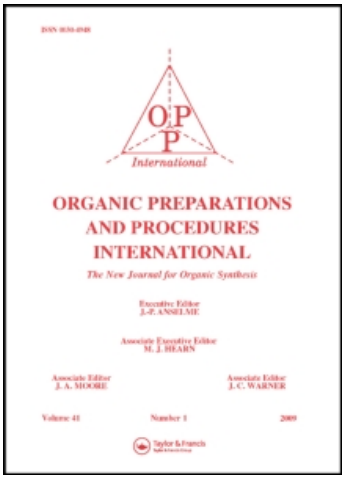

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CYCLIZATION OF ω-HALONITRILES WITH ORGANOLITHIUMS

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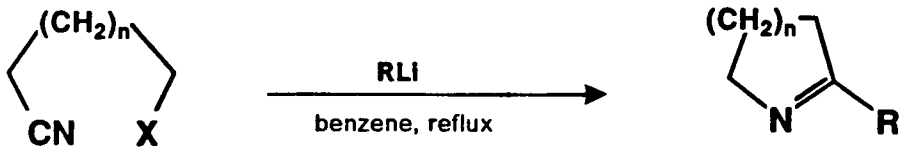
This report describes the conversion of ω-halonitriles such as *1* and *3* to 2-alkylpyrrolines and tetrahydropyridines, *2* and *4* respectively, by treatment with organolithium reagents. This conversion was previously described but only with nitriles without α-hydrogens. Our results show that α-deprotonation does not compete with addition and cyclization when the α-position of *1* or *3* (n = 1, 2) is unsubstituted.



1 (n=1)
3 (n=2)

2 (n=1)
4 (n=2)

We previously reported that organolithium reagents react with lactim ethers to give mixtures of 2H(5-alkyl)-3,4-dihydropyrroles and 6-alkyl-2,3,4,5-tetrahydropyridine derivatives, along with the corresponding 2,2-dialkylpyrrolidine and 2,2-dialkylpiperidine derivatives.[1] It was previously known that similar reaction with Grignard reagents gave the dihydropyrrole or tetrahydropyridine.[2] Our report was part of a continuing effort to prepare 2H(5-vinyl)-3,4-dihydropyrroles or 6-vinyl-3,4,5,6-tetrahydropyridines. Such compounds would function as azadienes in a heterocyclic Diels-Alder reaction for the synthesis of alkaloids. All attempts to prepare such compounds from lactim ethers and vinylmagnesium halides or vinyllithium reagents met with failure.

The nitrile cyclization method was suggested by the early work of Cloke and of Hixon.[3] Phenylmagnesium bromide reacted with 4-chlorobutanenitrile *1* (X = Cl, n = 1) to give 2H(5-phenyl)3,4-dihydropyrrole *2* (R = Ph, n = 1) in yields up

to 66%.[3] The 5-ethyl (46%), 5-benzyl (41%), and 5-*p*-tolyl (69%) derivatives were also prepared by this method. Reaction of vinylmagnesium bromide and ***1*** failed to give the desired product. In our work with lactim ethers, the organolithium reagents were significantly more reactive. We therefore hoped that vinyllithium would react with ***1*** to give the desired azadiene. Larcheveque had reported that 2,2-dimethyl-4-chlorobutanenitrile reacted with organolithiums to give the corresponding 2H(2-alkyl-3,3-dimethyl)-3,4-dihydropyrrole.[4] Reaction of ***1*** with vinyllithium, however, failed to produce the desired target, yielding only unreacted ***1***. One possible explanation was loss of the acidic α-hydrogen of the nitrile. Deprotonation by the basic organolithium could prevent the requisite addition. All of Larcheveque's examples involved 2,2-dialkyl nitriles where deprotonation was impossible. To test this premise we examined the reaction of 4-halo-butanenitrile ***1*** (n = 1) and 5-halopentanenitrile ***3*** (n = 2) with several organolithium reagents. Our results are presented in Table 1 and show that deprotonation is not a severe problem in this system and is not responsible for the failure of vinyllithium to give the azadiene. These results provide an interesting contrast to Larcheveque's work, however, and provide an alternative synthetic route to 5-alkyl-3,4-dihydro-2H-pyrroles and 6-alkyl-3,4,5,6-tetrahydropyridines.

The reaction clearly proceeds by initial addition to the nitrile, giving the imine salt. Internal displacement yields the cyclized imine, ***2*** (n = 1) or ***4*** (n = 2). In all cases starting nitriles ***1*** and ***3*** were recovered. Quenching experiments with D_2O and iodomethane failed to give the deuterio or 2-methylnitrile, as judged by GC/mass spectrometry, ^1H and ^{13}C NMR, indicating little or no deprotonation occurred. The isolated ***1*** and ***3*** are, therefore, assumed to be unreacted starting materials. Deprotonation does not explain the isolation of only starting material on reaction of ***1*** (X=Br) with vinyllithium. One is left with poor additivity to the nitrile as the only reasonable explanation, exacerbated by the relative instability of the reagent.

We had previously shown that reaction of organolithium reagents with lactim ethers led to a marked reduction in the yield of tetrahydropyridine derivatives (from ***3***) relative to the dihydropyrroles (from ***1***). Cyclization of ω-halonitriles , however, leads to essentially the same product ratios for both five and six mem-

bered rings and appears to be the superior method for preparation of the 2-alkyl imines. In our previous work with lactim ethers we found that reaction of methyllithium with *3* gave absolutely none of the imine *4c*. Reaction of methyllithium with *1* or *3*, however, gave good yields of the imine and is clearly superior to the lactim ether route. Another advantage to this method is the relatively clean formation of imine with only unreacted starting material as a contaminant, easily separable by chromatography. Reactions of lactim ethers with organolithiums always gave significant amounts of 2,2-dialkyl amines as major co-products. This contrasts with the ω-halonitrile cyclization which showed no trace of the dialkyl amine. Presumably, addition to the nitrile consumes most or all of the organolithium *prior* to cyclization to the imine.

Table 1. Reaction of ω-Halonitriles and Organolithium Reagents.

R	n	1/3	X	Time (hrs)	Products (%)			
					1[a]	2[b]	3[a]	4[b]
*n*Bu	1	*1a*	Cl	20	17	43	-	-
			Br	26	21	59	-	-
	2	*3a*	Cl	24	-	-	31	47
			Br	16	-	-	36	52
Ph	1	*1b*	Cl	70	34	30	-	-
			Br	22	35	43	-	-
	2	*3b*	Cl	66	-	-	24	25
			Br	25	-	-	26	42
Me	1	*1c*	Cl	20	35	58	-	-
			Br	22	31	64	-	-
	2	*3c*	Cl	19	-	-	31	49
			Br	20	-	-	36	58
*t*Bu	1	*1d*	Cl	26	41	35	-	-

[a] by VPC analysis [b] isolated yields (alumina chromatography)

Although we were unable to produce the desired azadiene by this method, we have shown that α-deprotonation is not an important competitive process in reactions of organolithiums with ω-halonitriles. Reaction of organolithium reagents with ω-halonitriles is a useful preparative route to substituted dihydropyrroles and tetrahydropyridines. These cyclic imines are produced in moderate to good yield. Unreacted halonitriles are easily separated and dialkylamines are not produced. This method is superior for the synthesis of 2-methyl-3,4,5,6-tetrahydropyridine.

EXPERIMENTAL SECTION

The ^1H spectra were recorded on an IBM 270-WY instrument at 270 MHz in deuteriochloroform, in ppm vs. tetramethylsilane. The ratio of products was determined on an HP 5985 GC/MS system using pyridine as an internal standard. All organolithiums and ω-halonitriles were obtained from Aldrich Chemical Company. The ether and THF was obtained from Baker and dried (CaH_2) prior to use. The benzene was distilled from sodium prior to use.

General Procedure for Reaction of ω-Halonitriles and Organolithiums . - A solution of the halonitrile in 0.1-0.2 L of dry benzene (argon head) was treated with the appropriate organolithium, dropwise via a syringe. The resulting solution was refluxed for the appropriate time, cooled and quenched with 1 mL of water. The solution was dried (Na_2SO_4) and the solvents were removed under reduced pressure. The oily residue was, *in all cases*, separated by chromatography (1:4 EtOAc:hexane, neutral alumina). The crude product contained a mixture of unreacted nitrile, imine and by-products of the organolithium. Simple distillation did not provide pure imine in any case. Isolation of each product was straightforward using liquid chromatography on neutral alumina, with the nitrile eluting first followed by the imine. The relative % of unreacted nitrile was determined by GC/MS analysis [methyl silicon capillary column (12.0 m x 0.2 mm i.d.), injected in ether and programmed from 30° → 250°C at 20°C min.$^{-1}$] with pyridine as an internal standard.

5-Butyl-3,4-dihydro-2H-pyrrole (2a). - Reaction of 3.04 g (29.3 mmol) of ***1*** (X = Cl) and 19 mL (30.4 mmol) of 1.6 M *n*-butyllithium in hexanes for 20 hrs gave after chromatography 1.57 g (12.6 mmol, 43%) of ***2a***: ^1H NMR ($CDCl_3$) δ 1.00(t, 3H), 1.2-1.6 (m, 4H), 1.7-1.9 (t, 2H), 2.0-2.2 (m, 2H), 2.5-2.7 (t, 2H), and 3.5-3.7 ppm[1,2a] (t, 2H) and 0.53 g (5.0 mmol, 17%) of recovered ***1***.

Similar reaction of 2.90 g (19.5 mmol) of ***1*** (X = Br) and 13.7 mL (22.0 mmol) of *n*-butyllithium for 26 hrs gave after chromatography 2.32 g (11.5 mmol, 59%) of ***2a*** and 0.74 g (5.0 mmol, 26%) of recovered ***1***.

2-Butyl-3,4,5,6-tetrahydropyridine (4a). - Reaction of 2.29 g (19.4 mmol) of ***3*** (X = Cl) and 14.2 mL (22.8 mmol) of *n*-butyllithium for 24 hrs gave after chromatography 1.28 g (9.2 mmol, 47%) of ***4a***: ^1H NMR ($CDCl_3$) δ 1.00 (t, 3H), 1.2-1.6 (m, 4H), 1.7-1.9 (t, 2H), 2.0-2.2 (m, 4H), 2.5 (t, 2H), and 3.5 ppm[1,2b] (t, 2H) and 0.70 g (6.0 mmol, 31%) of recovered ***1***.

Similar reaction with 2.36 g (14.5 mmol) of ***3*** (X = Br) and 11.2 mL (18.0 mmol) of *n*-butyllithium for 16 hrs gave after chromatography 1.04 g (7.5 mmol, 52%) of ***4a*** and 0.85 g (5.2 mmol, 36%) of recovered ***3***.

5-Phenyl-3,4-dihydro-2H-pyrrole (2b). - Reaction of 3.03 g (24.3 mmol) of ***1*** (X = Cl) and 27.7 mL (30.5 mmol) of 1.1 M phenyllithium in cyclohexane for 70 hrs gave after chromatography 1.29 g (8.9 mmol, 30%) of ***2b***: ^1H NMR ($CDCl_3$) δ 1.8-2.2 (m, 2H), 2.3-2.6 (t, 2H), 3.5-3.7 (t, 2H), 7.0-7.2 (m, 3H), and 7.4-7.7 ppm[1,2a,3] (m, 2H) and 1.01 g (9.8 mmol, 34%) of recovered ***1***.

Similar reaction of 2.66 g (17.8 mmol) of ***1*** (X = Br) and 18.4 mL (20.3 mmol) of phenyllithium for 22 hrs gave after chromatography 1.07 g (7.4 mmol, 43%) of ***2b*** and 0.89 g (6.0 mmol, 35%) of recovered ***1***.

2-Phenyl-3,4,5,6-tetrahydropyridine (4b) - Reaction of 2.29 g (19.0 mmol) of ***3*** (X = Cl) and 19.4 mL (21.4 mmol) of phenyllithium for 66 hrs gave after chromatography 0.73 g (4.9 mmol, 25%) of ***4b***:[1,5] ^1H NMR ($CDCl_3$) δ 1.6-1.9 (m, 4H), 2.2-2.4 (t, 2H), 3.3-3.5 (t, 2H), 7.0-7.2 (m, 3H), and 7.4-7.7 ppm (m, 2H) and 0.76 g (4.7 mmol, 24%) of recovered ***3***.

Similar reaction of 3.64 g (22.0 mmol) of *3* (X = Br) and 22.6 mL (24.9 mmol) of phenyllithium for 25 hrs gave after chromatography 1.50 g (9.3 mmol, 42%) of *4b* and 0.95 g (5.9 mmol, 26%) of recovered *3*.

5-Methyl-3,4-dihydro-2H-pyrrole (2c). - Reaction of 3.01 g (29.0 mmol) of *1* (X = Cl) and 25 mL (32.6 mmol) of 1.3 M methyllithium in ether for 20 hrs gave after chromatography 1.40 g (16.9 mmol, 58%) of *2c*: ^{1}H NMR ($CDCl_3$) δ 1.00-1.2 (s, 3H), 1.8-2.2 (m, 2H), 2.3-2.6 (t, 2H), and 3.5-3.7 ppm[1,2a] (t, 2H) and 1.05 g (10.2 mmol, 35%) of recovered *1*.

Similar reaction of 2.30 g (10.0 mmol) of *1* (X = Br) and 17.0 mL (22.0 mmol) of methyllithium for 22 hrs gave after chromatography 1.07 g (12.9 mmol, 64%) of *2c* and 0.91 g (6.2 mmol, 31%) of recovered *1*.

2-Methyl-3,4,5,6-tetrahydropyridine (4c). - Reaction of 2.31 g (22.0 mmol) of *3* (X = Cl) and 16.7 mL (21.7 mmol) of methyllithium for 19 hrs gave after chromatography 0.95 g (9.7 mmol, 49%) of *4c*: ^{1}H NMR ($CDCl_3$) δ 1.00-1.2 (s, 3H), 1.7-1.9 (m, 4H), 2.2-2.4 (t, 2H), and 3.4-3.6 ppm[2a] (t, 2H) and 0.72 g (6.1 mmol, 31%) of recovered *3*.

Similar reaction of 2.300 g (19.0 mmol) of *3* (X = Br) and 14.7 mL (19.0 mmol) of methyllithium gave after chromatography 0.80 g (8.2 mmol, 58%) of *4c* and 0.83 g (5.1 mmol, 36%) of recovered *3*.

5-(1,1-Dimethylethyl)-3,4-dihydro-2H-pyrrole (2d). - Reaction of 2.59 g (25.0 mmol) of *1* (X = Cl) and 20.4 mL (30.6 mmol) of 1.5 M *t*-butyllithium in pentane for 26 hrs gave after chromatography 1.10 g (8.8 mmol, 35%) of *2d*: ^{1}H NMR ($CDCl_3$) δ 1.5 (s, 9H), 1.8-2.2 (m, 2H), 2.3-2.6 (t, 2H), and 3.5-3.7 ppm[1,6] (t, 2H) and 1.06 g (10.3 mmol, 41%) of recovered *1*.

REFERENCES

1. C. A. Zezza, M. B. Smith, B. A. Ross, A. Arhin, and P. L. E. Cronin ***J. Org. Chem., 49***, 4397 *(1984)*.
2. (a) A. Etienne and Y. Correia ***Bull. Soc. Chim. Fr.***, 3704 *(1969)*; (b) R. Lukes and M. Cerny ***Coll. Czech. Chem. Com., 26***, 2886 *(1961)*; (c) O. Cervinka ***Ibid., 24***, 1146 *(1959)*; (d) R. Lukes and O. Cervinka ***Ibid., 16***, 641 *(1947)*; (e) J. I. Seeman ***Synthesis***, 498 *(1977)*; (f) J.S. Bielowski, S. Brandange and L. Lindblom ***J. Heterocyclic Chem., 15***, 97 *(1978)*; (g) N. Dudek and L. Kuan ***Coll. Czech. Chem. Com., 30*** , *2472 (1965)*.
3. (a) B. Cloke ***J. Am. Chem. Soc., 51***, 1174 *(1929)*; (b) D. F. Starr, H. Bulbrook and R. M. Hixon ***ibid., 54***, 3971 *(1932)*; (c) L. C. Craig, H. Bulbrook and R. M. Hixon ***ibid., 53***, 1831 *(1931)*.
4. M. Larcheveque, A. Debal and T. Cuvigny ***Bull. Chem. Soc. Fr.***, 1710 *(1974)*.
5. C. P. Axiotis, R. Gautier and M. Chastrette ***J. Organomet. Chem., 166***, 87 *(1979)*.
6. B. P. Mundy, K. B. Lipkowitz, M. Lee and B. R. Larsen ***J. Org. Chem., 39***, 1963 *(1974)*.

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