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Catalytic cyanosilylation of ketones using organic catalyst 1,1,3,3-tetramethylguanidine

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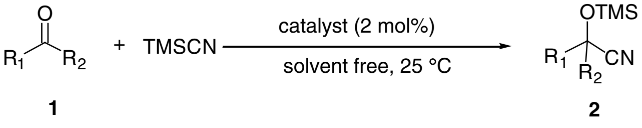
Abstract—1,1,3,3-Tetramethylguanidine acts as a highly effective catalyst for cyanosilylation of various ketones and aldehydes to the corresponding cyanohydrin trimethylsilyl ethers in up to 99% yield. The reaction proceeds smoothly with 0.1 mol % catalyst loading at 25 °C under solvent-free conditions.

Guanidines can be classified as organic bases, like amines and amidines, which are regarded as the strongest organic bases[1] due to the resonance stability of their conjugated acids.[2] As a strong organic base catalyst, 1,1,3,3-tetramethylguanidine (TMG) has been used for C–C bond formation,[3–5] for instance Michael addition[4] and aldol condensation.[5] Some applications of modified guanidines to asymmetric synthesis as chiral bases can also be found in the literature.[6–10]

Cyanosilylation of ketones is one of the most powerful procedure for the synthesis of cyanohydrins, which can be readily converted to various important building blocks.[11] Many catalysts have been used to promote the cyanosilylation.[12] For example, acidic catalysts,[13] inorganic solid bases,[14] solubilized anionic species,[15] neutral metal compounds,[16] as well as diamino functionalized polymers,[17] and inorganic/organic salts.[18] Recently, many chiral catalysts have been successfully applied to this reaction.[19,20] Amine has been employed for the cyanosilylation of aldehyde,[21] however it did not work well for ketones. We consider that guanidines with stronger basicity may both activate TMSCN and catalyze the cyanosilylation of ketones.

Initially, several organic bases were examined with acetophenone as a model substrate (Scheme 1). As shown in Table 1, the effect of catalysts was related to the basicity of these organic bases. The stronger the basicity of catalyst used, the better the yield obtained. Guanidines and DBU catalysts could achieve good to excellent yields (Table 1, entries 9–11). N,N,N',N'-tetramethylethylenediamine (Table 1, entry 7) and DMAP (Table 1, entry 8) could also catalyze cyanosilylation of ketones with



Scheme 1. Cyanosilylation of ketones.

Table 1. Optimization catalyst[a]

Entry	Catalyst	Yield (%)[b]
1	Pyridine	N.R.
2	2,6-Dimethylpyridine	N.R.
3	N,N-Dimethylaniline	N.R.
4	$\mathrm{Et_2NH}$	N.R.
5	$\mathrm{Et_3N}$	5
6	$\mathrm{Pr^{\mathit{i}}_2NEt}$	15
7	N,N,N',N'-Tetramethylethylenediamine	48
8	DMAP	44
9	DBU	77
10	1,3-Diphenylguanidine	94
11	1,1,3,3-Tetramethylguanidine	99
12	2-Benzoyl-1,1,3,3-tetramethylguanidine	49

[a] Reactions were carried out on a 0.4 mmol scale with 1.2 equiv of TMSCN and 2 mol % catalyst loading at 25 °C in 8.5 h under solvent-free condition without stirring.

[b] Isolated yield.

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moderate yields. On the other hand, tertiary amines such as Et_3N, Pr^i_2NEt were detected to have catalytic effect on this reaction with poor yields (Table 1, entries 5 and 6). When pyrrolidine, Et_2NH and other alkalescent amines (Table 1, entries 1–4) were employed as catalysts, no reaction was observed. In addition, when 2-benzoyl-1,1,3,3-tetramethylguanidine was used, an obvious decrease of the yield was observed compared with TMG catalyst. This might be due to the decrease of the basicity comparing with tetramethylguanidine (Table 1, entry 12).

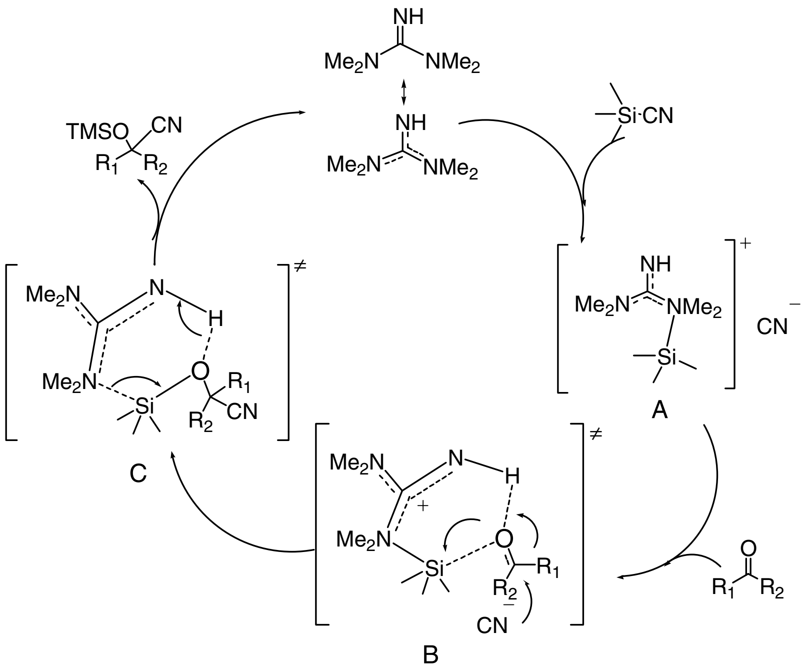
A mechanism of the cyanosilylation of ketones catalyzed by TMG was proposed (Scheme 2). In this reaction, electrophilic silicon atom was activated by a catalytic amount of TMG. The TMG could be converted to reactive, but resonance-stabilized, guanidinium salt **A** by quarternization with TMSCN (when TMSCN and TMG were mixed, colorless crystal was formed).[22] The key intermediate **A** readily reacted with ketone, via six-membered ring transition states **B** and **C**, to give the corresponding cyanohydrin trimethylsilyl ether along with TMG.

The catalytic system was applicable for a wide range of carbonyl compounds with excellent yield. The results are summarized in Table 2.

The data illustrated in Table 2 demonstrates that a variety of aryl and alkyl ketones may be employed in the TMG-catalyzed process and give the corresponding trimethylsilyl ethers in 90–99% yields. Ketones bearing electron-donating groups such as Me– or MeO– (Table 2, entries 6 and 7), were more active than those with electron-withdrawing groups (Table 2, entries 8–12). The reaction with aliphatic ketones afforded the corresponding products in very good yields in shorter time compared with aromatic and heterocyclic ketones (Table 2, entries 18 and 19). The reactions may also be performed with lower catalyst loading (0.1 mol %) by prolonging the reaction time (Table 2, entry 5).

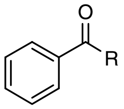
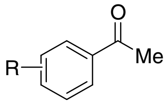
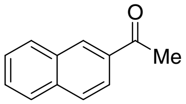
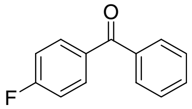
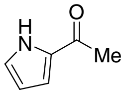
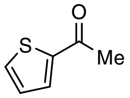
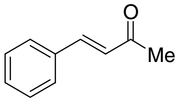
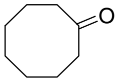
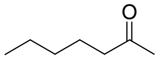
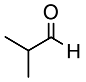
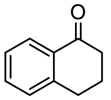
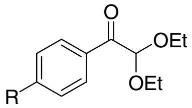
Although TMG was optimized for the reaction of ketones, it was also found to be an efficient catalyst for the cyanosilylation of aldehydes. Thus, both benzaldehyde and isobutylaldehyde underwent cyanosilylation with TMG (0.1 mol %) within 4 h in 99% yields (Table 2, entries 1 and 20). Less catalyst loading required longer reaction time. The reaction can be carried out by simply keeping the reaction mixture in a vial to stand in a 25 °C water bath without stirring. Enlarging the reaction scale to 10 mmol without stirring did not affect the cyanosilylation rate (Table 2, entry 3). After the first run, colorless crystal guanidinium salt **A**, which was considered to be a stable catalytic intermediate, was obtained by filtration. It can be used directly for the second run (Table 2, entry 4) with nearly the same activities (up to 99% yield within 8.5 h).

In summary, we have identified a readily available organic catalyst that effectively promoted the cyanosilylation of carbonyl compounds with low catalyst loading under mild conditions. This guanidine-catalyzed reaction may contribute to the development of green chemistry because of its possible application in solvent-free condition. Moreover, it provided a feasible direction of the asymmetric reaction by using the chiral guanidine. Chiral guanidine-catalyzed enantioselective cyanosilylation of carbonyl compounds is currently under investigation.



Scheme 2. Proposed mechanism of the cyanosilylation of ketones catalyzed by TMG.

Table 2. Cyanosilylation of ketones catalyzed by 1,1,3,3-tetramethylguanidine[a]

Entry	Carbonyl compounds			Time (h)	Yield[b] (%)
1[c]		R = H	**1a**	4	99
2		R = Me	**1b**	8.5	99
3[d]		R = Me	**1b**	8.5	99
4[e]		R = Me	**1b**	8.5	99
5[c]		R = Me	**1b**	13	99
6		R = *p*-Me	**1c**	10	97
7		R = *p*-OMe	**1d**	10	98
8		R = *p*-Cl	**1e**	10	91
9		R = *p*-F	**1f**	15	90
10		R = *o*-F	**1g**	15	99
11		R = *p*-NO_2	**1h**	15	98
12		R = *m*-NO_2	**1i**	15	95
13			**1j**	10	99
14			**1k**	10	99
15			**1l**	13	93
16			**1m**	11	98
17			**1n**	11.5	97
18			**1o**	5	95
19			**1p**	5	95
20[c]			**1q**	4	99
21			**1r**	5	95
22		R = H	**1s**	4	98
23		R = OMe	**1t**	4	99

[a] Reactions were carried out on a 0.4 mmol scale with 1.2 equiv of TMSCN and 2 mol % catalyst loading at 25 °C, with solvent-free condition without stirring.

[b] Isolated yield.

[c] The reaction was carried out with 0.1 mol % catalyst loading.

[d] Reactions were carried out on a 10 mmol scale with 1.2 equiv of TMSCN at 25 °C, with solvent-free condition without stirring.

[e] Recycling experiment was examined with 2 mol % catalyst loading under the same condition.

Acknowledgments

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22. IR spectra shows that when TMSCN and TMG was mixed, the N–H and C=N peak of TMG were shifted from 3334.0 and 1596 cm^{-1} to 3282 and 1562 cm^{-1}, respectively.