

P(MeNMCH₂CH₂)₃N: an effective catalyst for trimethylsilylcyanation of aldehydes and ketones

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Abstract

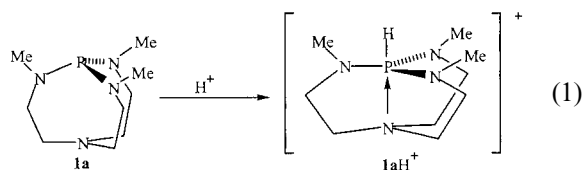
The title non-ionic phosphazane base promotes the trimethylsilylcyanation of aryl and alkyl aldehydes and ketones in moderate to high yields at room temperature. ²⁹Si-NMR spectral evidence for the intermediacy of a phosphazane phosphorus–silicon adduct is presented. © 2002 Published by Elsevier Science B.V.

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1. Introduction

The addition of cyanotrialkylsilanes to carbonyl compounds, and especially the development of catalysts for this transformation, has attracted considerable attention owing to the role of cyanohydrin trialkylsilylethers and cyanohydrins as versatile intermediates in organic synthesis [1]. A variety of catalysts has been developed [2] for such reactions including Lewis acids [3], titanium and ruthenium Schiff base complexes [4], Cu(OTf)₂ [5], 18-crown-6 complexes of potassium and cesium [6], tetracyanoethylene [7], solid acidic montmorillonite, and solid bases such as CaO and MgO [8]. Several optically active catalysts for asymmetric cyanohydrin formation are also effective [9]. Although uncatalyzed cyanohydrations have been reported [10], reactions of ketones with TMSCN under such conditions are extremely sluggish. Kobayashi was the first to report the trimethylsilylcyanation of aldehydes catalyzed by Lewis bases, such as, amines, tributylphosphine, triphenylantimony and triphenylarsine [11]. The reactions were carried out under mild conditions to afford cyanohydrin silylethers in high yield. However, no mention was made of ketones as substrates for this reaction.

The phosphazane **1a**, first synthesized in our laboratories [12], has a p*K*_a of approximately, 33 in acetonitrile [13], and it is easily protonated to trigonal–bipyramidal **1aH**⁺ which is stabilized by three five-membered (Eq. (1)) chelate rings.



Compound **1a** has enjoyed growing utility in recent years in effecting useful transformations for organic synthesis. Thus, it functions as a stoichiometric strong nonionic base in the synthesis of oxazoles [14], pyrroles [14] and α -C-acylamino acids [14], in mono-alkylating active methylene compounds [15], in synthesizing Wittig and Wittig–Horner reaction products [16] and *trans*-epoxides [17], in dehydrohalogenating alkyl halides [18], in making α,β -unsaturated esters [19], 3-substituted coumarins [20], and substituted benzofuran-ethyl-2-carboxylates [21], and in producing somewhat stable and stable sulfur ylides [22]. Non ionic base **1a** also serves as an efficient catalyst or promoter in trimerizing isocyanates to isocyanurates [23], in acylating [24] and de-acylating [25] alcohols, in transesterifying [25] and silylating [26] alcohols, in directly synthesizing α,β -unsaturated nitriles [27], in α,β -dimerizing unsaturated nitriles [28], in synthesizing β -hydroxy nitriles [29] and

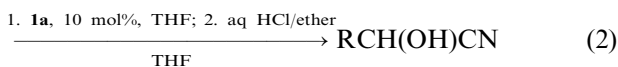
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nitroaldol reaction products [30], in dehydrohalogenating alkyl halides [31], in converting aldoximes to nitriles [32], in reducing aldehydes and ketones with polymethylhydrosiloxane [33], in desilylating silylated ethers [34] and in synthesizing oxazolines [35].

Herein, we report that **1a** is an effective catalyst for the addition of trimethylsilyl cyanide to aldehydes and ketones under mild conditions, giving rise to cyanohydrins and cyanohydrin silyethers, respectively, in moderate to high yields (reactions 2 and 3). When reactions of benzaldehyde or heptaldehyde were carried out with TMSCN in the presence of 10 mol% of **1a** while being monitored by TLC, the conversions were

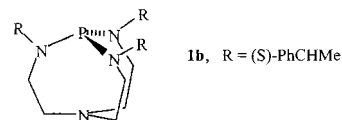
RCHO + TMSCN



found to be complete in 30 min at room temperature. However, the corresponding cyanohydrins were observed together with the cyanohydrin silyethers. Desilylation persisted even when the reaction temperature was decreased to 0 °C. The cyanohydrins were obtained exclusively in high yields by treating the reaction mixture with aqueous HCl. To have an idea of the ratio of silylated to desilylated product formed in these reactions, benzaldehyde was allowed to react with TMSCN under the conditions given in Table 1. However, no aqueous acid was added at the end of the reaction and instead, the volatiles were removed under vacuum in order to secure a sample for ¹H-NMR spectral analysis. It was found that the main product was the cyanohydrin silyl ether (67%), the minor product was the desilylated product mandelonitrile (23%) and the remaining 10% was comprised of unreacted benzaldehyde. The need for **1a** as a promoter was established by carrying out the reaction of benzaldehyde with TMSCN under the conditions given in Table 1 except that **1a** was omitted. No product was detected by ¹H-NMR spectral analysis. Upon allowing the mixture to warm to room temperature and extending the reaction time by an additional 12 h, 8% of the silylated product was detected by ¹H-NMR spectral integration.

The results of the trimethylcyanation of aldehydes are summarized in Table 1. This table shows that *para*-methoxybenzaldehyde also reacts with TMSCN to give the corresponding substituted cyanohydrin in 94% yield. However, aromatic aldehydes bearing electron withdrawing Cl or CN substituents gave low yields of the corresponding cyanohydrins. This result may be associated with a charge transfer interaction between the phosphorus of **1a** and the aromatic aldehyde [36]. Other aldehydes such as naphthaldehyde, furaldehyde and cyclohexanecarboxaldehyde gave the correspond-

ing cyanohydrins in good to excellent yields (83–92%). When the optically active strong base **1b** [37] was employed to promote the cyanohydration of benzaldehyde with TMSCN, the cyanohydrin was isolated in 95% yield but no enantioselectivity was observed.



As shown in Table 2, the reaction of both aromatic and aliphatic ketones (entries 1, 2 and 9) with TMSCN in the presence of **1a** proceeded smoothly at room temperature to give the corresponding cyanohydrin silyethers in moderate to high yields. α,β -Unsaturated ketones (entries 3 and 4) react with TMSCN to give 1,2-addition products regioselectively, and no 1,4-adducts were detected. The reaction of 4-*t*-butylcyclohexanone with TMSCN in the presence of **1a** affords a mixture of axial and equatorial cyanide in a ratio of 84:16. Also worth mentioning are the reactions of TMSCN with the two chiral ketones (–)-menthone and (1R)-(+)-camphor (entries 7 and 8). (–)-Menthone reacted with TMSCN to give the cyanohydrin silyether in 94% yield. However, diastereoselectivity was poor, resulting in a product that was isolated as a mixture of diastereomers (66:34). For the reaction of (1R)-(+)-camphor, the yield was only 33%, but diastereoselectivity was excellent in that only one diastereomer was observed.

The trimethylsilylcyanation intermediate in our reactions is assumed to involve a penta-coordinate silicon formed from **1a** and TMSCN as shown in Scheme 1, analogous to that suggested by Kobayashi for an amine, a phosphine, a stibine, or an arsine ligand [11]. We have adduced evidence that bases of type 1 coordinate to four-coordinate silicon in intermediates formed during trimethylsilyl allylations of aromatic aldehydes (**1c**) [38] and in reductions of aldehydes and ketones with polymethylhydrosiloxane (**1a**) [39]. A wide variety of examples of pentacoordinate silicate species (both stable and unstable) are also known [36,40]. In the case at hand we sought evidence for a hypercoordinate silicon intermediate(s) by examining the ²⁹Si-NMR spectrum of an equimolar mixture of TMSCN and **1a** dissolved in C₆D₆. In addition to a resonance at –12.4 ppm for TMSCN, a peak about half as tall at 7.5 ppm was also observed. We believe that the latter peak is associated with a four-coordinate silicon species in which the cyanide substituent has been displaced. If the lower-field resonance were due to a five-coordinate silicon species, a peak further upfield than –12.4 ppm would have been expected [41]. A ³¹P-NMR spectrum in C₆H₆ of the four-coordinate

silicon species revealed a peak at 72.2 ppm, which is consistent with a four-coordinate phosphorus. The pathway for the trimethylsilylcyanation of aldehydes and ketones shown in Scheme 1 is consistent with the data thus far accumulated. Since six-coordinate silicon species are also well known [40b,42], **A** in Scheme 1 may undergo nucleophilic attack by the carbonyl oxygen of the aldehyde or ketone to give rise to the six-coordinate intermediate **D** shown below. This intermediate may then decompose to product and

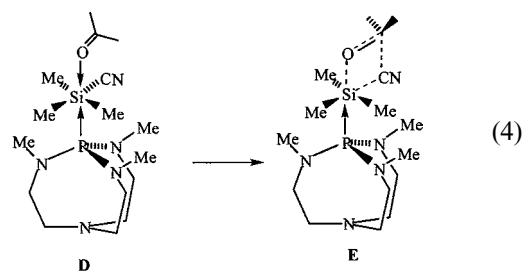


Table 1
The reduction of aldehydes with TMSCN using **1a** as a catalyst^a

entry	aldehyde	reaction condition T (°C)/t (h)	product	yield (%) ^b
1		0/1		92
2		0/1		94
3		rt/0.5		68
4		rt/0.5		59
5		rt/0.5		83
6		0/1		84
7		0/2		90
8		0/1		92
9	CH ₃ (CH ₂) ₅ CHO	rt/0.5	CH ₃ (CH ₂) ₅ CH(CN)OH	95

^a All reactions were conducted under argon. THF was freshly distilled over 4 Å molecular sieves.

^b Isolated yields are based on the aldehyde.

Table 2
The reduction of ketones with TMSCN using **1a** as a promoter^a

entry	ketones	product	yield (%) ^b
1			94
2			91
3			86
4			54 ^c
5			88
6			89 (84:16) ^{d,e}
7			94 (66:34) ^f
8			33 ^c
9			90 ^d

^a All reactions were conducted at room temperature for 1 h under argon unless stated otherwise. THF was freshly distilled from Na and stored over 4 Å molecular sieves.

^b Isolated yields are based on the ketone.

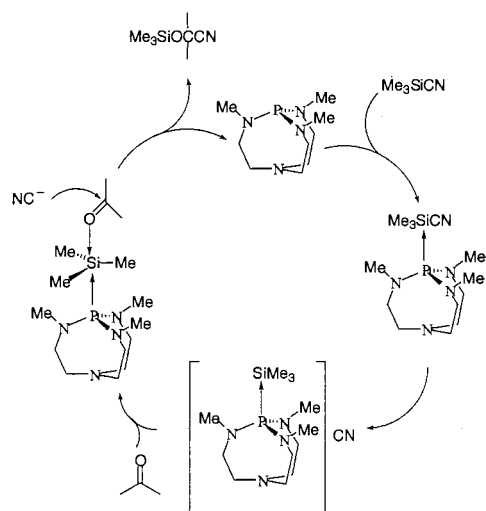
^c Reaction time was 5 h. ^d Reaction time was 0.5 h.

^e The diastereomeric ratio was determined by ¹³C-NMR spectroscopic integration.

regenerated catalyst **1a** via the 4-center intermediate depicted in **E**. Of course, a combination of both pathways is also possible. The lack of enantioselectivity mentioned earlier for the reaction of benzaldehyde with TMSCN in the presence of optically active **1b** may at least in part be ascribed to the distance of the carbonyl of the substrate from the optically active environment in the intermediates **C–E**. Efforts to further elucidate the mechanism of this reaction and to broaden its scope with other aminophosphine bases are underway.

2. Experimental

A typical procedure for reaction of aldehydes with TMSCN follows. To a solution of **1a** (0.15 mmol) in THF (2.0 ml) was added TMSCN (1.8 mmol) at 0 °C, followed by addition of the aldehyde (1.5 mmol). After the reaction conditions stated in Table 1 had been met, an aqueous solution of HCl (1M, 5 ml) and ether (20 ml) was added and the mixture was then stirred at room temperature for another 1 h. The phases were separated and the water layer was washed with ether



Scheme 1.

(3 × 20 ml). The organic layers were combined, washed with brine (2 × 20 ml) and then dried over MgSO₄. The solvent was removed with a rotary evaporator and then under reduced pressure on a vacuum line to give the crude product which was purified by flash chromatography (hexane:ethyl acetate = 10:1) to give the cyanohydrin.

A typical procedure for the reaction of ketones with TMSCN follows. To a solution of **1a** (0.15 mmol) in THF (2.0 ml) was added TMSCN (1.8 mmol) at room temperature, followed by addition of the ketone (1.5 mmol). After the reaction conditions stated in Table 2 had been met, the solvent was removed under reduced pressure on a vacuum line to give the crude product which was purified by flash chromatography (hexane:ethyl acetate = 100:1) to give the cyanohydrin silylether.

Acknowledgements

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