649–3682; (b) Brunel, J.-M.; Holmes, I. P. Chemically catalyzed asymmetric cyanohydrin syntheses. *Angew. Chem. Int. Ed.* **2004**, *43*, 2752–2778.
2. (a) Mowry, D. T. The preparation of nitriles. *Chem. Rev.* **1948**, *42*, 189–283; (b) Ananthakrishnanadar, P.; Kannan, N. Equilibria in cyanohydrin formation from, and the kinetic of reduction by sodium borohydride of, substituted acetylbiphenyls. *J. Chem. Soc., Perkin Trans 2* **1980**, 749–751.
3. (a) Evans, D. A.; Truesdale, L. K. Carbonyl insertion reactions of silicon pseudohalides: Catalysis. *Tetrahedron Lett.* **1973**, 4929–4932; (b) Gassman, P. G.; Talley, J. J. Cyanohydrins: A general synthesis. *Tetrahedron Lett.* **1978**, 3773–2776; (c) Yang, Y.; Wang, D. The addition of trimethylsilyl cyanide to carbonyl compounds using $Yb(OTf)_3$ as Lewis acid catalyst. *Synlett.* **1997**, 1379–1380; (d) Saravanan, P.; Ananad, R. V.; Singh, V. K. Cu(OTf)2 catalyzed trimethylsilyl cyanide addition to carbonyl compounds. *Tetrahedron Lett.* **1998**, *39*, 3823–3824.
4. Tian, S.-K.; Hong, R.; Deng, L. Catalytic asymmetric cyanosilylation of ketones by chiral Lewis base. *J. Am. Chem. Soc.* **2003**, *125*, 9900–9901.
5. (a) Kurono, N.; Yamagushi, M.; Suzuki, K.; Ohkuma, T. Lithium chloride: An active and simple catalyst for cyanosilylation of aldehydes and ketones. *J. Org. Chem.* **2005**, *70*, 6530–6532; (b) Iwanami, K.; Aoyagi, M.; Oriyama, T. An efficient and facile one-pot synthesis of cyanohydrin esters from carbonyl compounds catalyzed by iron(III) chloride. *Tetrahedron Lett.* **2005**, *46*, 7487–7490; (c) Kim, S. S.; Rajagobal, G.; Song, D. H. Mild and efficient silylcyanation of ketones catalyzed by cesium fluoride. *J. Organomet. Chem.* **2004**, *689*, 1734–1738.
6. (a) Trost, B. M.; Martinez-Sanchez, S. Enantioselective synthesis of cyanohydrins by a novel aluminium catalyst. *Synlett* **2005**, *4*, 627–630; (b) Shan, Y.; Feng, X.; Li, Y.; Zhang, G.; Jiang, Y. Asymmetric cyanosilylation of ketones catalyzed by bifunctional chiral N-oxide titanium complex catalysts. *Eur. J. Org. Chem.* **2003**, 129–137.
7. (a) Song, J. J.; Gallou, F.; Reeves, J. T.; Tan, Z.; Yee, N. K.; Senanayake, C. H. Activation of TMSCN by N-heterocyclic carbenes for facile cyanosilylation of

carbonyl compounds. *J. Org. Chem.* **2006**, *71*, 1273–1276; (b) Fetterly, B. M.; Verkade, J. G. P($RNCH_2CH_2$)N: Efficient catalysts for cyanosilylation of aldehydes and ketones. *Tetrahedron Lett.* **2005**, *46*, 8061–8066; (c) Wang, L.; Huang, X.; Jiang, J.; Liu, X.; Feng, X. Catalytic cyanosilylation of ketones using organic catalyst 1,1,3,3-tetramethylguanidine. *Tetrahedron Lett.* **2006**, *47*, 1581–1584.

8. (a) Manju, K.; Trehan, S. Uncatalysed trimetrhylsilyl cyanide addition to aldehydes. *J. Chem. Soc. Perkin Trans. 1* **1995**, 2383–2384; (b) Watahiki, T.; Obha, S.; Oriyama, T. Cyanobenzoylation and hydrocyanation of aldehydes with benzoyl cyanide using no catalyst. *Org. Lett.* **2003**, *5*, 2679–2681; (c) Iwanami, K.; Hinakubo, Y.; Oriyama, T. Catalyst-free DMSO-promoted synthesis of cyanohydrin carbonates from aldehydes. *Tetrahedron Lett.* **2005**, *46*, 5881–5883.
9. (a) Salama, T. A.; Elmorsy, S. S.; Khalil, A. M. Tandem reductive coupling–rearrangement of ketones utilizing tetrachlorosilane-zinc reagent under mild conditions. *Proc. Ischia Advanced School of Organic Chemistry, Napoli, Italy, September 18-23,* **2004**, 102; (b) Salama, T. A.; El-Ahl, A. S.; Khalil, A. M.; Girges, M. M.; Lackner, B.; Steindl, C.; Elmorsy, S. S. Convenient synthesis of conjugated tetrazole derivatives via reaction of dienones with tetrachlorosilane–sodium azide reagent and their NMR structure assignment Monatsh. *Chem.* **2003**, *134*, 1241–1252; (c) El-Ahl, Al.-A. S. A novel uncatalyzed insertion reaction of in situ formed trichlorosilyl cyanide with imines: A facile silicon mediated synthesis of α-aminonitriles. *Synth Commun.* **2003**, *33*, 989–998; (d) Elmorsy, S. S.; Khalil, A. M.; Girges, M. M.; Salama, T. A. New routes for synthesis of branched functionalized benzenoid compounds by using tetrachlorosilane-ethanol reagent. *Tetrahedron Lett.* **1997**, *38*, 1071–1074.
10. (a) Denmark, S. E.; Fan, Y. Catalytic enantioselective α -additions of isocyanides: Lewis base catalyzed Passerini-type reactions. *J. Org. Chem.* **2005**, *70*, 9667–9676; (b) Denmark, S. E.; Beutner, G. L.; Wynn, T.; Eastgate, M. D. Lewis base activation of Lewis acids: Catalytic, enantioselective addition of silyl ketene acetals to aldehydes. *J. Am. Chem. Soc.* **2005**, *127*, 3774–3789; (c) Acocella, M. R.; De Rosa, M.; Massa, A.; Palombi, L.; Villano, R.; Scettri, A. Silicon tetrachloride in organic synthesis: New applications for the vinylogous aldol reaction. *Tetrahedron* **2005**, *61*, 4091–4097; (d) Tokouka, E.; Kotani, S.; Matsunaga, H.; Ishizuka, T.; Hashimoto, S.; Nakajima, M. Asymmetric ring opening of meso-epoxides catalyzed by the chiral phosphine oxide BINAPO. *Tetrahedron Asymmetry* **2005**, *16*, 2391–2392.
11. Agami, C.; Fadlallah, M. Stereochimie-LVIII: Condensation du cyanure de trimethylsilyle sur les enones. Cyanohydrines α,β-ethyleniques. *Tetrahedron* **1983**, *39*, 777–779.
12. Evans, D. A.; Carroll, G. L.; Truesdale, L. K. Synthetic applications of trimethylsilyl cyanide: an efficient synthesis of β-aminomethyl alcohols. *J. Org. Chem.* **1974**, *39*, 914, and references cited therein.
13. Nerdel, F.; Rachel, H. Die synthese von Mandlsaeure-analogen, II-Mitteil.: Ueber Styrylglikolsaeuren Chem. Ber **1956**, *89*, 671–675.
14. Frank, R. L.; Berry, R. E.; Shotwell, O. L. The synthesis of phellandral. *J. Am. Chem. Soc.* **1949**, *71*, 3889–3893.