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Protonation of Acyllithium Reagents by Acetonitrile: Synthesis of β-Hydroxy Nitriles

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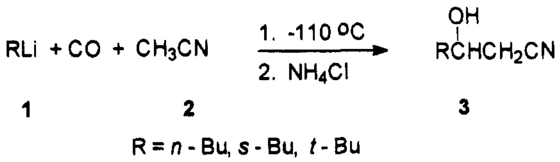
Introduction

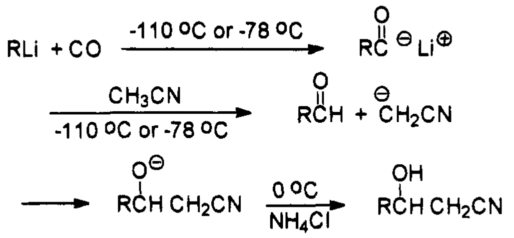
In recent years, the reaction of electrophiles with acyllithium (RCOLi) reagents has been extensively studied and has proven to be a convenient route to acylated products.[1-6] For example, Seyferth reported that acyllithium reagents, generated *in situ* from an alkyllithium and carbon monoxide at −110 °C to −135 °C, would react with aldehydes,[1] ketones,[1] esters,[7] lactones,[8] isocyanates,[9] isothiocyanates,[9] carbodiimides,[10] carbon disulfide,[11] carbonyl sulfide,[11] organic disulfides,[12] iron pentacarbonyl,[13] and trimethylchlorosilane[14] to give acylated products. Nudelman found that the acyllithium generated from phenyllithium in the presence of alkyl bromides gave diphenylalkylcarbinols.[15,16] We recently reported that trialkylboranes reacted with acyllithium reagents to afford ketones in modest yields.[17]

Although Seyferth predicted[2] that acyl anion reagents might react with nitriles to afford addition products such as α-diketones, no report of a reaction of acyl anion reagents with nitriles has appeared in literature. Recently, we reported the first example of the protonation of acyllithium reagents by dichloromethane and dichloroarylmethane.[18] The reaction affords the corresponding α,α-dichloro alcohols in excellent yields. We wish to report a new synthesis of β-hydroxy nitriles which is based on the reaction of acyllithium with acetonitrile, Scheme 1.

Scheme 1



Scheme 2



Results and Discussion

The reaction of acyllithium reagents with acetonitrile is achieved via the slow addition of an alkyllithium reagent to a solution of acetonitrile in a 4:4:1 (by volume) solvent system of THF:ethyl ether:pentane saturated with carbon monoxide, at low temperature. After addition of the alkyllithium is complete, the reaction mixture is stirred at low temperature for 1−4 h and then hydrolyzed with saturated aqueous NH_4Cl at 0 °C. The reaction affords β-hydroxy nitriles which are isolated using silica gel column chromatography. The results of a study using various lithium reagents with carbon monoxide and acetonitrile are shown in Table 1. In all experiments, no α-hydroxy ketone or α-diketone byproducts were detected indicating that the acyl anion does not add to either the nitrile or carbonyl functional groups.

The reaction presumably occurs via the intermediate formation of an aldehyde generated by proton abstraction from acetonitrile by the initially formed acyl anion. The aldehyde then reacts with the acetonitrile anion as outlined in Scheme 2.[19]

As shown in Table 1, the use of excess acetonitrile results in an increased yield of β-hydroxy nitrile (Table 1, entries 1−5); the reaction of the *n*-butyl derivative with a 100% excess of acetonitrile gives the β-hydroxy nitrile in 60% yield (Table 1, entry 4). Hence, in most experiments, 100% excess nitrile was used (Table 1, entries 6−17). The protonation of acyllithium reagents by acetonitrile also occurs at a higher temperature (−78 °C, Table 1, entries 6−13 and 16) and in more concentrated solutions (Table 1, entries 11, 13, 14, 16). However, if the amount of solvent is decreased by more than 50%, the yield of β-hydroxy nitriles is diminished (Table 1, entry 12). The use of a mixed solvent system of THF:Et_2O:pentane (4:4:1 by volume) results in higher yields than those obtained in a single solvent (Table 1, entries 7−10). The self-condensation of acetonitrile becomes a serious side reaction when the reaction is carried out in pure pentane (Table 1, entry 10). The self-condensation is also observed when methyllithium or phenyllithium are used in the reaction. For example, when methyllithium is added to a mixture of carbon monoxide and acetonitrile at −110 °C in the mixed solvent system, the condensation product, 3-aminocrotononitrile, is isolated in 60% yield and no protonation product is observed. Other nitriles (allyl cyanide, benzyl cyanide, octaneni-

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[1] Seyferth, D.; Weinstein, R. M.; Hui, R. C.; Wang, W.-L.; Archer, C. M. *J. Org. Chem.* **1992**, *57*, 5620 and references cited therein.

[2] Seyferth, D.; Weinstein, R. M.; Wang, W.-L.; Hui, R. C.; Archer, C. M. *Isr. J. Chem.* **1984**, *24*, 167.

[3] Seyferth D.; Hui, R. C.; Weinstein, R. M.; Wang, W. -L. *Nova Acta Leopold* **1985**, *59*, 335; *Chem. Abstr.* **1988**, *108*, 6056t.

[4] Narayana, C.; Periasamy, M. *Synthesis* **1985**, 253.

[5] Wakefield, B. J. Organolithium Methods; Academic Press: London, 1988; pp 95−97.

[6] Hui, R. C.; Seyferth, D. *Org. Synth.* **1990**, *69*, 114.

[7] Seyferth, D.; Weinstein, R. M.; Hui, R. C.; Wang, W. -L; Archer, C. M. *J. Org. Chem.* **1991**, *56*, 5768.

[8] Weinstein, R. M.; Wang, W.-L.; Seyferth, D. *J. Org. Chem.* **1983**, *48*, 3367.

[9] Seyferth, D.; Hui, R. C. *Tetrahedron Lett.* **1984**, *25*, 5251.

[10] Seyferth, D.; Hui, R. C. *J. Org. Chem.* **1985**, *50*, 1985.

[11] Seyferth, D.; Hui, R. C. *Tetrahedron Lett.* **1984**, *25*, 2623.

[12] Seyferth, D.; Hui, R. C. *Organometallics* **1984**, *3*, 327.

[13] Dötz, K. H.; Wenicker, V.; Müller, G.; Alt, H. G.; Seyferth, D. *Organometallics* **1986**, *5*, 2570.

[14] Seyferth, D.; Weinstein, R. M. *J. Am. Chem. Soc.* **1982**, *104*, 5534.

[15] Nudelman, N. S.; Vitale, A. A. *J. Org. Chem.* **1981**, *46*, 4625.

[16] Vitale, A. A.; Doctorovich, F.; Nudelman, N. S. *J. Organomet. Chem.* **1987**, *332*, 9.

[17] Kabalka, G. W.; Gotsick, J. T.; Pace, R. D.; Li, N.-S. *Organometallics* **1994**, *13*, 5163.

[18] Kabalka, G. W.; Li, N.-S.; Yu, S. *Organometallics* **1995**, *14*, 1565.

[19] The intermediacy of an acetonitrile anion is supported by an experiment in in which the less acidic trideuterioacetonitrile[20] was used in place of acetonitrile. As expected, 2,2,3-trideuterio-3-hydroxyheptanenitrile was formed along with a significant quantity of the coupling byproduct.[1]

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Table 1. β-Hydroxynitrile (3) Prepared via Reaction of Acetonitrile

entry[a]	R	ratio 1:2[b]	solvent[c] (ML)	reaction temp (°C)	reaction time (h)	% yield[d] of 3
1	*n*-Bu	1:15	150	−110	1	74
2	*n*-Bu	1:6	150	−110	1	63
3	*n*-Bu	1:4	150	−110	1	62
4	*n*-Bu	1:2	150	−110	1	60
5	*n*-Bu	1:1	150	−110	1	38
6	*n*-Bu	1:2	150	−78	1	61
7	*n*-Bu	1:2	150	−78	4	70
8	*n*-Bu	1:2	150[e]	−78	4	42
9	*n*-Bu	1:2	150[f]	−78	4	36
10	*n*-Bu	1:2	150[g]	−78	4	3[h]
11	*n*-Bu	1:2	75	−78	4	70
12	*n*-Bu	1:2	45	−78	4	57
13	*s*-Bu	1:2	75	−78	4	32
14	*s*-Bu	1:2	75	−110	1	35
15	*s*-Bu	1:2	150	−110	1	35
16	*t*-Bu	1:2	75	−78	4	44
17	*t*-Bu	1:2	150	−110	1	42

[a] All experiments were carried out on a 5 mmol scale. [b] Molar ratio of alkyllithium **1** to acetonitrile (**2**). [c] All experiments were carried out in a 4:4:1 (by volume) solvent system of THF:Et$_2$O:pentane except where noted. [d] Isolated yields based on alkyllithium reagent. [e] The experiment was carried out in THF. [f] The experiment was carried out in Et$_2$O. [g] The experiment was carried out in pentane. [h] Self-condensation of acetonitrile was observed in this experiment.

trile, benzonitrile) were also examined. A condensation reaction also occurs with allyl cyanide; although the product has not been fully characterized, evidence suggests that it might be a trimer of allyl cyanide (based on the ^{1}H NMR and ^{13}C NMR data). Both octanenitrile and benzonitrile are recovered unchanged after quenching their reaction mixture with aqueous ammonium chloride. Although benzyl cyanide is readily deprotonated by the base, it also is recovered unchanged after protonolysis. However, quenching the reaction mixture with deuterium oxide produces α-deuterobenzyl cyanide. Furthermore, TLC analysis indicates that 5-nonanol and 6-hydroxy-5-decanone are not formed as byproducts. These results suggest that *n*-butyllithium reacts more rapidly with benzyl cyanide than with carbon monoxide.

Conclusion

The reaction of various acyllithium reagents with acetonitrile has been investigated. The acyllithium reagents are protonated by acetonitrile to generate aldehydes which produce β-hydroxy nitriles. The reaction of nitriles other than acetonitrile leads to recovery of starting materials or undesired byproducts.

Experimental Section

All reagents and solvents were transferred using techniques designed to eliminate contact with air. All glassware and syringes were oven-dried for 24 h prior to use. THF and diethyl ether were distilled from sodium benzophenone ketyl, and pentane was distilled from calcium hydride. Alkyllithium and phenyllithium reagents were purchased from Aldrich Chemical Co. and used as received. Nitriles, Aldrich Chemical Co., were dried and purified by distillation from calcium hydride. Carbon monoxide (technical grade) was obtained from National Specialty Gases, a Division of National Welders Supply Co., and dried by passing it through a column containing solid potassium hydroxide. ^{1}H NMR, and ^{13}C NMR spectra were obtained using a Bruker AC-250 (250 MHz) NMR spectrometer.

The synthesis of β-hydroxyheptanenitrile (Table 1, entry 11) is representative: To a three-necked, 125 mL, round bottomed flask equipped with a magnetic stirrer, glass-enclosed thermocouple probe, and a fritted-glass gas dispersion tube were added acetonitrile (0.41 g, 0.53 mL, 10 mmol) and 75 mL of a 4:4:1 (by volume) mixture of THF:diethyl ether:pentane. The solution was cooled to −78 °C by means of a dry-ice bath. Carbon monoxide was then continuously introduced into the solution. After 30 min of carbon monoxide addition, *n*-butyllithium (5.0 mmol, 3.1 mL of a 1.6 M solution in hexane) was added slowly, dropwise, via syringe over a period of approximately 45 min. After the addition was complete, the reaction mixture was stirred at −78 °C for 4 h and then allowed to warm to 0 °C. Hydrolysis was achieved by adding saturated aqueous ammonium chloride (20 mL). The two phases were separated, and the aqueous phase was extracted with diethyl ether (3 × 15 mL). The organic phases were combined, washed with a saturated NaCl solution (15 mL), and then dried over anhydrous MgSO$_4$. The solvent was removed and the residue subjected to silica gel chromatography [hexane/ethyl acetate = 7/3 (v/v) as eluent] to give β-hydroxyheptanenitrile:[21] 0.446 g (70% yield). ^{1}H NMR (CDCl$_3$, TMS): δ 3.93 (m, 1H), 3.00−2.70 (brs, 1H), 2.53 (m, 2H), 1.68−1.51 (m, 2H), 1.51−1.22 (m, 4H), 0.92 (t, 3H, $J = 6.9$); ^{13}C NMR (CDCl$_3$): δ: 117.8, 67.6, 36.1, 27.4, 25.9, 22.3, 13.8.

β-Hydroxy-γ-methylhexanenitrile (0.203 g, 32% yield) was prepared as outlined in the above procedure (Table 1, entry 13). Anal. Calcd for $C_7H_{13}NO$, C, 66.09; H, 10.31; N, 11.02. Found: C, 66.07; H, 10.32; N, 10.94. The ratio of the two diastereoisomers was 46:54, based on the ^{1}H NMR data. ^{1}H NMR (CDCl$_3$, TMS): δ 3.87 (m, 0.46 H), 3.77 (m, 0.54 H), 3.00−2.66 (brs, 1H), 2.54 (m, 2H), 1.70−1.04 (m, 3H), 0.93 (m, 6H). ^{13}C NMR (CDCl$_3$): δ 118.3, 71.4, 70.7, 39.8, 39.5, 25.5, 24.5, 23.6, 23.2, 14.4, 13.1, 11.4, 11.1.

β-Hydroxy-γ,γ-dimethylpentanenitrile[22] (0.282 g, 44% yield) was prepared as outlined in the above procedure (Table 1, entry 16). ^{1}H NMR (CDCl$_3$, TMS): δ 3.65 (dd, 1H, $J = 3.1$, $J = 9.5$), 2.95−2.68 (brs, 1H) 2.64−2.31 (m, 2H), 0.94 (s, 9H). ^{13}C NMR (CDCl$_3$): δ 119.1, 75.4, 34.9, 25.2, 21.5.

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(20) Jones, R. L.; Pearson, D. E.; Gordon, M. *J. Org. Chem.* **1972**, *37*, 3369.

(21) Mitchell, D.; Koenig, T. M. *Tetrahedron Lett.* **1992**, *33*, 3281.

(22) Barhdadi, R.; Gal, J.; Heintz, M.; Troupel, M.; Perichon, J. *Tetrahedron* **1993**, *49*, 5091.