



## An expeditious synthesis of cyanohydrin trimethylsilyl ethers using tetraethylammonium 2-(carbamoyl)benzoate as a bifunctional organocatalyst

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### ABSTRACT

Phthalimide and tetraethylammonium hydroxide react via an unusual pathway to afford tetraethylammonium 2-(carbamoyl)benzoate (TEACB) which is of interest as a bifunctional organocatalyst. TEACB (0.5 mol %) was found to catalyze the addition of trimethylsilyl cyanide (TMSCN) to carbonyl compounds under solvent-free conditions at room temperature with very short reaction times. A wide variety of aldehydes and ketones were transformed into the corresponding cyanohydrin trimethylsilyl ethers in high to quantitative yields.

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Cyanohydrins are highly versatile synthetic intermediates, which can easily be converted into various important building blocks including  $\alpha$ -hydroxy acids,  $\alpha$ -amino acids,  $\alpha$ -hydroxy aldehydes or ketones,  $\beta$ -amino alcohols, and vicinal diols.<sup>1–5</sup> They are also components of commercially important compounds such as the pyrethroid insecticides, cypermethrin and fluralate.<sup>5</sup> However, the preparation of cyanohydrins by the addition of highly toxic HCN to carbonyl groups is not a straightforward process and the procedure should be undertaken with caution. The other problem which affects the yields of the products originates in the existence of equilibrium conditions between the reactants and the products.<sup>3,5a</sup> To overcome these problems, the reaction of trimethylsilyl cyanide (TMSCN)<sup>6</sup> with carbonyl compounds in the presence of Lewis acid,<sup>7</sup> Lewis base<sup>3,8</sup> and double activating<sup>1c,9</sup> or bifunctional<sup>10</sup> catalytic systems has been described. Since the pioneering works,<sup>11</sup> a plethora of catalysts have been reported in the literature for both racemic and asymmetric addition of TMSCN to aldehydes and ketones.<sup>7–10</sup> The majority of these catalytic systems require metallic Lewis acidic species<sup>7</sup> which may contain a variety of ligands to enable enantioselective transfer of cyanide to carbonyls.<sup>1,4a,b,9,10</sup> On the other hand, the recent organocatalytic protocols are particularly attractive because of the mildness of the reaction conditions, operational simplicity, the potential for the development of large

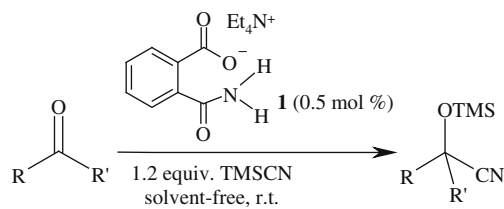
scale or asymmetric versions of the reaction, the ready availability and low toxicity of the organocatalysts.<sup>3,12–20</sup>

In contrast to the traditional catalytic systems, organocatalytic protocols for cyanosilylation of carbonyl compounds have mainly demonstrated their advantages as Lewis basic catalysts;<sup>3,12–21</sup> methods using Lewis acidic catalysts are scarce.<sup>22</sup> More recently, bifunctional organocatalysts have received attention for cyanosilylation of carbonyl compounds.<sup>23–25</sup> It is noteworthy that most of the above catalytic systems rely on the activation of only one of the reacting species. Inspired by the multipoint binding sites of enzymes, attention has recently turned to the development of bi- and poly-functional catalytic systems.<sup>10,22–26</sup> All these developments have advanced significantly the frontier of organocatalytic cyanohydrin synthesis. However, there is still room for improvement, particularly with regard to reaction generality, catalyst simplicity, safer solvents and especially reaction rate. In view of our continuing interest in the use of organocatalysts for efficient cyanosilylation of carbonyl compounds,<sup>13,15</sup> we herein disclose the first application of tetraethylammonium 2-(carbamoyl)benzoate (TEACB, **1**) as an effective bifunctional organocatalyst for this transformation under solvent-free conditions (Scheme 1).

Potassium phthalimide (PPI) has been traditionally used as a suitable nucleophile in the Gabriel synthesis of primary amines.<sup>27</sup> However, it has received less attention as a catalyst in organic synthesis.<sup>28,29</sup> In our previous works, PPI and the sodium salt of saccharin combined with tetrabutylammonium iodide (TBAI) were shown to be effective Lewis basic organocatalysts for the activation of TMSCN in the cyanosilylation of carbonyl compounds<sup>15</sup> or

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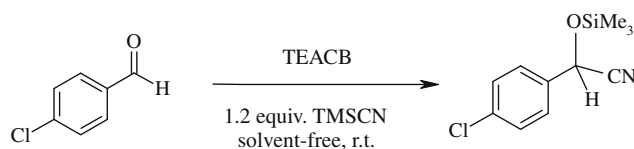
**Scheme 1.** Cyanosilylation of carbonyl compounds catalyzed by TEACB.

cyclotrimerization of isocyanates.<sup>29,30</sup> In continuation of our interest to develop more effective phthalimide-based nucleophilic organocatalysts, we decided to investigate the possibility of using tetraethylammonium phthalimide (TEAPI, **4**) for the addition of TMSCN to carbonyl compounds. Since phthalimide (PI, **2**) has a  $pK_a$  of 8.3, it reacts with different alkali metal hydroxides in EtOH to give the corresponding phthalimide salts.<sup>27</sup> Despite this well-known chemistry, it was observed that TEACB **1** was produced exclusively upon reaction of **2** and tetraethylammonium hydroxide (TEAOH, **3**) in EtOH. Similar results were observed in other solvents such as water and toluene. However, the yield of **1** was significantly improved in water (Scheme 2).<sup>31</sup>

A systematic study on the cyanosilylation of 4-chlorobenzaldehyde, as a model compound, was carried out using different amounts of the bifunctional organocatalyst **1** at room temperature and the results are summarized in Table 1. It was found that the best result in terms of turnover number (TON) and turnover frequency (TOF) could be achieved with a catalyst loading of 0.5 mol % (Table 1, entry 2).<sup>32</sup> Furthermore, the reaction of benzoic acid and TEAOH gave a viscous liquid and no crystals were obtained. Hence, the catalytic activity of combined potassium benzoate and tetraethylammonium iodide (TEAI) was examined under similar reaction conditions to **1**. On the other hand, combination of PPI and TEAI required longer reaction times for complete conversion of 4-chlorobenzaldehyde under similar reaction conditions (entries 4 and 5). Interestingly, no reaction was observed when using benzamide or in the absence of TEACB under similar reaction conditions (entries 7 and 8). Therefore, the low catalyst loading required for this transformation underscores the extraordinary catalytic activity of the bifunctional organocatalyst **1** in activating both silicon-based reagents such as TMSCN<sup>33,34</sup> and carbonyl compounds.<sup>10f,23,24</sup> For example, with the previously introduced organocatalysts, 5 mol % of trisaminophosphine in THF (0.5 h at room temperature),<sup>17</sup> 5 mol % of N-heterocyclic carbenes (NHCs) in THF (2 h at room temperature),<sup>18a</sup> or 2.5 mol % of potassium *p*-toluene-

**Table 1**

Optimization of the TEACB catalyst loading for cyanosilylation of 4-chlorobenzaldehyde<sup>a</sup>



Entry	Mol %	Time (min)	Conversion (%)	TON <sup>b</sup>	TOF <sup>c</sup>
1	1.0	12	95	95	475
2	0.5	15	98	196	784
3	0.25	45	93	372	496
4 <sup>d</sup>	0.5	30	98	196	392
5 <sup>e</sup>	0.5	45	97	194	259
6 <sup>f,15</sup>	2.5	30	96	38.4	76.8
7 <sup>g</sup>	0.5	120	0	0	0
8	—	120	0	0	0

<sup>a</sup> TMSCN (1.2 mmol) was added to a mixture of 4-chlorobenzaldehyde (1.0 mmol) under solvent-free conditions at room temperature.

<sup>b</sup> Turnover number.

<sup>c</sup> Turnover frequency.

<sup>d,e</sup> Potassium benzoate and PPI were used as catalysts, respectively (0.5 mol % of TEAI was used as cocatalyst).

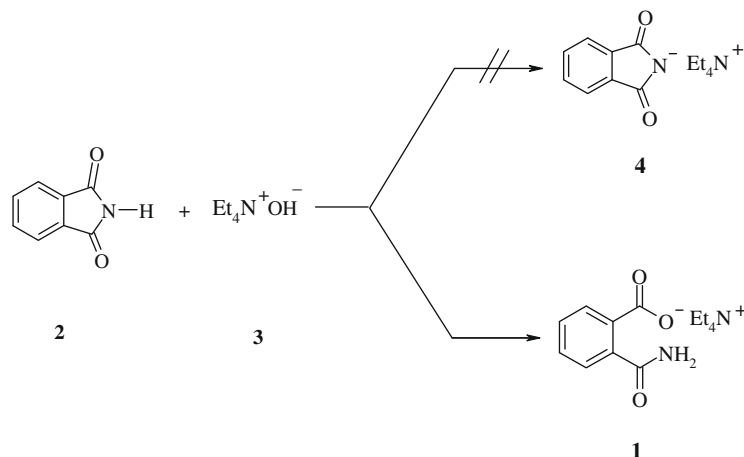
<sup>f</sup> PPI as catalyst.

<sup>g</sup> Benzamide as catalyst.

sulfinate (45 min at room temperature)<sup>13c</sup> were employed to promote cyanosilylation of 4-chlorobenzaldehyde to the corresponding trimethylsilylated cyanohydrin with yields of 80%, 98% and 98%, respectively.

Encouraged by these results, aromatic, heteroaromatic, conjugated and aliphatic aldehydes or ketones were subjected to cyanosilylation under the optimized reaction conditions (TEACB; 0.5 mol %, 1.2 equiv of TMSCN, 25 °C, solvent-free conditions).<sup>32</sup> Table 2 shows the scope of the reaction using a number of representative carbonyl compounds wherein high to quantitative yields of cyanohydrin trimethylsilyl ethers **5** were obtained within short reaction times in all the cases studied (Table 2, entries 1–20).

No by-products such as products of benzoin condensation or desilylation were observed.<sup>17</sup> This protocol tolerated acid-sensitive substrates such as furfural, thiophene-2-carbaldehyde and cinnamaldehyde which can decompose or polymerize under acidic conditions (Table 2, entries 10–12).<sup>7e</sup> Notably, the cyanosilylation of (*E*)-cinnamaldehyde afforded the corresponding 1,2-addition product, exclusively (entry 12). Furthermore, carbonyl compounds



**Scheme 2.** Unusual reaction pathway of phthalimide and tetraethylammonium hydroxide.

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