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N-Heterocyclic carbene-catalyzed cyanomethylation of aldehydes with TMSAN

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ABSTRACT

N-Heterocyclic carbenes (NHCs) have been served as efficient catalysts for cyanomethylation of carbonyl compounds. In the presence of 5 mol % NHC, various aldehydes and 2,2,2-trifluoroacetophenone reacted with trimethylsilylacetonitrile (TMSAN) to give β-hydroxynitriles in moderate to high yields.

β-Hydroxynitriles are useful building blocks for the synthesis of β-hydroxycarboxylic acids and their derivatives, γ-amino alcohols as well as other important functionalities.[1] Typically, the addition of acetonitrile to carbonyl compounds under the assistance of strong alkali metal base is the most straightforward method to prepare β-hydroxynitriles.[2] However, the reversibility of the reaction and the facile dehydration of β-hydroxynitriles usually give the desired products in unsatisfactory yields.[3] To overcome the above problems, great efforts have been made to improve the reaction yields.[4] Among them, the commercially available trimethylsilylacetonitrile (TMSAN) was found to be a valid alternative nucleophile for the cyanomethylation, it is considered that the formation of the *O*-silyl ether inhibits the reversibility and therefore, high yields can be obtained.[5] Several fluorides such as TASF,[6] KF,[7] CuF,[8] and alkali-metal acetate[9] have been utilized successfully to promote the reaction. Strong basic proazaphosphatrane[5] and tris (2,4,6-trimethoxyphenyl) phosphine (TTMPP),[10] are also used as highly efficient organocatalysts to mediate the addition reaction. However, catalytic methods for cyanomethylation reaction are still scarce and efficiently organocatalytic approach for the preparation of β-hydroxynitriles is extremely desirable.

As an important type of organocatalysts, N-Heterocyclic carbenes (NHCs)[11] have attracted considerable attention in recent years. We and others have illustrated the remarkable ability of NHCs to activate the silylated reagents in a series of important transformations, such as trifluoromethylation reaction,[12] cyanation reaction,[13] Mukaiyama aldol reaction,[14] Pudovik type reaction,[15] and other reactions.[16] In this Letter, we would like to disclose our preliminary results on NHCs-catalyzed addition of TMSAN with carbonyl compounds, giving β-hydroxynitriles in high yields.

At the onset of this study, the reaction of TMSAN and *p*-chlorobenzaldehyde was selected as a model and various NHCs were examined. When 1,3-bis (2,6-diisopropylphenyl) imidazol-2-ylidene (IPr)[17] was employed, the addition proceeded smoothly in tetrahydrofuran and afforded β-hydroxynitrile in 72% isolated yield (Table 1, entry 1). NHC generated from imidazolium salt 2 and different bases, can also catalyze the reaction efficiently (Table 1, entries 2–4). Whereas NHCs generated from precursors 3 or 4 promoted the addition in low efficiency (Table 1, entries 5–7). To our surprise, NHC generated from triazolium salt 5 did not catalyze the reaction at all (Table 1, entry 8). Other reaction media, such as toluene, DCM, ether, dichloroethane, acetonitrile, DMSO, and DMF were also surveyed and the results indicated that DMF was the best choice with respect to yield (Table 1, entries 9–15).[18] Lowered the catalyst loading to 5 mol %, higher yield was obtained (Table 1, entry 16). However, further decreased the catalyst loading to 1 mol % led to a dramatic decrease of the yield (Table 1, entry 17). And finally, control experiment showed that the reaction cannot occur in the absence of NHC catalyst (Table 1, entry 18).

After the optimal reaction conditions were established (DMF, 5 mol % IPr), the generality of the cyanomethylation was evaluated and the results were summarized in Table 2. Both aromatic and aliphatic aldehydes were suitable electrophiles. For aromatic aldehydes, substitution of an electron-withdrawing group on the aromatic ring resulted in higher yield than those bearing electron-donating groups (Table 2, entries 1–6). However, strong

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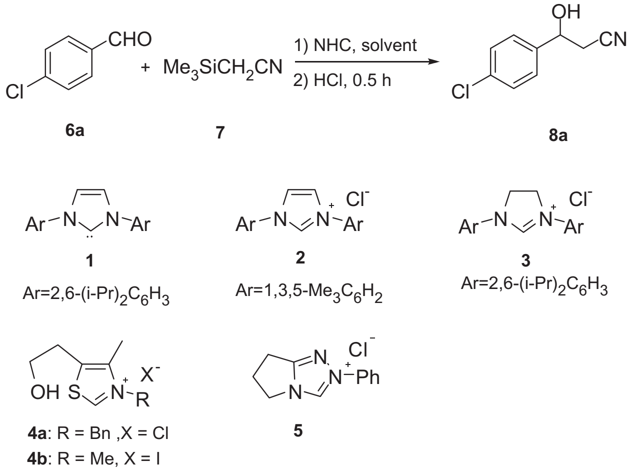
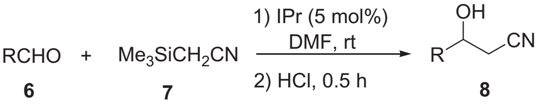
Table 1
NHCs catalyzed cyanomethylation of *p*-chlorobenzaldehyde with TMSAN[a]

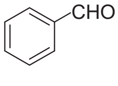
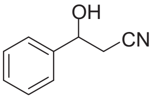
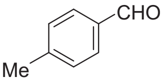
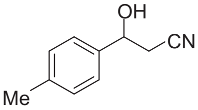
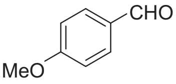
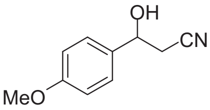
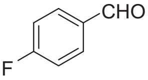
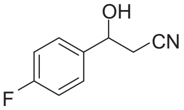
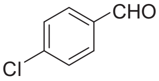
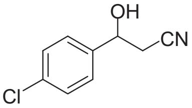
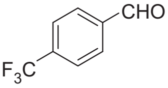
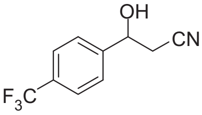
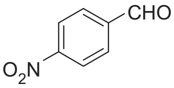
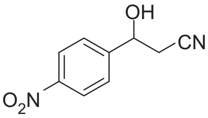
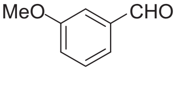
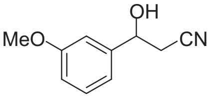
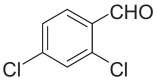
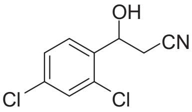
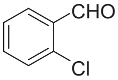
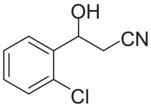
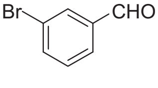
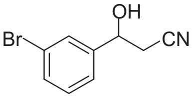
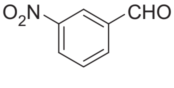
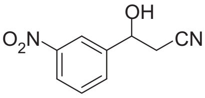
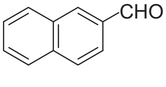
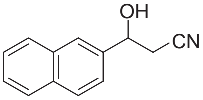
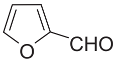
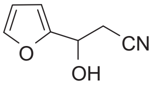
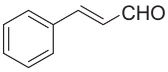
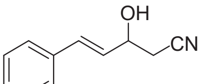
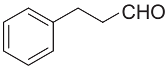
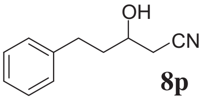
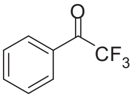
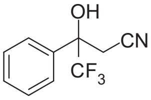


Entry	NHC	Solvent	Time (h)	Yield (%)[b]
1	1, (10 mol %)	THF	20	72
2[c]	2, KOt-Bu (10 mol %)	THF	20	70
3[c]	2, Cs_2CO_3 (10 mol %)	THF	20	44
4[c]	2, DBU (10 mol %)	THF	20	66
5[c]	3, KOt-Bu (10 mol %)	THF	20	33
6[c]	4a, KOt-Bu (10 mol %)	THF	20	6
7[c]	4b, KOt-Bu (10 mol %)	THF	20	16
8	5, KOt-Bu (10 mol %)	THF	20	NR
9	1, (10 mol %)	Toluene	20	42
10	1, (10 mol %)	DCM	20	73
11	1, (10 mol %)	Et_2O	20	49
12	1, (10 mol %)	DMF	20	76
13	1, (10 mol %)	DCE	20	52
14	1, (10 mol %)	CH_3CN	30	14
15	1, (10 mol %)	DMSO	30	72
16	**1, (5** mol %**)**	**DMF**	30	83
17	1, (1 mol %)	DMF	30	53
18	No catalyst	DMF	30	

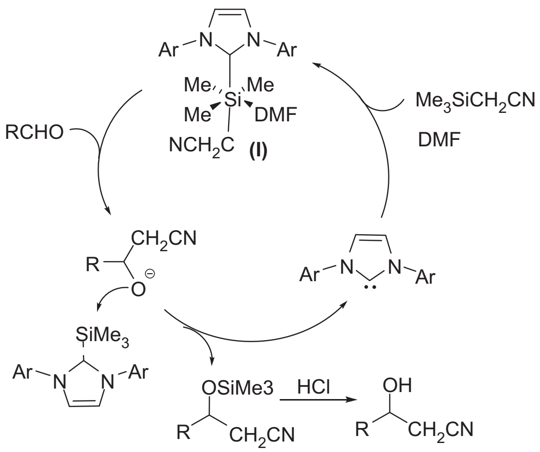
[a] 7 (1.5 equiv), 6a (1.0 equiv), solvent: 2.0 mL rt.
[b] Isolated yields.
[c] Using 12 mol % NHC-precursors and 10 mol % base.

Table 2
NHCs catalyzed cyanomethylation of aldehydes with TMSAN[a]



Entry	Carbonyl compounds	Time (h)	Product	Yield (%)[b]
1		40	 **8a**	70
2		40	 **8b**	61
3[c]		40	 **8c**	66
4		45	 **8d**	84
5		30	 **8e**	83
6		45	 **8f**	80
7[d]		30	 **8g**	65
8		40	 **8h**	80
9		30	 **8i**	76
10		45	 **8j**	65
11		45	 **8k**	82
12		45	 **8l**	71
13		45	 **8m**	68
14[c]		40	 **8n**	63
15		30	 **8o**	63
16		40	 **8p**	65
17		45	 **8q**	89

[a] 7 (1.5 equiv), 6 (1.0 equiv), IPr 5 mol %, solvent: 2.0 mL, rt.
[b] Isolated yields.
[c] Using 10 mol % IPr.
[d] Performed the reaction at −50 °C-rt.



Scheme 1. Proposed mechanism of NHC-catalyzed cyanomethylation of aldehydes.

electron-withdrawing group such as nitro-group, led to low yield (Table 2, entry 7). Additionally, different positions of the substituted group on the aromatic ring were all well tolerated and the desired products were obtained in good to high yields (Table 2, entries 8–12). Interestingly, naphthaldehyde and heteroaromatic aldehyde were also proved to be good candidates for this reaction (Table 2, entries 13, 14). The experiment results indicated that aliphatic aldehydes such as cinnaldehyde and 3-phenylpropionaldehyde were also good reactants, provided alkyl-substituted β-hydroxynitriles in good yields (Table 2, entries 15, 16). It is worthwhile noting that the addition of 2,2,2-trifluoroacetophenone and TMSAN proceeds smoothly to give **8q** in 89% yield, which contains a quaternary carbon center (Table 2, entry 17).

A plausible reaction mechanism was proposed and illustrated in Scheme 1. NHC attacks the silicon atom of TMSAN to form a possible hexavalent silicon intermediate **I** in DMF and thus the Si-C bond was activated, which might trigger the following addition to aldehyde and give the desired β-hydroxynitrile after acidic work up.

In conclusion, we have demonstrated a NHC-promoted cyanomethylation reaction of TMSAN with various aldehydes. The mild conditions, simple procedure provides a valuable approach for the preparation of β-hydroxynitriles. Further exploration and application of this methodology are underway in our laboratory.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.02.080.

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18. It was reported that DMF can coordinate the silicon atom of TMSAN to form hexa-coordinated silicon species, which activated the C-Si bond and led to high yield of the final product. For details see Ref. 10