

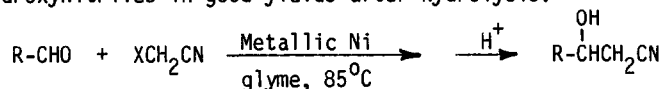
REFORMATSKY TYPE ADDITIONS OF HALOACETONITRILES TO ALDEHYDES MEDIATED BY METALLIC NICKEL

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Summary: Nickel in the metallic state was found to carry out the Reformatsky type addition of haloacetonitriles to aldehydes via cyanomethylnickel halides to give β -hydroxynitriles in good yields.











The Reformatsky type reaction of α -halonitriles mediated by zinc and the related addition reaction of α -cyano anions to carbonyl compounds have been known as a useful method for the preparation of β -hydroxynitriles. However, the promoting reagents in these reactions were limited to main group metals such as zinc,¹ magnesium,² or lithium³ and to inorganic bases,^{4,5} and the substrates used were generally ketones and aromatic aldehydes.⁸ Transition metals in the metallic state have not been acceptable reagents except for a few examples⁶ due to their low reactivity toward organic halides. We now report that haloacetonitriles react with aryl and alkyl aldehydes in the presence of metallic nickel at 85°C in 1,2-dimethoxyethane (glyme) to give β -hydroxynitriles in good yields after hydrolysis.⁹



Metallic nickel was prepared in glyme (25 ml) at room temperature in 12 h by the reduction of nickel iodide (4.71 g, 15.1 mmol) with lithium (0.241 g, 34.7 mmol) in the presence of naphthalene (0.193 g, 1.23 mmol) as an electron carrier. To the nickel in refluxing glyme, a mixture of benzaldehyde (1.23 g, 11.6 mmol) and bromoacetonitrile (1.81 g, 15.1 mmol) was added dropwise for 30 min. Additional heating was continued for 10 min and the reaction mixture was cooled and poured into separatory funnels containing 3% hydrochloric acid (100 ml) and was extracted with chloroform. The extracts were washed with water, dried over anhydrous sodium sulfate, and concentrated. Crude oil was submitted to silica gel chromatography eluted with hexane/EtOAc (3/1) to give 2-hydroxy-2-phenylpropanenitrile (1.44 g, 85%): bp 115-117°C/0.45 mm Hg (lit.³ bp 154-155°C/1 mm Hg).

In a similar manner, chloro- and iodoacetonitriles reacted with benzaldehyde to give the nitrile in 67% and 77% yields, respectively. When bromoacetonitrile was added to a mixture of benzaldehyde and nickel, reduction of the aldehyde by the nickel was observed; benzyl alcohol was formed in 15% yield along with β -hydroxynitrile (60%). The use of bromoacetate failed to yield satisfactory results. Also, the addition of bromoacetonitrile to ketones gave poor yields under similar conditions. The addition reaction to aldehydes is reasonably explained by the smooth oxidative addition of haloacetonitriles to metallic nickel to give cyanomethylnickel halides,⁷ which would add to aldehydes to yield β -hydroxynitriles after hydrolysis. The advantages of the present method are that the self-condensation of aldehydes is minimized because of

Table I. The preparation of β -hydroxynitriles by the reaction of bromoacetonitriles with aldehydes mediated by metallic nickel^{a)}

Aldehyde	Product ^{b)}	Bp(°C/mm Hg)	IR (cm ⁻¹)		NMR (δ)		Yield ^{c)} (%)
			ν_{OH}	ν_{CN}	CH ₂ CN	CHOH	
C ₆ H ₅ CHO	C ₆ H ₅ CH(OH)CH ₂ CN	115-117/0.45 ^{d)}	3430	2240	2.63	4.90	84
Br-  CHO	Br-  CH(OH)CH ₂ CN	147-148/0.49	3430	2245	2.68	4.93	76
NC-  CHO	NC-  CH(OH)CH ₂ CN	165/0.24 ^{e)}	3530	2240 2220	2.78	5.10	81
C ₆ H ₅ C=CCHO	C ₆ H ₅ C=CCH(OH)CH ₂ CN	142/0.83	3410	2240	2.82	4.88	63
C ₃ H ₇ CHO	C ₃ H ₇ CH(OH)CH ₂ CN	114/11 ^{f)}	3420	2240	2.52	3.93	57
C ₅ H ₁₁ CHO	C ₅ H ₁₁ CH(OH)CH ₂ CN	83/0.34	3430	2240	2.50	3.91	59
C ₃ H ₇  CHO	C ₃ H ₇  CH(OH)CH ₂ CN	93/0.92	3430	2240	2.57	4.42	76
C ₆ H ₅  CHO	C ₆ H ₅  CH(OH)CH ₂ CN	143/0.41	3420	2240	2.58	4.53	77
C ₄ H ₉  CHO	C ₄ H ₉  CH(OH)CH ₂ CN	107/0.15	3420	2240	2.58	4.45	59

a) The reaction was carried out by adding a mixture of aldehyde and bromoacetonitrile to metallic nickel in refluxing gyne (85°C). b) All compounds gave satisfactory results on microanalyses (C, H, and N: \pm 0.29%). c) Isolated by silica gel chromatography. d) lit.³ bp 115-117°C/0.45 mm Hg. e) mp 84.5-85.5°C. f) lit.⁴ bp 57°C/0.2 mm Hg.

lower basicity of cyanomethylnickel halides compared with the corresponding zinc reagents, and that the gentle exothermic reaction proceeds smoothly at 85°C. Moreover, the selective addition to aldehydes and not to ketones may prove to be a great synthetic advantage in certain cases.

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8. Very few reactions are common to both our studies and the cited work. Reference 3 reports a 78% yield of reaction of benzaldehyde and bromoacetonitrile while reference 2 reports a 32% yield. Our study includes more varied and sensitive aldehydes.
9. The only β -halonitriles we have studied to date are the β -haloacetonitriles.

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