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Highly turnover number cyanosilylation of carbonyl compounds catalyzed by tetraethylammonium 2-(hydroxycarbamoyl)benzoate as a bifunctional organocatalyst: The role of hydrogen bonding

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Abstract

It was found that tetraethylammonium hydroxide reacts with *N*-hydroxyphthalimide as a nucleophile rather than a base to afford tetraethylammonium 2-(hydroxycarbamoyl)benzoate (TEAHCB). The TEAHCB was found to be able to efficiently catalyze the cyanosilylation of a wide range of carbonyl compounds as a bifunctional organocatalyst at very low catalyst loading (0.2 mol%).

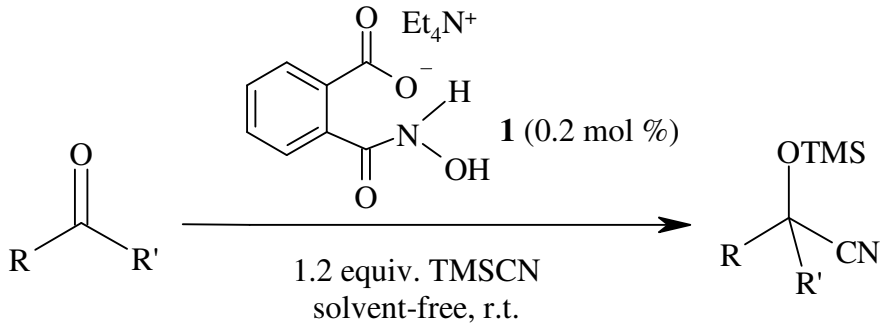
Keywords: Bifunctional organocatalysis; Cyanosilylation; tetraethylammonium (hydroxycarbamoyl)benzoate; Carbonyl compounds; Cyanohydrins; Hydrogen bonding.

1. Introduction

Hydrocyanation and cyanosilylation of carbonyl compounds are among the most important strategies for C–C bond-forming reactions in organic synthesis. The adduct products provide versatile intermediates such as cyanohydrins and cyanohydrin tyrialkylsilyl ethers, respectively. In particular, cyanohydrin trimethylsilyl ethers are industrially valuable and important intermediates for the synthesis of α-hydroxy acids and esters, acyloins, α-amino acids, vicinal diols, β-amino alcohols and other biologically active compounds [1-3]. For instance, cyanosilylation is the key step in manufacturing of Ditropan or its analogues [4], cypermetrin and fluvaliate [5]. Cyanohydrin tyrialkylsilyl ethers are generally prepared by the addition of trimethylsilyl cyanide (TMSCN), a safe and easily handled reagent compared to HCN, NaCN or KCN, to carbonyl compounds [1-3] in the presence of Lewis acid [5-11], Lewis base [12-14] and double activating [2,15-16] or bifunctional [17-20] catalytic systems. Therefore, a large body of work has been devoted to the development of cyanohydrin trimethylsilyl ethers synthesis [1-20]. However, many of these protocols often require heavy or expensive transition metal catalysts, poor yield of the products or prolonged reaction times, inert atmosphere or anhydrous solvents, the use of hygroscopic catalysts, and tedious work-up procedures [5-20]. The majority of these catalytic systems require metallic Lewis acidic species [5-11] which may contain a variety of ligands to enable enantioselective transfer of cyanide to carbonyls [2,15-20]. On the other

hand, organocatalytic protocols have received great attention from both practical and environmental standpoints due to their ability to perform organic reactions in wet solvents or solvent-free conditions under an aerobic atmosphere and to avoid the possibility of metal contamination of the products that may occur with traditional metal catalyst systems [21,22].

Despite of the traditional catalytic systems, cyanosilylation by organocatalysts often proceeds by Lewis basic catalysts which activate TMSCN for cyanide transfer to carbonyl compounds [3,12,23-28]. Hence, the number of methods employing Lewis acidic catalysts, which activates carbonyl compounds in turn, is quiet limited [29]. It should be noted that the most of the above catalytic systems rely on the activation of only one of the reacting species. More recently, bifunctional organocatalysts have received attention for cyanosilylation of carbonyl compounds [30-35]. A number of recent studies have shown that bifunctional and multifunctional catalysts possess special characteristics for both catalysis and asymmetric synthesis. These catalysts must contain at least a Lewis base moiety that activates a nucleophilic substrate and a Lewis acid moiety that activates an electrophilic substrate. The positioning of the two reactive partners in close proximity and with the correct relative geometry by such a catalytic system assembly facilitates a reaction in a manner similar to that of nature's enzymatic processes. Dual coordination by such catalyst assemblies further assists the reaction by simultaneously enhancing the electrophilic character of one partner and the nucleophilic character of the other [20]. In continuation of our interest to develop more efficient organocatalysts for cyanosilylation of carbonyl compounds [25-28,35], we wish herein to report our recent finding on the improved and smooth addition of TMSCN to carbonyl compounds using tetraethylammonium 2-(hydroxycarbamoyl)benzoate (TEAHCB, **1**), as a new bifunctional organocatalyst, under solvent-free conditions (Scheme 1).



R= Aryl, Heteroaryl, Alkenyl, Alkyl
R'= H, Alkyl, Aryl

Scheme 1. Cyanosilylation of carbonyl compounds using tetraethylammonium 2-(hydroxycarbamoyl)benzoate (TEAHCB, **1**).

2. Results and discussion

In a preceding paper, we introduced a novel bifunctional organocatalyst for expeditious synthesis of cyanohydrin trimethylsilyl ethers using tetraethylammonium 2-(carbamoyl)benzoate (TEACB) under solvent-free conditions [35]. The TEACB bifunctional organocatalyst was produced through an unusual pathway upon reaction of phthalimide and tetraethylammonium hydroxide. Indeed, it was found that the hydroxide ion in tetraethylammonium hydroxide (TEAOH) acts as a nucleophile to react with carbonyl groups of the imide moiety rather than a base which in turn prefers abstracting of the more acidic N–H proton. In continuation of this study, we found that although the imide moiety in the structure of *N*-hydroxyphthalimide (NHPI) survived through the reaction with tetrabutylammonium hydroxide (TBAOH) or alkali metal hydroxides [26,27], the situation is considerably altered in the reaction with TEAOH to afford the TEAHCB **1** as a bifunctional organocatalyst.

On the basis of our experience with TEACB-catalyzed cyanide addition reactions with TMSCN [35], we postulated that the TEAHCB can promote the reaction in an analogous fashion. It was found that the best result in terms of turnover number (TON) and turnover frequency (TOF) could be achieved by using catalyst **1** (0.2 mol% loading). It is noteworthy that no reaction was observed in the absence of TEAHCB under similar reaction conditions (entry 4). Therefore, the lower catalyst loading required for this transformation compared to many organocatalytic systems having oxygen as their sole nucleophilic site [12,26-28] and even TEACB [35] embosses the role of hydrogen bonding formed between the (*N*-hydroxycarbamoyl) moiety of the catalyst and carbonyl group of the substrates.

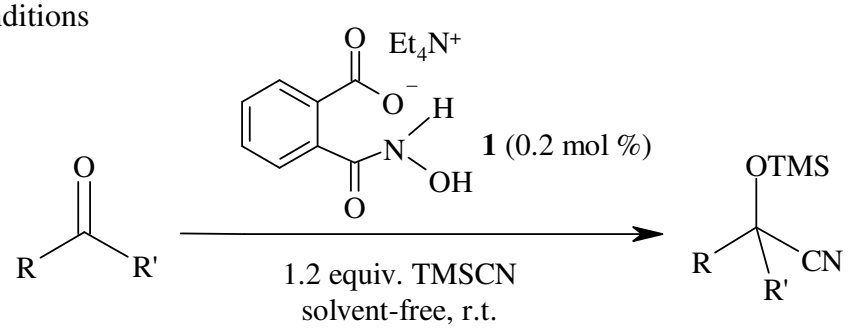
Encouraged by these results, other carbonyl compounds were subjected to cyanosilylation under optimal reaction conditions (TEAHCB; 0.2 mol %, 1.2 equiv of TMSCN, room temperature, solvent-free conditions). Table 1 shows that aromatic, heterocyclic and aliphatic carbonyl compounds have been effectively converted to the corresponding products. The reactions proceed very cleanly at room temperature under mild conditions. After completion of the reaction (monitored by TLC), the catalyst could be easily separated by aqueous extraction from the reaction mixture. Therefore, a simple work-up affords the desired products. In general, the reaction conditions are very mild and high to quantitative yields of the products could be obtained within very short reaction times.

As shown in Table 2, electronic effects and the nature of the substituents on the aromatic ring showed relatively strong effects on the required reaction time for the complete conversion of aldehydes. As a consequence of proposed bifunctional organocatalysis, substrates containing electron-withdrawing groups (Entries 1-3) react much faster than ones bearing electron-donating groups (Entries 5–7). Furthermore, due to the steric bulk, ketones such as acetophenone and cyclohexanone required longer reaction times than aldehydes for completion of their reactions with TMSCN (Entries 10-14) [8,12].

3. Conclusion

We have achieved a catalytic cyanosilylation reaction with broad substrate generality using TEAHCB as a new bifunctional organocatalyst in relatively short reaction time at room temperature. This can be the first example of use of TEAHCB as a bifunctional organocatalyst in organic synthesis. The important features of our method are: mild reaction conditions, very low catalyst loading, simple work-up, wide substrate scope, high to quantitative yield, and simple preparation of the catalyst from inexpensive precursors.

Table 1. Organocatalytic cyanosilylation of various carbonyl compounds by TEAHCB at optimized conditions



2 **3**

Entry	Carbonyl compound (**2**)	Time (min)	Product (**6**)	Conversion (%)
1	4-Chlorobenzaldehyde **(2a)**	8	**3a**	100
2	4-Nitrobenzaldehyde **(2c)**	2	**3c**	100
3	4-Cyanobenzaldehyde **(2e)**	3	**3e**	99
4	Benzaldehyde **(2f)**	10	**3f**	100
5	4-Methylbenzaldehyde **(2g)**	15	**3g**	97
6	4-Methoxylbenzaldehyde **(2i)**	15	**3i**	100
7	Furfural **(2j)**	15	**3j**	99
8	Cinnamaldehyde **(2m)**	15	**3m**	99
9	Octanal **(2o)**	20	**3o**	100
10	diethyl ketone **(2p)**	15	**3p**	98
11	Cyclohexanone **(2r)**	20	**3r**	96
12	Acetophenone **(2s)**	25	**3s**	90
13	4-Nitroacetophenone **(2t)**	20	**3t**	100
14	Benzophenone **(2u)**	30	**3u**	70

[a] TMSCN (3 mmol) was added to a mixture of 4-chlorobenzaldehyde (2.5 mmol) under solvent-free conditions at room temperature except for entry 3 which the reaction was performed on a 5 mmol scale.

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