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Synthesis of β-hydroxy nitriles and 1,3-amino alcohols from epoxides using acetone cyanohydrin as a LiCN precursor

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Abstract—The reaction of acetone cyanohydrin with MeLi affords a LiCN·acetone complex that can be made to react with epoxides in THF, either in one-pot or using isolated samples of the cyanide complex, to cleanly afford β-hydroxy nitriles upon aqueous workup; in situ hydride reduction of nitriles affords 1,3-amino alcohols.

1. Introduction

β-Hydroxy nitriles are useful synthetic intermediates[1] that can be prepared by reaction of epoxides with HCN,[2] NaCN,[1,3] KCN,[4] LiCN,[5] cyanide exchange resin,[6] TBAF/TMSCN in CH_3CN,[7] or cyanide formed upon treatment of acetone cyanohydrin with various bases.[8] The reaction of epoxides with NaCN, KCN or HCN usually requires extended reaction times,[1,3b,c,4c] protic solvents[1–3,4a,b] or additives;[3a,4c] some reactions can afford mixtures of regio-[4c,6,7] or stereoisomers.[2] In 1992,[5a] we reported a simple and effective method to convert functionalized epoxides to β-hydroxy nitriles using LiCN in refluxing THF; its advantages are (1) high regioselectivity, (2) short reaction times relative to standard conditions using HCN or alkali metal cyanides in protic solvents, (3) clean conversion of epoxide to nitrile and (4) the use of an inert, aprotic solvent that permits in situ transformations using acid- and moisture-sensitive reagents, such as LAH. This method has recently been applied to the synthesis of marine diterpenes,[9] sugar moiety analogs of a nucleoside antibiotic,[10] an antiviral nucleoside,[11] and an antifungal agent.[8a] Synthetic studies towards 1-*N*-iminosugars[12,13] and several chiral building blocks[14] have shown that 2,3-epoxy-1-alkanols and LiCN in THF react with high regio- and stereoselectivity.

LiCN is hygroscopic, and the limited availability and poor quality of commercial LiCN has been a concern.[5b,8a] Others[8a,9] have reported improvement in nitrile yields and ease of handling by performing one-pot reactions with LiCN, which they prepared from acetone cyanohydrin and LiH using a literature method;[15] however, reaction times were similar to those we reported. LiH is flammable, moisture-sensitive, and, like LAH, it releases an irritating and potentially explosive dust when handled in air. The solubility of LiH in organic solvents is poor; this precludes its storage and transfer in solution. Therefore, we investigated the reaction of acetone cyanohydrin with alkyllithiums, since solutions of the latter are commercially available, readily transferred by syringe and easily titrated.

We found that treatment of acetone cyanohydrin in anhyd hexanes at −5 to −10 °C with 0.5–1.0 equiv of MeLi[16] immediately afforded a LiCN·acetone complex as a white precipitate; solvent evaporation provided good yields of the complex on either a milligram or multigram scale. Reaction of the cyanide complex with epoxides, either in one-pot or using isolated samples of the complex, gave the corresponding β-hydroxy nitriles in good yields, cleanly, and in reaction times notably shorter than those we reported for reactions using commercial samples of LiCN.[5a] In situ nitrile reduction with either LAH or BH_3:THF afforded amino alcohols in satisfactory yields (Scheme 1). The LiCN/acetone ratio of the cyanide complex varied slightly (approx. 1:1, estimated by ^{13}C NMR peak intensity and integration of CN and C=O in comparison with an authentic 1:1 sample); acetone could not be removed in vacuo (overnight,

Keywords: Epoxide; Lithium cyanide; β-Hydroxy nitrile; Amino alcohol; One-pot; Anhydrous conditions.
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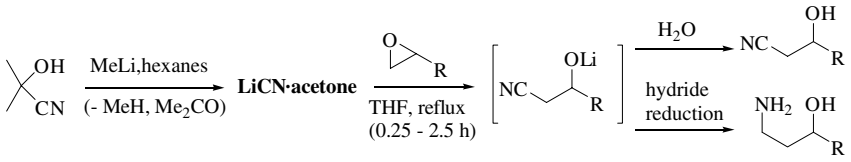


Scheme 1.

room temp) or by sample filtration and sequential washing with solvents; however, it evaporated readily from samples that were placed in a drying pistol (<0.1 mmHg; refluxing toluene).

1.1. Conversion of epoxides to β-hydroxy nitriles

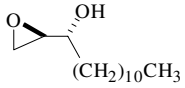
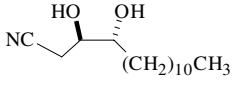
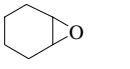
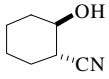
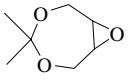
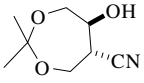
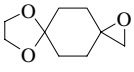
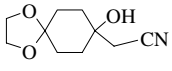
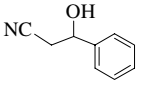
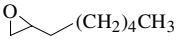
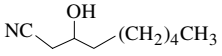
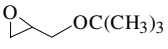
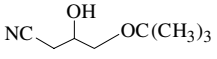
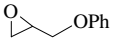
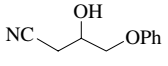
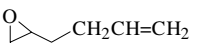
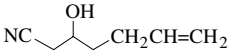
We previously reported that treatment of epoxides with 3–4 equiv of commercial LiCN in refluxing anhyd THF gave the corresponding nitriles (60–88% yields) in average reaction times of 4 h for monosubstituted epoxides and 8 h for di- and trisubstituted epoxides.[5a] Reaction of monosubstituted epoxides (Table 1, entries 1, 5–9) with the LiCN·acetone complex using a one-pot procedure afforded nitriles (68–85% yields) cleanly, in reactions using less LiCN and much less time (an average of 40 min); some epoxides reacted completely within 20 min (Table 1, entries 7–9). Disubstituted epoxides reacted in 0.3–2.5 h when treated with 2.5–4.5 equiv LiCN (Table 1, entries 2–4). Reactions of epoxides with samples of the cyanide complex (2–3.5 equiv) that were isolated and stored for several weeks or longer also cleanly afforded nitriles (62–93% yields; 40 min average reaction time for all entries in Table 1; entries 7–9 reacted within 15 min). All reactions were highly regio- and stereoselective; only one isomer was detected by NMR spectroscopy.

1.2. One-pot conversion of epoxides to 1,3-amino alcohols

In situ LAH reduction of nitriles (LAH/epoxide = 1.5:1) was complete within 1 h at reflux (Table 2); BH_3:THF could also be used for nitrile reduction (8:1 BH_3/epoxide, 3 h reflux, followed by overnight heating with 10% NaOH; Table 2, entries 1 and 2). Amino alcohols were afforded in good purity and in satisfactory yields.

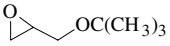
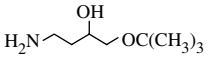
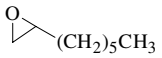
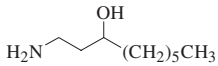
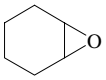
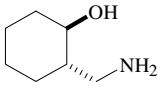
In summary, we report that LiCN can be conveniently prepared by reaction of MeLi and acetone cyanohydrin in anhyd hexanes: solvent evaporation affords a cyanide–acetone complex that can be stored indefinitely in a desiccator; heating in vacuo removes acetone; reaction of the cyanide–acetone complex with epoxides in THF affords the corresponding β-hydroxy nitriles in good

Table 1. Conversion of epoxides to β-hydroxy nitriles with LiCN·acetone in THF[a]

Entry	Substrate	Product	LiCN (equiv)	Using isolated cyanide		One-pot preparation		Ref.
				Time (h)	Yield (%)	Time (h)	Yield (%)	
1			3.5–4	2.0	89	1	82	21
2			2.5	0.5 (4)	70 (71)	2	67	4c,5a
3			3.5	1.5 (3)	93 (79)	2.5	90	5a,22
4			3.0–4.5	0.3	62	0.3	66	23
5			2.5	0.5 (2.3)	89 (60)	1	84	1,5a
6			2.5–3	0.5 (6.5)	92 (88)	1	85	4c,5a,8b
7			2	0.25 (5.5)	86 (78)	0.25	68	5a,19
8			2	0.25 (13.5)	93 (81)	0.3	80	3b,5a
9			2.5	0.25 (3)	75 (79)	0.3	71	5a

[a] All yields are for isolated products. Parenthetical data are those we reported in Ref. 5a using commercial LiCN, and are included for comparison.

Table 2. One-pot preparation of amino alcohols: in situ LAH reduction of nitriles

Entry	Substrate	Product	Isolated yield (%)[a]	Ref.
1			77 (66)	19
2			81 (83)	20
3			65	2

[a] Parenthetical yields: reduction using 8:1 BH_3/epoxide, 3 h reflux, overnight heating with 10% NaOH.

yields and in greatly shortened reaction times in comparison to previous reports by our group and others. We also report an effective one-pot, two-step synthesis of 1,3-amino alcohols by in situ hydride reduction of nitriles obtained from reaction of epoxides with LiCN.

2. Experimental[17]

2.1. LiCN·acetone complex. CAUTION: TOXIC[18]

MeLi in diethyl ether (1.6 M, 24 mL, 38 mmol) was added via syringe over 15 min to an anhyd hexane (150 mL) solution of acetone cyanohydrin (5.00 g, 58.7 mmol) stirring at ~−10 °C under N_2. The resulting white suspension was quickly warmed to room temperature and stirred for 15 min. Rotary evaporation (1 h) and exposure to <0.1 mmHg (1 h) afforded LiCN·acetone as a white solid (3.4 g, 98% yield for a 1:1 complex). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.05 (s, CH_3COCH_3). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 30.95 (CH_3), 166.73 (CN), 206.95 (C═O); only δ 167.35 (CN) for a sample exposed to < 0.1 mmHg in a drying pistol warmed with refluxing toluene.

2.2. β-Hydroxy nitriles

LiCN·acetone (stored in a desiccator for several weeks or longer) and epoxide in anhyd THF (6 mL) were refluxed until TLC analysis revealed absence of unreacted epoxide (see Table 1 for LiCN/epoxide ratios and reaction times). Treatment with water (40 mL), ether extraction, drying ($MgSO_4$), filtration, rotary evaporation and concentration in vacuo afforded nitriles (62–93% yields).

2.3. β-Hydroxy nitriles by one-pot reaction of LiCN with epoxides

LiCN·acetone was prepared as described above (MeLi/cyanohydrin = 1:1.5 or 1:2) and exposed to <1.0 mmHg for 20 min. Immediate addition of an anhyd THF solution of epoxide (see Table 1 for LiCN/epoxide ratios and reaction times) and heating to reflux afforded nitriles (66–90% yields) after an aqueous workup.

2.4. 1,3-Amino alcohols by in situ nitrile reduction

After reaction of epoxide with cyanide was complete, the mixture was cooled to room temperature, treated with LAH in THF (1.5 equiv) and refluxed until TLC analysis revealed absence of unreacted nitrile (1 h). Water (4 equiv based on LAH) was added slowly via syringe to the ice-cold mixture followed by ethyl acetate (3 mL), stirring at room temperature (30 min), filtration through Celite® (30 × 15 mm; ethyl acetate as eluent) and drying ($MgSO_4$). Filtration, addition of toluene (2 mL, to drive off water) and concentration in vacuo afforded amino alcohols (65–81% yields; Table 2).

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16. LiCN from reaction of acetone cyanohydrin and *n*-BuLi afforded nitriles rapidly and in good yields, but with occasional traces of 2-methyl-2-hexanol formed by addition of *n*-BuLi to acetone. Any *t*-butanol that might have formed by addition of MeLi to acetone would have been removed in vacuo or during an aqueous workup.
17. Reactions were performed using 0.44–31 mmol epoxide. Spectroscopic and physical data were consistent with previous reports (see references in Tables 1 and 2) and new compounds displayed satisfactory spectroscopic data (Refs. 21–23); crude products were generally pure enough to be used for further reactions, as determined by TLC, ^{13}C (75 MHz) and ^{1}H NMR (300 MHz) analyses. Product entries 4 and 8 (one-pot preparation), Table 1, were purified by column chromatography (SiO_2, pet. ether/EtOAc); product entry 2 (one-pot preparation), Table 1, was purified by recrystallization (hexanes/EtOH); product entry 3, Table 2, was purified by vacuum distillation.
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21. (±)-*threo*-3,4-Dihydroxypentadecanenitrile (Table 1, product entry 1): ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3H), 1.36–1.53 (m, 20H), 2.64 (d, 2H), 3.55 (m, 1H), 3.82 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.6, 22.7, 25.2, 29.3, 29.51, 29.56, 29.59, 29.6, 31.8, 33.2, 69.8, 73.0, 118.1; HRMS calcd for $C_{15}H_{28}NO$ (M − OH) 238.21709, found 238.21756.
22. (±)-*trans*-6-Hydroxy-2,2-dimethyl-1,3-dioxepane-5-carbonitrile (Table 1, product entry 3): ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 3H), 1.40 (s, 3H), 2.8 (m, 1H), 3.50 (s, 1H, exchangeable with D_2O), 3.65 (dd, 1H), 3.78 (dd, 1H), 3.93 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 24.2, 24.3, 39.2, 56.9, 62.4, 69.0, 102.0, 118.5; HRMS calcd for $C_8H_{12}DNO_3$ (sample from D_2O exchange reaction) 172.09582, found 172.09558.
23. (8-Hydroxy-1,4-dioxaspiro[4.5]dec-8-yl)acetonitrile (Table 1, product entry 4): ^{1}H NMR ($CDCl_3$) δ 1.55–1.65 (m, 2H), 1.70–2.00 (m, 6H), 2.55 (s, 2H), 2.95 (s, 1H, exchangeable with D_2O), 3.95 (m, 4H); ^{13}C NMR δ 30.0, 31.8, 34.2, 64.0, 64.2, 68.8, 107.8, 117.4; HRMS calcd for $C_{10}H_{15}NO_3$ 197.10519, found 197.10522.