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Lithium perchlorate/diethylether-catalyzed three-component coupling reactions of aldehydes, hydroxylamines and trimethylsilyl cyanide leading to α -cyanohydroxylamines

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Abstract

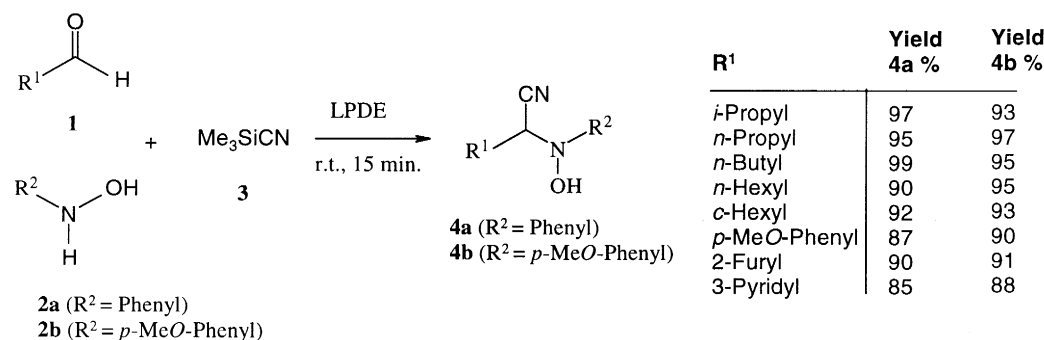
Three-component coupling reactions of aldehydes, hydroxylamines and trimethylsilyl cyanide proceeded smoothly in the presence of lithium perchlorate/diethylether solution (5 M) to afford α -cyanohydroxylamine derivatives in high yields. © 2000 Elsevier Science Ltd. All rights reserved.

We have already reported that lithium perchlorate/diethylether (5.0 M) LPDE is an excellent catalyst for the activation of nitrogen-containing compounds (for example, aldimines).¹ Many Lewis acids are deactivated or sometimes decomposed by nitrogen containing reactants; even when the desired reactions proceed, more than stoichiometric amounts of the Lewis acids are needed because the acids are trapped by nitrogen.² On the other hand, it has been demonstrated that LPDE (1–5 M)³ retains activity in the presence of nitrogen-containing compounds, for example Mannich-type reactions⁴ proceed smoothly in the presence of the LPDE solution.

Nitrones are a particularly interesting class of compounds by virtue of their utility in organic synthesis. They are reactive starting materials in a large number of 1,3-dipolar cycloadditions and can act as electrophiles with a variety of both carbon and heteronucleophiles. Lewis acids are known to promote these reactions. However, some nitrones, especially α -aliphatic nitrones, are unstable under these conditions and low yields are sometimes observed.⁵ It is desirable from a synthetic point of view that nitrones, which are prepared in situ from aldehydes and hydroxylamines, immediately react with nucleophiles. Although a solution of aldehyde **1**, phenylhydroxylamine **2a** and trimethylsilylcyanide **3** in diethylether remains unchanged after 4 h at room temperature, the reaction in 5 M ethereal LiClO₄ solution, followed by hydrolysis, leads to the formation of the α -cyanohydroxylamine **4**, within 15 min, in high yields.⁶ α -Cyanohydroxylamines are an important class of compounds. Hydrolysis of

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α -cyanohydroxylamines gives *N*-hydroxylamino acids, which undergo catalytic hydrogenation to give amino acids. *N*-Hydroxyamino acids are a biologically important class of compounds which are produced by metabolism of amino acids⁷ and act as antibiotics and growth factors.⁸ It is noteworthy that α -cyanohydroxylamine can be converted into the corresponding nitrones upon treatment with bases with elimination of hydrogen cyanide.⁹ It should be noted that most Lewis acids cannot be used in this reaction since they are decomposed or deactivated by the amines and water which exist at the stage of nitron formation.⁵ Several examples of the present three-component coupling reactions are summarized in Scheme 1. Not only aromatic, but also aliphatic and heterocyclic aldehydes reacted smoothly under these conditions.



Scheme 1.

In summary, we have found that 5.0 M LPDE promotes the reaction of TMS-CN with aldehydes to give α -cyanohydroxylamines. This method has some noteworthy features: (1) excellent yields can be obtained for aromatic, aliphatic and heterocyclic aldehydes. In particular, α -aliphatic nitrones, are stable under these conditions and excellent yields are observed; and (2) operational simplicity at ambient temperature.

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