Monatsh Chem (2012) 143:461–465
DOI 10.1007/s00706-011-0613-4

ORIGINAL PAPER

A single-step, mild, neutral, catalyst-free method for cyanohydrin synthesis

Mariam S. Degani · Manoj D. Kakwani · Nutan H. Palsule Desai · Ranjeet Bairwa

Received: 12 July 2010 / Accepted: 5 August 2011 / Published online: 26 August 2011

Abstract A wide variety of carbonyl compounds can be transformed to their corresponding cyanohydrins in a single step using a dimethyl sulfoxide (DMSO)–water system in excellent yields (75–94%). The major advantages of this system are that the reaction conditions are mild and neutral; the reaction proceeds without catalyst and gives the corresponding cyanohydrins in short time (15–120 min).

Keywords Carbonyl compounds · Ketones · Aldehydes · TMSCN · K_2CO_3 · DMSO

Introduction

Cyanohydrins are versatile intermediates which can be easily transformed into a wide variety of valuable compounds, such as α-amino acids, α-hydroxy acids, β-amino alcohols, vicinal diols, and α-hydroxy ketones that are useful as pharmaceuticals, agrochemicals, and insecticides [1, 2].

Cyanohydrins are usually synthesized by interaction of a carbonyl compound with a nucleophilic cyanide source. Several valuable cyanation reagents have been reported in the literature [3, 4]. Amongst them, trimethylsilyl cyanide (TMSCN) seems to be one of the most effective and comparatively safer sources for nucleophilic addition of cyanide to carbonyl compound as compared with sodium cyanide (NaCN) or potassium cyanide (KCN). However, the initial product obtained with TMSCN is the cyanohydrin trimethylsilyl ether, which needs to be cleaved further to the corresponding cyanohydrin using acid such as hydrochloric acid, trifluoroacetic acid, etc. [5].

Catalysts such as metal ligand complexes, polymer-supported metal catalysts, Lewis acids, ionic bases, ionic liquids, earth metal salts, N-heterocyclic carbene, etc. in either stoichiometric or catalytic amounts have been used to catalyze cyanation of carbonyl compounds [6–13]. Besides, an in situ generated catalytic system consisting of a Lewis acid and *N*,*N*-dimethylaniline *N*-oxide [14] has also been used for generation of cyanohydrins using TMSCN. Catalytic cyanosilylation of ketones with phosphonium salt [15] and potassium carbonate (K_2CO_3) in dimethyl formamide (DMF) [16] is also reported. Most of these procedures have drawbacks such as harsh reaction conditions, tedious methods for work-up, and toxic or expensive catalysts. Reaction between TMSCN and carbonyl compounds without catalyst has not been reported.

In continuation of our interest in process chemistry, using various techniques including microwave-assisted reactions and ionic liquids as solvents [17–20], we have successfully developed a simple, catalyst-free, one-step, environmentally benign synthetic protocol for cyanohydrin formation from carbonyl compounds.

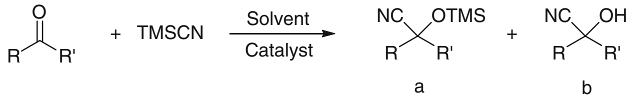
Results and discussion

While synthesizing novel intermediates useful in focused small-molecule library synthesis, we had attempted the reaction using a reported method, i.e., K_2CO_3 in DMF [16], to catalyze addition of TMSCN to carbonyl compounds to

---

Electronic supplementary material The online version of this article (doi:10.1007/s00706-011-0613-4) contains supplementary material, which is available to authorized users.

M. S. Degani (✉) · M. D. Kakwani · N. H. Palsule Desai · R. Bairwa
Department of Pharmaceutical Sciences and Technology, Institute of Chemical Technology, Mumbai, India
e-mail: ms.degani@ictmumbai.edu.in



Scheme 1

Table 1 Effect of solvent on reaction

Entry	Solvent	Catalyst	Yield/%[a]	
			Trimethylsilyl ether (**a**)	Cyanohydrin (**b**)
1	DMF	K_2CO_3	90	–
2	DMF–water	K_2CO_3	25	63
3	DMSO	K_2CO_3	25	–
4	DMSO–water	K_2CO_3	20	60
5	Water	K_2CO_3	–	–
6	DMSO–water	None	–	95
7	Water	None	–	–
8	DMSO	None	95	–

give trimethylsilyl ether, which could be further converted to the corresponding cyanohydrin using acid such as hydrochloric acid, trifluoroacetic acid, etc. However the acidic reaction conditions could not be tolerated by substrates having acid-labile functional groups. Hence, to make the reaction applicable to such compounds, a mild, neutral, one-step synthetic methodology would be valuable.

In this work, efforts have been directed to develop a simple synthetic methodology for one-step cyanohydrin formation in a mild and neutral reaction environment (Scheme 1).

Effects of different solvents on cyanohydrin formation were studied. A set of reactions (listed in Table 1) were attempted to optimize a suitable dipolar aprotic solvent in conjunction with K_2CO_3, which was reported as a catalyst earlier. It is observed that addition of water in small quantity to the DMF–K_2CO_3 system resulted in conversion of the intermediate trimethylsilyl ether to cyanohydrins. This was also observed in the case of the dimethyl sulfoxide (DMSO)–K_2CO_3 system (Table 1, entry 4). Water alone as a solvent did not generate the desired product, probably due to insolubility of substrates. To understand the role of K_2CO_3, a reaction was attempted without it. However, surprisingly, the DMSO–water system without any other catalyst resulted in direct conversion of carbonyl substrate to cyanohydrin in excellent yields.

Carbonyl compounds with diverse functional groups were converted to their corresponding cyanohydrins using the newly developed DMSO–water system with TMSCN, and results are listed in Table 2.

This DMSO–water system was applicable to a wide range of carbonyl compounds with excellent yields. The reactions were monitored by thin-layer chromatography (TLC) for completion, and the products were isolated and further confirmed by spectral analysis. The data illustrated in Table 2 demonstrate that a variety of acyclic, alicyclic, and aromatic aldehydes as well as ketones may be employed in the DMSO–water system to obtain the corresponding cyanohydrin in 75–95% yields. Among all substrates, cyclohexanone shows the maximum yield and minimum reaction time, i.e., 95% in just 15 min. Bridged cyclic rings such as adamantanone, camphor, etc. require more time. In case of α,β-unsaturated carbonyl compounds, up to 90 min reaction time was required, probably due to the lower temperature used to achieve selectivity at the carbonyl center. Aromatic aldehydes or ketones can also be transformed to the corresponding cyanohydrins using the DMSO–water system. To check the stability of the acid-labile group in the newly developed DMSO–water system, an *N*-BOC protected ketone was subjected to similar reaction conditions. The reaction led to formation of the corresponding cyanohydrin without cleavage of BOC, which is acid labile. Hence it can be concluded that the reaction can also be applicable to compounds containing acid-labile groups.

A plausible mechanism for synthesis of cyanohydrin using TMSCN in the DMSO–water system is illustrated in Scheme 2. This reaction presumably occurs via activation of the trimethylsilyl cyanide by coordination of the DMSO oxygen atom with the silicon atom of TMSCN, leading to the formation of intermediate I. The observation that pH in the DMSO–water system remains at 6–7 throughout the reaction, while if only water is used the pH changes to 2–3 on addition of TMSCN, further indicates that hydrogen cyanide does not form in the DMSO–water system.

The carbonyl substrate forms an intermediate II with this activated trimethylsilyl cyanide complex. In other reported methods [16], intermediate II breaks down to give trimethylsilyl ether III and releases solvent, and trimethylsilyl ether, which are isolated. However, in our process, unlike in the DMF–K_2CO_3 system, intermediate III is neither observed by TLC during the course of reaction nor isolated. Instead, because of water, the complex II breaks down directly to cyanohydrin and trimethylsilyl hydroxide.

In conclusion, the DMSO–water system for cyanohydrin formation in a single step using TMSCN as cyanating agent was developed as a novel methodology with mild and neutral conditions and is applicable to diverse carbonyl compounds. Further, this reaction system works at room temperature without any catalyst or any special activation. The reaction is also applicable to aromatic carbonyl compounds and compounds having acid-labile functionalities. The mild reaction conditions, without catalysts, good

Table 2 List of substrates converted to corresponding cyanohydrins

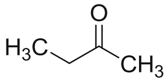
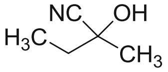
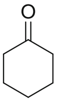
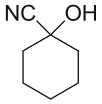
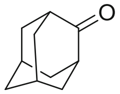
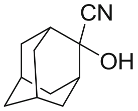
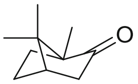
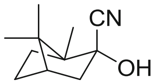
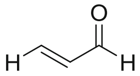
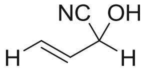
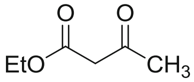
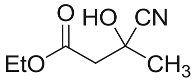
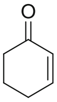
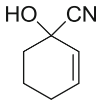
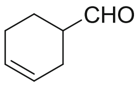
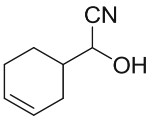
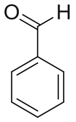
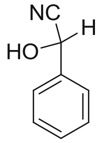
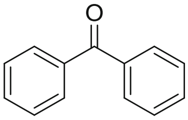
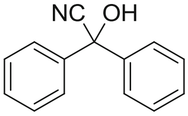
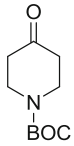
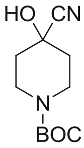
Entry[a]	Substrates	Product	TMSCN[b]/mmol	Time/min	Yield[c]/%	m.p./°C [Lit]
1			1.3	30	85	Oil [21]
2			1.3	15	90	29 [10]
3			1.5	60	93	258 [22]
4			1.5	60	88	193 [23]
5[d]			1.5	30	78	Oil [24]
6			1.3	45	90	Oil [25]
7[d]			1.5	30	93	Oil [26]
8[d]			1.3	30	94	Oil [27]
9			1.5	30	80	Oil [28]

Table 2 continued

Entry[a]	Substrates	Product	TMSCN[b]/mmol	Time/min	Yield[c]/%	m.p./°C [Lit]
10			1.5	40	75	130 [29]
11			1.5	120	75	Oil [30]

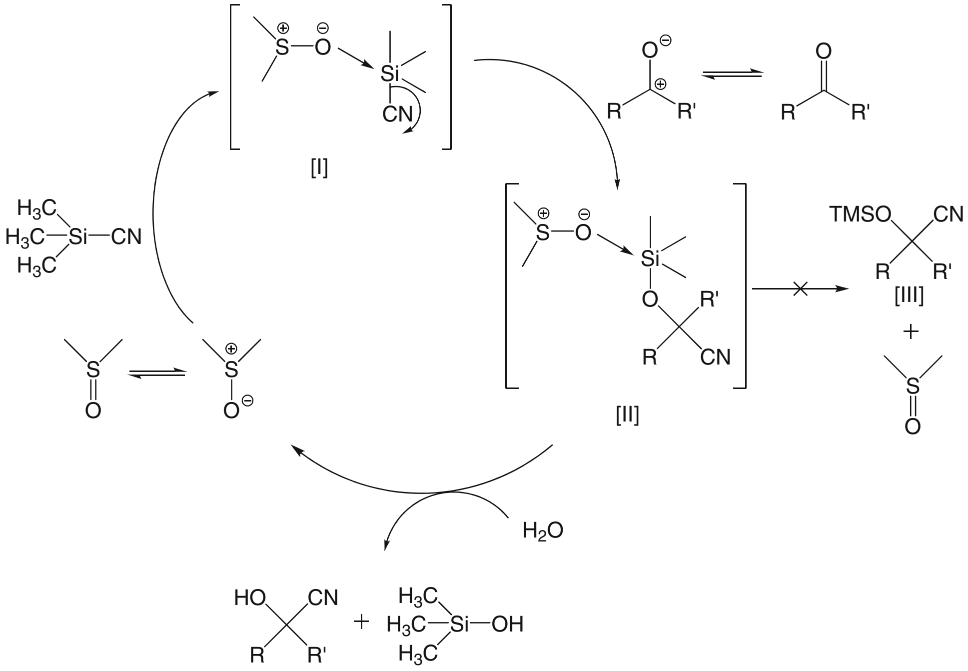
[a] All reactions carried out using DMSO–water system (10:2) at room temperature unless otherwise specified

[b] mmol compared with substrate (1 mmol)

[c] Isolated yield

[d] Reaction carried out at 0–10 °C

Scheme 2



yields, and the simplicity of the procedure make this method attractive for scale-up purpose.

Experimental

Infrared (IR) measurements were done as KBr pellets for solids using a PerkinElmer Spectrum RXI FT-IR. The ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded in DMSO-d_6 and CDCl$_3$ with a JEOL 300-MHz high-resolution NMR spectrometer using tetramethylsilane (TMS) as internal standard. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), multiplet (m), and broad (br). Melting points were determined on Veego VMP-DS melting point apparatus. Analytical TLC was performed on precoated plastic sheets of silica gel G/UV-254 of 0.2 mm thickness (Merck).

Representative general procedure

To a solution of carbonyl compound (0.5 mmol) in 5 cm^3 DMSO–water (5:1 v/v) trimethylsilyl cyanide (0.7 mmol) was added slowly. The reaction mixture was stirred at room temperature. The reaction was monitored by TLC for consumption of starting material. The reaction mixture was extracted with ethyl acetate (2 × 25 cm^3), and the combined layer was washed with water (2 × 10 cm^3) and concentrated in vacuo to obtain a crude mixture. The products were purified from the crude mixture by flash chromatography using silica gel G as stationary phase and petroleum ether:ethylacetate (8:2) as mobile phase.

Acknowledgments The authors N.H.P.D. and R.B. thank UGC, and M.D.K. thanks DBT, New Delhi for their financial support. Authors are grateful to Centaur Pharmaceuticals Pvt. Ltd. for recording NMR spectra.

References

1. Gregory R (1999) Chem Rev 99:3649
2. North M (2003) Tetrahedron Asymmetr 14:147
3. Groutas WC, Felker D (1980) Synthesis 861
4. North M, Usanov DL, Young C (2008) Chem Rev 108:5146
5. Surya KD, Richard AG (2005) J Mol Catal A: Chem 232:123
6. Chen F, Feng X, Jiang Y (2003) Arkivoc (ii):21
7. Cordoba R, Csaky AG, Plumet J (2004) Arkivoc (iv):94
8. Lundgren S, Ihre H, Moberg C (2008) Arkivoc (vi):73
9. Saravanan P, Anand RV, Singh VR (1998) Tetrahedron Lett 39:38
10. Gassman PG, Talley JJ (1978) Tetrahedron Lett 40:3773
11. Jenner G (1999) Tetrahedron Lett 40:491
12. Whitesell JK, Apodaca R (1996) Tetrahedron Lett 37:2525
13. Curini M, Epifanio F, Marcotullio MC, Rosati O, Rossi M (1999) Synlett 315
14. Chen F, Feng X, Qin B, Zhang G, Jiang Y (2003) Synlett 558
15. Wang X, Tian S (2007) Tetrahedron Lett 48:6010
16. Surya Prakash GK, Vaghoo H, Panja C, Surampudi V, Kultyshev R, Mathew T, Olah GA (2007) Proc Natl Acad Sci 104:3026
17. Sharma YO, Degani MS (2009) Green Chem 11:526
18. Sharma YO, Degani MS (2007) J Mol Cat A: Chem 277:215
19. Bag S, Vaze VV, Degani MS (2006) J Chem Res 267
20. Chavan SS, Sharma YO, Degani MS (2009) Green Chem Lett Rev 175
21. Terashima S, Jew S (1977) Tetrahedron Lett 18:1005
22. Berezin GH (1972) US Patent 3 697 593; (1972) Chem Abstr 77:61845
23. Gray G, Toyne K, Lacey D, Holmes D (1992) Eur Pat Appl 333 760 B1
24. Kirsten CN, Herm M, Schrader TH (1997) J Org Chem 62:6882
25. Marco JL, Ingate ST, Chinchon PM (1999) Tetrahedron 55:7625
26. Schmidt M, Herve S (1996) Tetrahedron 5:7833
27. Nanda S, Kato Y (2006) Tetrahedron Asymmetr 17:735
28. Ohno H, Mori A, Inoue S (1993) Chem Lett 22:375
29. Gassman PG, Talley JJ (1990) Organic syntheses collect Vol VII. Wiley, New York, p 20
30. Kiyoshi K, Hiroki S, Chikara U (2006) WO/2006/090279 A1; (2006) Chem Abstr 154:292877