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Tetrahedron Letters 46 (2005) 8061–8066
Tetrahedron Letters

P(RNCH$_2$CH$_2$)N: efficient catalysts for the cyanosilylation of aldehydes and ketones

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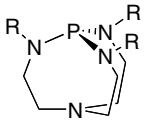
Received 3 August 2005; revised 7 September 2005; accepted 7 September 2005
Available online 30 September 2005

Abstract—The 1,2-addition of trialkylsilylcyanides to aldehydes and ketones produces the corresponding protected cyanohydrins in good to excellent yields when carried out at 0 °C to room temperature in the presence of catalytic amounts of the nonionic strong base P(RNCH$_2$CH$_2$)N (R = Me, *i*-Pr) in THF. These catalysts are easily removed from the product by hydrolysis or column filtration through silica gel.

1. Introduction

Cyanohydrins and cyanohydrin trialkylsilylethers are versatile intermediates in organic synthesis.[1] It is therefore no surprise that many catalysts have been developed for the reaction of trimethylsilylcyanide (TMSCN) with aldehydes and ketones.[2] Because trimethylsilyl groups are easily removed under a variety of reaction conditions,[3] bulkier trialkylsilylcyanides such as *tert*-butyldimethylsilyl cyanide (TBSCN) or *tert*-butyldiphenylsilyl cyanide (TBDPSCN) are advantageous. TBS or TBDPS-protected alcohols possess two of the most popular silyl protecting groups currently used and are approximately 10^4 times more resistant to hydrolysis than the corresponding TMS-protected alcohol.[3] Such protected alcohols are also stable to a variety of organic transformations carried out on other functional groups in the molecule, and these bulkier silyl groups are also easily removed by a variety of methods.[3] Despite the usefulness of TBS and TBDPS-protected cyanohydrins, a one step conversion to this functionality from aldehydes and ketones is still rare.[4]

We have previously reported the synthesis of exceedingly strong nonionic bases **1a**[5] and **1b**[6] whose conjugate acids have pK_a's of 32.90 and 33.63, respectively.[7] Bases of this type have been shown to catalyze a variety of organic reactions.[8] Here, we report improvements to a procedure previously published by our group.[9] The previous procedure involved the use of 10 mol % of **1a** to afford products in moderate to excellent yields at room temperature. We now show that the use of **1b** gives yields that are not only better in most cases than those previously published, but also require lower catalyst loading.



1a R = Me
1b R = *i*-Pr
1c R = *i*-Bu

After testing a series of trisaminophosphines (Table 1), we concluded that base **1b** is the optimal catalyst for reactions of the type shown in this table, providing an appropriate balance of basicity and steric bulk. As in our previous work with **1a**, we still observed desilylation after work-up when the reactions were performed with aldehydes in the presence of **1b** (Table 2). However, this table also shows that the low yields previously associated with the use of aromatic aldehydes bearing electron withdrawing groups were greatly improved using catalyst **1b** instead of **1a** (entries 3 and 4). In our previous work, it was suggested on the basis of analogy with a mechanism proposed in the previous literature that

Keywords: Proazaphosphatrane; Aldehyde; Ketone; Trimethylsilylcyanide; Cyanohydrin.
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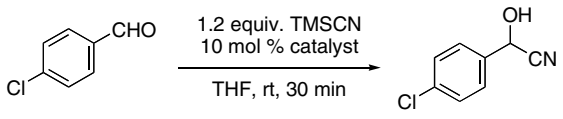
0040-4039/$ - see front matter © 2005 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2005.09.032

Table 1. Screening of trisaminophosphines



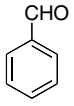
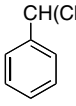
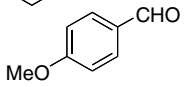
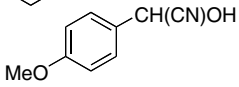
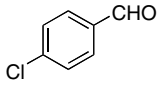
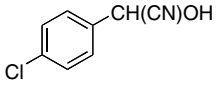
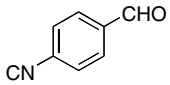
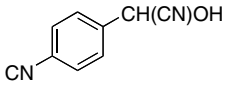
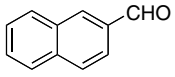
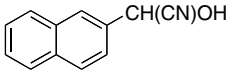
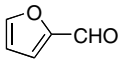
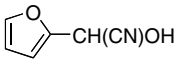
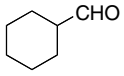
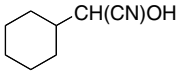
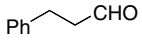
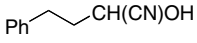
Catalyst	Yield (%)
$(Me_2N)_3P$	0
$(i\text{-}Bu_2N)_3P$	50
$EtC(CH_2N\text{-}i\text{-}Bu)_3P$[a]	25
1b	99
1c	15

[a] Ref. 13.

trimethylsilylation proceeds via Lewis base activation of silicon by the phosphorus of **1a**.[9] It may be that the EWG on the phenyl ring results in a more electropositive carbonyl oxygen which requires a more electron rich silicon for the formation of a higher concentration of a more robust activated species.[10] Such a species would be provided by the more basic **1b**, even though this catalyst is more bulky than **1a**. In this regard, too much bulk may be the reason that **1c** gives rise to a poor yield in the screening reaction in Table 1. Other aldehydes, such as furfural, hydrocinnamaldehyde, and heptaldehyde, gave the corresponding cyanohydrins in very good to excellent yields (89–99%). As shown in Table 2, yields in the reactions catalyzed by **1b** meet or exceed those obtained when **1a** is used as a catalyst and are better than those found in the literature in seven out of the nine reactions studied in the present work.

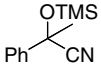
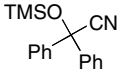
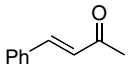
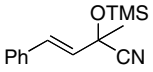
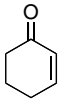
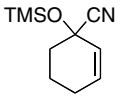
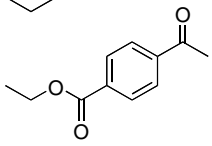
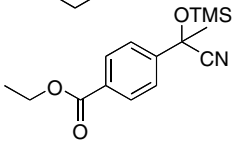
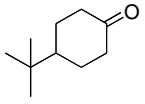
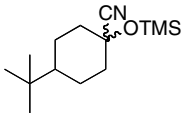
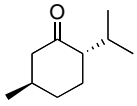
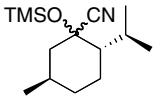
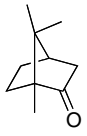
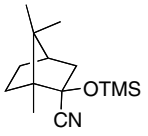
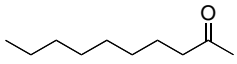
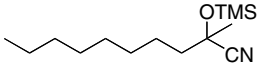
The results of the trimethylsilylcyanation of ketones in the presence of **1b** are shown in Table 3. Ketones of

Table 2. The reaction of aldehydes with TMSCN using **1b** as a catalyst[a]

Entry	Aldehyde	Reaction condition T (°C)/t (h)/catalyst (mol %)	Product	Yield (%)	Yield w/**1a** (%)	Lit. yield (%)
1		0/1/1		97[b]	92	62–99[d,e,f]
2		0/1/3		98	94	60–92[g,h,i j,k,l]
3		rt/0.5/5		99[c]	68	60–85[d,g]
4		rt/0.5/3		97	59	60[j,k]
5		rt/0.5/3		99	83	76–88[g,i,j,k]
6		0/1/3		89	84	79–86[d,f,h]
7		0/2/3		99	90	70–86[d,j,k,l]
8		0/1/3		98	92	85–97[f,j,k]
9	$CH_3(CH_2)_5CHO$	rt/0.5/3	$CH_3(CH_2)_5CH(CN)OH$	95	95	62–99[f,i]

[a] 3 mol % catalyst was used unless stated otherwise.
[b] 1 mol % catalyst was used.
[c] 5 mol % catalyst was used.
[d] Ref. 14.
[e] Ref. 15.
[f] Ref. 16.
[g] Ref. 17.
[h] Ref. 18.
[i] Ref. 19.
[j] Ref. 20.
[k] Ref. 21.
[l] Ref. 22.

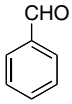
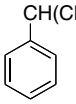
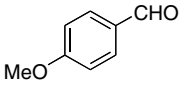
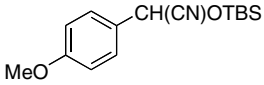
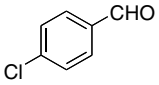
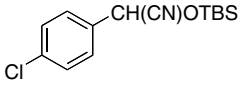
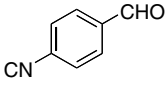
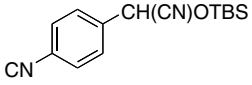
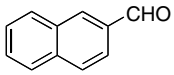
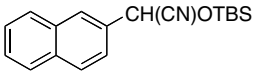
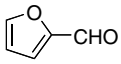
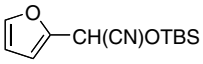
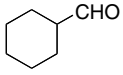
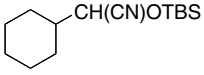
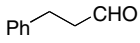
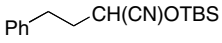
Table 3. The reaction of ketones with TMSCN using **1b** as a catalyst[a]

Entry	Ketone	Product	Yield (%)	Yield w/**1a** (%)	Lit. yield (%)
1			90	94	50–99[g,h,i,j,k,l,m]
2			87[e]	91	61–98[h,i,j,n]
3			99	86	97[j,o]
4[b]			99	54	
5			99	88	
6[c]			85 (79:21)[d]	89	86–99[l,p]
7			99 (53:47)[d]	94	
8[b]			26[f]	33	68–95[j,l]
9[c]			99	90	

[a] All reactions were conducted for 1 h with 3 mol % catalyst unless stated otherwise.
[b] Reaction time was 5 h.
[c] Reaction time was 0.5 h.
[d] The diastereomeric ratio was determined by ^{13}C NMR spectroscopic integration.
[e] 5 mol % catalyst was used.
[f] 10 mol % catalyst was used.
[g] Ref. 23.
[h] Ref. 2a.
[i] Ref. 24.
[j] Ref. 25.
[k] Ref. 26.
[l] Ref. 2b.
[m] Ref. 27.
[n] Ref. 28.
[o] Ref. 29.
[p] Ref. 30.

various types react smoothly with TMSCN to afford the corresponding products in good to excellent yields. α,β-Unsaturated ketones (entries 3 and 4) react solely in the 1,2 mode, and no Michael addition products were detected. Interestingly, (−)-menthone affords an excellent yield of product, but with no diastereoselectivity (entry 7). (1*R*)-(+)-Camphor, on the other hand (entry 8), was found to afford only the diastereomeric product shown,[11] but the overall yield for this reaction was only 26% at a 10 mol % catalyst loading. Our yields in the reactions catalyzed by **1b** (Table 3) were improved in five of the nine cases studied compared with the yields obtained when **1a** was used as a catalyst. A comparison of literature yields found for five reactions in Table 3 reveals that our yields obtained with **1b** exceed those in the literature in only one case, with camphor again showing very disappointing results for reasons that may be steric in origin.

Table 4. The reaction of aldehydes with TBSCN using **1b** as a catalyst[a]

Entry	Aldehyde	Reaction condition T (°C)/t (h)	Product	Yield (%)	Lit. yield (%)
1		0/1		99	98[4c]
2		0/1		99	
3		rt/0.5		99	
4		rt/0.5		99	
5		rt/0.5		99	
6		0/1		99	95[4c]
7		0/2		99	
8		0/1		99	
9	$CH_3(CH_2)_5CHO$	rt/0.5	$CH_3(CH_2)_5CH(CN)OTBS$	99	

[a] 3 mol % catalyst was used.

Because products obtained from the reaction of aldehydes and ketones with TMSCN are easily hydrolyzed by adventitious water, we decided to use TBSCN, which affords a product that is less sensitive to hydrolysis.[3] Although we found earlier[12] that both **1a** and **1b** catalyze the hydrolysis of TBS ethers, those reactions employ longer times and higher temperatures than those required herein. Under our conditions, no desilylation products were found in the reactions of TBSCN with aldehydes (Table 4). Furthermore, the reactions proceeded much more cleanly than those in which TMSCN was used. Our yields shown in this table are uniformly nearly quantitative and exceed those reported for the two cases found in the literature.

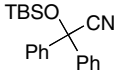
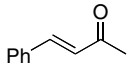
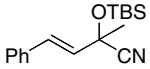
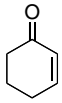
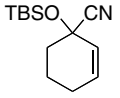
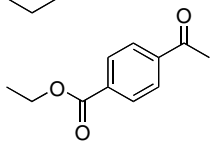
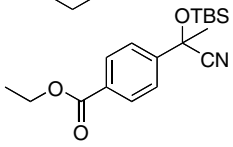
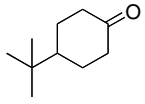
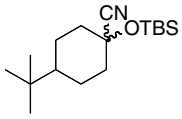
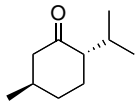
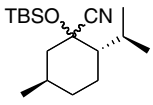
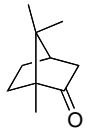
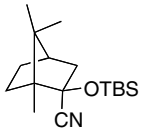
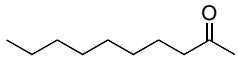
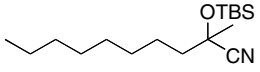
The results of the reactions of TBSCN with ketones are shown in Table 5. Acetophenone (entry 1) requires 7 mol % of catalyst **1b** to obtain the near-quantitative product yield realized with 3 mol % of catalyst for seven other ketones. Also noteworthy is the nearly twofold increase in yield in the reaction of (1*R*)-(+)-camphor with TBSCN compared with TMSCN, again with no loss of diastereoselectivity. Using TBSCN instead of TMSCN in the reaction of (−)-menthone, on the other hand, provided no significant increase in diastereoselectivity. Our yields in the reactions catalyzed by **1b**, as shown in Table 5, exceed those found in the literature in two cases, but with camphor as a substrate (entry 8) a yield was realized, which is significantly below the range reported.

In summary, although other methods are known for cyanosilylating aldehydes and ketones, they either involve lengthy reaction times or the use of a Lewis acid or crown ether/KCN as a catalyst.[9] Herein, a wide range of aldehydes and ketones have been shown to undergo trialkylsilylcyanation in generally excellent yield, with the use of the proazaphosphatrane **1b**. Aryl aldehydes and ketones react cleanly under mild conditions, tolerating many different types of functional groups. The catalyst is easily removed by filtration through a pad of silica gel, affording NMR-pure products in a substantial number of cases. Catalyst **1b** is also a generally superior catalyst for the *t*-butyldimethylsilylcyanation of aldehydes and ketones.

2. Typical procedure for reaction of aldehydes with TMSCN

In this and subsequent typical procedures, all reactions were carried out in an argon atmosphere, and THF was freshly distilled from Na and stored over 4 Å molecular sieves. To a solution of TMSCN (1.8 mmol) and an aldehyde (1.5 mmol) in THF (2.0 mL) was added (commercially available from Aldrich and Strem) **1b** (1–

Table 5. The reaction of ketones with TBSCN using **1b** as a catalyst[a]

Entry	Ketone	Product	Yield (%)	Lit. yield (%)
1			99[e]	86[4b]
2			99	
3			98	83[4b]
4[b]			99	
5			99	
6[c]			99 (63:37)[d]	
7			99 (61:39)[d]	
8[b]			42[f]	91–94[4a,b]
9[c]			99	

[a] All reactions were conducted for 1 h with 3 mol % catalyst unless stated otherwise.
[b] Reaction time was 5 h.
[c] Reaction time was 0.5 h.
[d] The diastereomeric ratio was determined by ^{13}C NMR spectroscopic integration.
[e] 7 mol % catalyst was used.
[f] 10 mol % catalyst was used.

5 mol % of aldehyde, as specified in Table 2) at 0 °C. After the reaction conditions stated in Table 2 had been met, an aqueous solution of HCl (1 M, 5 mL) and ether (20 mL) was added and the mixture was stirred at room temperature for another hour. The phases were separated and the water layer was washed with brine (2 × 20 mL) and dried over $MgSO_4$. The solvent was removed with a rotary evaporator to give the crude product, which was purified by flash chromatography (hexane–ethyl acetate = 10:1) to give cyanohydrin.

3. Typical procedure for the reaction of ketones with TMSCN

To a solution of TMSCN (1.8 mmol) and a ketone (1.5 mmol) in THF (2.0 mL) was added **1b** (3–10 mol % as specified in Table 3) at room temperature. After the reaction conditions stated in Table 3 had been met, the reaction mixture was loaded onto a small silica gel column for elution (ether–methanol = 20:1). Removal of the solvent from the eluate under reduced pressure afforded the crude product which was purified by flash chromatography (hexane–ethyl acetate = 100:1) to give the cyanohydrin silyl ether.

4. Typical procedure for the reaction of aldehydes and ketones with TBSCN

To a solution of TBSCN (1.8 mmol) and an aldehyde or ketone (1.5 mmol) in THF (2.0 mL) was added **1b** (3–10 mol % of aldehyde or ketone, as specified in Tables 4 and 5) at 0 °C. After the reaction conditions in Tables

4 and 5 had been met, the reaction mixture was loaded onto a small silica gel column for elution (ether–methanol = 20:1). Removal of the solvent from the eluate under reduced pressure afforded the crude product which was purified when necessary by flash chromatography (hexane–ethyl acetate = 100:1) to give the cyanohydrin silyl ether.

Acknowledgements

The authors are grateful to the Petroleum Research Fund administered by the American Chemical Society, for Grant support of this research.

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