

A simple, economical, and highly efficient synthesis of β -hydroxynitriles from epoxide under solvent free conditions

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Abstract

A simple, rapid, and highly regioselective green protocols for the synthesis of β -hydroxynitriles by the direct reaction of epoxides with trimethylsilyl cyanide in the presence of catalytic amount of lithium perchlorate under solvent free conditions in high to quantitative yield is reported.

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1. Introduction

As a consequence of the necessity to minimize the amount of toxic waste and by-products from chemical processes, there is a need to develop new and more environmentally friendly synthetic methods in which fewer toxic substances are used. Nowadays in the development of new syntheses, ecological points of view must also be taken into consideration and apportioned due to importance in the assessment of viability [1]. Many organic solvents are ecologically harmful, and their use should therefore be minimized as much as possible or should be avoided.

β -Hydroxynitriles are useful synthetic intermediates in organic synthesis [2], and it is a versatile moiety for the synthesis of 1,3-amino alcohols. The reaction of epoxides with different cyanide sources, such as hydrogen cyanide [3], cyanids [4], and asymmetric ring opening with TMSCN in organic solvent [5], or cyanide formed upon treatment of acetone cyanohydrin with various bases, are among the most direct methods for the preparation of these compounds [6]. The reaction of epoxides with NaCN, KCN, or HCN usually requires long reaction times, protic and harmful solvents. They also lack appreciable regioselectivity when dealing with sensitive and bulky epoxides. Furthermore, to the best of our knowledge ring-opening reactions with TMSCN have not been reported under solvent free conditions.

2. Results and discussions

In continuation of our interest on the application of lithium perchlorate for various organic transformations [7], we herein describe a simple, efficient, and highly regioselective method for the synthesis of β -hydroxynitriles using a catalytic amount of lithium perchlorate under solvent free conditions.

A series of preliminary experiments was performed on cyclohexene oxide in order to determine the best reaction conditions. No reaction was observed in the absence of the lithium perchlorate. Reactions in solvents such as THF, CH_2Cl_2 , acetone, DMF gave lower yields of the desired product after prolonged reaction time. The best conversion was observed when the reaction was performed under solvent free conditions. For the sake of comparison, the reaction of cyclohexene oxide with TMSCN was carried out in the presence of other anhydrous perchlorate, such as $\text{Mg}(\text{ClO}_4)_2$, $\text{Ni}(\text{ClO}_4)_2$, $\text{Fe}(\text{ClO}_4)_3$, and $\text{LiClO}_4\text{-SiO}_2$ under solvent free conditions. However, these perchlorates showed lower activity than lithium perchlorate in this process.

The best reaction conditions require the presence of small amount of $\text{LiClO}_4\cdot 3\text{H}_2\text{O}$ (10 mol%) and 1.1 equivalents of trimethylsilyl cyanide, TMSCN, with respect to the epoxide at room temperature. The reaction times are short with simple work up and good yields. The operation conditions are mild and no side products or rearrangements have been observed. The data in Table 1 clearly show that all reactions proceeds smoothly under these conditions to afforded the desired products in excellent yields with high regioselectivity and high purity.

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Table 1
LiClO₄·3H₂O—catalyzed reactions of epoxides with TMSCN

Entry	Epoxide	Product	Yield (%)
1			92 ^a
2			96 95 97
3			94 92
4			96
5			97
6			96
7			97
8			97
9			84

^a Reaction was carried out at -10°C then warmed to room temperature.

The regioselectivity in the reaction of unsymmetrical epoxides is governed by both steric and electronic effects. The regioselectivity was determined by ¹H NMR and by comparison with the known β -hydroxynitriles [4,5]. Unsymmetrical oxiranes underwent cleavage by a TMSCN with preferential attack at the less substituted carbon of epoxides.

Complete selectivity for nucleophilic attack at the less hindered carbon of the aliphatic epoxide such as glycidyl phenyl ether, propylene oxide, butane oxide, and glycidyl 4-methoxyphenyl ether was observed. This process was also chemoselective for epichlorohydrin and epibromohydrin with two reaction positions, which resulted in the formation of the corresponding β -hydroxynitriles by the nucleophilic attack at the terminal carbon of the epoxides. Table 1. The only exception is styrene oxide, in which two regioisomers were formed in the ratio of 92:8.

Furthermore, addition of TMSCN to the epoxides is completely selective with the exclusive formation of nitriles, and even a trace of the corresponding isonitrile derivative was not detected by ¹H NMR spectroscopy.

The role of LiClO₄ in catalyzing the opening of epoxide rings with TMSCN is perhaps fulfilled through the coordination of Li⁺ with epoxide oxygen, rendering the epoxide more susceptible to nucleophilic attack by TMSCN followed by silylation and formation of β -siloxy nitriles. The comparison of the present methods with respect to the amount of the catalyst used, reaction time, temperature, the yields, and regioselectivity with those reported in the literature reveals that this method is superior to the previous procedures.

In summary, we have developed an economical and practical method for the synthesis of a wide range of β -hydroxynitriles by using inexpensive and readily available reagents under neutral conditions. This process imposes moderate conditions and simple work up procedure with high efficiency and regioselectivity. The reactions proceed smoothly in solvent free conditions, which is an important feature for the development of green chemistry.

3. Experimental

3.1. General

NMR spectra were recorded on a Bruker ACF 500 spectrometer. IR spectra were measured with Perkin-Elmer 1600 FTIR spectrometer. Reactions were performed under argon. Lithium perchlorate and other chemicals were purchased from Acros Organics or Merck. All compounds were characterized on the basis of their spectroscopic data (IR, NMR) and by comparison with those reported in the literature.

3.2. General procedure for the preparation of β -hydroxynitriles

To the mixture of epoxide (3 mmol) and LiClO₄·3H₂O (0.05 g) in a test tube, TMSCN (3.3 mmol) was added, and the mixture was stirred at 0 °C for a few minutes and then at room temperature for 10–180 min. The reaction was monitored with TLC or GC. Then water (5 mL) was added and the organic materials were extracted with diethyl ether (2 mL × 10 mL). The organic layer was separated and dried over anhydrous Na₂SO₄, and solvent was removed under reduced pressure to give the β -siloxy nitriles [8] in the pure product.

3.3. Selected spectroscopic data

3.3.1. **2a** (Table 1, entry 1)

Yield 92%; $^1\text{H NMR}$ (500 MHz, CDCl_3): δ 0.11 (s, 9 H), 3.01–3.38 (m, 2 H), 4.92–4.95 (t, $J=6.1$ Hz, 1 H), 7.20–7.38 (m, 5 H).

3.3.2. **2c** (Table 1, entry 2)

Yield 95%; $^1\text{H NMR}$ (500 MHz, CDCl_3): δ 0.13 (s, 9 H), 0.83 (t, $J=7.3$ Hz, 3 H), 1.43 (t, $J=7.3$ Hz, 2 H), 2.11 (q, $J=7.2$ Hz, 2 H), 3.66–3.71 (qu, $J=5.8$ Hz, 1 H),

3.3.3. **2e** (Table 1, entry 3)

Yield 94%; $^1\text{H NMR}$ (500 MHz, CDCl_3): δ 0.12 (s, 9 H), 2.08–2.11 (m, 2 H), 3.09–3.12 (m, 2 H), 3.70–3.75 (m, 1 H).

3.3.4. **2f** (Table 1, entry 3)

Yield 92%; $^1\text{H NMR}$ (500 MHz, CDCl_3): δ 0.12 (s, 9 H), 2.19–2.29 (m, 2 H), 3.04–3.12 (m, 2 H), 3.79–3.83 (m, 1 H).

3.3.5. **2h** (Table 1, entry 5)

Yield 97%; $^1\text{H NMR}$ (500 MHz, CDCl_3): δ 0.13 (s, 9 H), 1.08 (d, $J=6.2$ Hz, 6 H), 2.22–2.24 (m, 2 H), 3.17–3.19 (m, 1 H), 3.29–3.31 (m, 1 H), 3.44–3.45 (m, 1 H), 3.85–3.86 (m, 1 H).

3.3.6. **2j** (Table 1, entry 7)

Yield 97%; $^1\text{H NMR}$ (500 MHz, CDCl_3): δ 0.17 (s, 9 H), 2.60–2.80 (m, 2 H), 3.90–4.11 (m, 2 H), 4.30–4.40 (m, 1 H), 6.91–6.93 (m, 2 H), 7.01–7.02 (m, 1 H), 7.31–7.34 (m, 2 H).

3.3.7. **2k** (Table 1, entry 8)

Yield 97%; $^1\text{H NMR}$ (500 MHz, CDCl_3): δ 0.12 (s, 9 H), 2.40–2.48 (m, 2 H), 3.65 (s, 3 H), 3.70–3.73 (m, 1 H), 3.80–3.83 (m, 1 H), 4.12–4.13 (m, 1 H), 6.74–6.88 (m, 4 H).

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