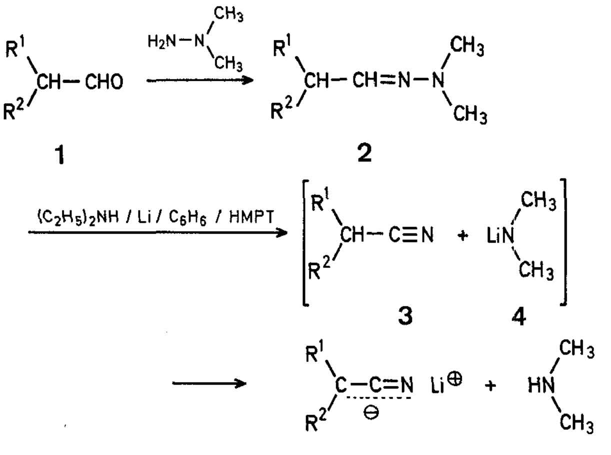
Hyperbasic Media. II. Metallation of Hydrazones. Synthesis of Substituted or Functional Nitriles, 2-Iminotetrahydrofurans and γ-Butyrolactones

J. F. Le Borgne, T. Cuvigny, M. Larchevêque, H. Normant*

Laboratoire de Synthèse Organique, Université Pierre et Marie Curie, Tour 44–45, 4 Place Jussieu, 75230 Paris Cedex 05, France.

In the preceeding communication we reported a very convenient method for the synthesis of nitriles **3** from the hydrazones **2** by reaction with "activated amides". The success of this process is essentially due to the presence of hexamethylphosphoric triamide. The reaction does not occur with the "usual amides". A direct synthesis of nitriles **3** from aldehydes **1** is thus achieved.

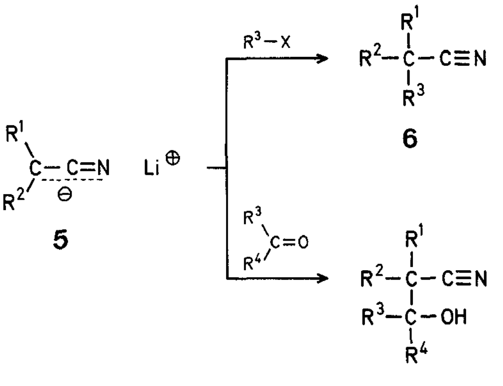
As shown in Scheme **A** the formation of lithium *N*,*N*-dimethylamide (**4**) occurs in the course of the reaction. This base, in the aprotic solvent hexamethylphosphoric triamide is very strong and metallates the nitrile **3** at a position α to the cyano group. The protonation of the anion of **5** then gives the nitrile (hydrolysis).



Scheme **A**

The conversion of **2** to **5** can be carried out rapidly with only one equivalent of activated amide. Compound **5** may also react with various electrophiles besides $H^{\oplus}$. The solutions of **5** thus obtained are allowed to react with alkyl halides or other alkylating agents such as methyl sulfate. In all cases, the trisubstituted nitriles **6** are obtained in satisfactory yields. The results are listed in Table 1. The role of hexamethylphosphoric triamide is two-fold: it makes the metallation easier and it enhances the nucleophilicity of **5** towards the alkylating agents.

β-Hydroxynitriles **7** may be prepared easily from **5** by reaction with aldehydes and ketones. The reaction is of wide scope, giving good yields (>80%) for straight or branched chain carbonyl compounds too. The results are listed in Table 2 (see Scheme **B**). Nitriles have also been alkylated in the α-position using sodium amide in toluene[2a].



Scheme **B**

When **5** is treated with oxiranes the condensation reaction occurs between +5° and +10°; 2,2-dimethyloxirane reacts immediately after the addition is complete and the reaction mixture is then hydrolyzed. This treatment of **5** with oxiranes does not lead to the γ-hydroxynitriles. They undergo a spontaneous cyclisation and are readily converted into the corresponding 2-iminotetrahydrofurans **9** when the reaction mixture is quenched with water. Tartaric acid hydrolysis leads to substituted γ-butyrolactones (**10**, see Scheme **C** and Table 3). The latter compounds are useful in organic synthesis as they afford cyclopentenones very easily[2b].

Metallation of α-branched *N*,*N*-dimethylhydrazones with activated amides thus provides a convenient one flask proce-

Table 1. Nitriles **6** from Hydrazones **2** via Lithiation and Alkylation

R^1	R^2	R^3-X	Yield (%)	b.p./torr	n_D (temp.)	I.R. (neat) ν cm⁻¹ (—C≡N)	Empirical formula[a]
CH_3	CH_3	C_4H_9Br	88	67°/14	1.4196 (23°)	2238	$C_8H_{15}N$ (125.2)
C_2H_5	C_2H_5	$(H_3C)_2SO_4$	77	46°/14	1.4104 (23°)	2239	$C_7H_{13}N$ (111.2)
C_2H_5	C_2H_5	C_2H_5Br	93	64°/14	1.4215 (23°)	2238	$C_8H_{15}N$ (125.2)
C_2H_5	C_2H_5	C_4H_9Br	94	93°/14	1.4322 (22°)	2238	$C_{10}H_{19}N$ (153.3)
C_2H_5	C_2H_5	$H_2C{=}CH{-}CH_2Br$	87	75°/14	1.4401 (22°)	2240	$C_9H_{15}N$ (137.2)

[a] All products gave satisfactory elemental analyses (C ±0.34%, H ±0.10%, N ±0.26%).

Table 2. Hydroxynitriles **7** from Hydrazones **2** via Lithiation and Condensation with Aldehydes or Ketones

R^1	R^2	R^3	R^4	Yield (%)	b.p./torr	n_D (temp.)	¹H-N.M.R. (CCl_4) δ ppm (OH)	I.R. (neat) ν cm⁻¹ (C≡N)	Empirical formula[a]
CH_3	CH_3	H	C_3H_7	87	68°/0.05	1.4398 (21°)	3.55	2242	$C_8H_{15}NO$ (141.2)
C_2H_5	C_2H_5	H	C_3H_7	83	84°/0.05	1.4537 (22°)	3.45	2240	$C_{10}H_{19}NO$ (169.3)
CH_3	CH_3	H	*i*-C_3H_7	85	64°/0.05	1.4445 (22°)	2.26	2240	$C_8H_{15}NO$ (141.2)
C_2H_5	C_2H_5	CH_3	CH_3	88	76°/0.1	1.4562 (22°)	2.95	2235	$C_9H_{17}NO$ (155.2)
CH_3	CH_3	C_6H_5	C_6H_5	90	m.p. 161°	–	2.50	2245	$C_{17}H_{17}NO$ (251.6)

[a] All products gave satisfactory elemental analyses (C ±0.16%, H ±0.20%, N ±0.17%).

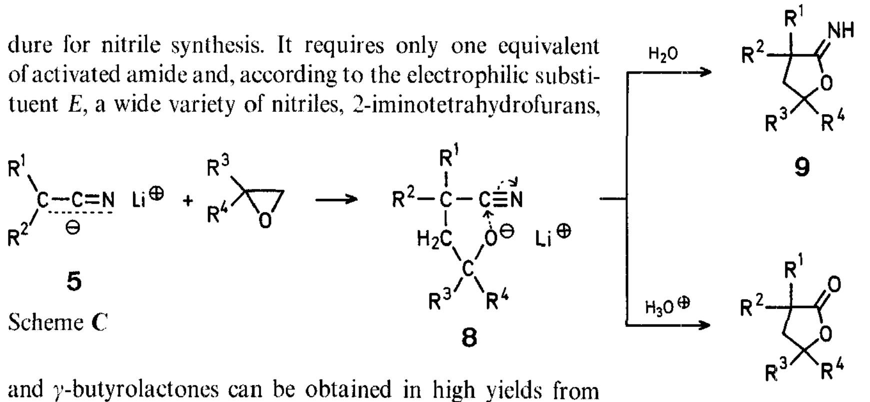
Table 3. 2-Iminofurans **9** and γ-Butyrolactones **10** from Hydrazones **2** via Lithiation and Condensation with Oxiranes

R^1	R^2	R^3	R^4	Yield (%) **9**	Yield (%) **10**	b.p./torr	n_D (temp.)	I.R. (neat) ν cm^{-1}	Empirical formula[a]
CH_3	CH_3	H	CH_3	69	–	56°/14	1.4456 (23°)	1685 (>C=N–)	$C_{17}H_{13}NO$ (127.2)
C_2H_5	C_2H_5	H	CH_3	80	–	86°/14	1.4582 (21°)	1680 (>C=N–)	$C_9H_{17}NO$ (155.2)
CH_3	CH_3	CH_3	CH_3	83	–	57°/14	1.4425 (22°)	1677 (>C=N–)	$C_8H_{15}NO$ (141.2)
C_2H_5	C_2H_5	CH_3	CH_3	89	–	32°/0.01	1.4555 (22°)	1675 (>C=N–)	$C_{10}H_{19}O$ (169.3)
CH_3	H	CH_3	CH_3	–	72	m.p. 51–52° m.p. 51°[3]	–	1762[b] (>C=O)	–
CH_3	CH_3	CH_3	CH_3	–	89	m.p. 41° m.p. 37°[4]	–	1769[b] (>C=O)	–

[a] All products gave satisfactory elemental analyses (C ±0.25%, H ±0.2%, N ±0.18%).

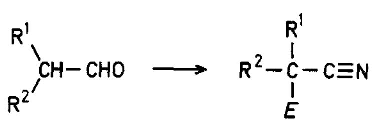
[b] Solvent $CHCl_3$.

dure for nitrile synthesis. It requires only one equivalent of activated amide and, according to the electrophilic substituent *E*, a wide variety of nitriles, 2-iminotetrahydrofurans,



Scheme C

and γ-butyrolactones can be obtained in high yields from aldehydes.



The structure of all products obtained were established by I.R. and N.M.R. spectroscopy. The I.R. spectra were recorded on a Perkin-Elmer 457 spectrometer. The ^{1}H-N.M.R. spectra were recorded on a Perkin-Elmer R 12 using 30% tetrachloromethane solutions and TMS as internal standard.

For the preparation of the activated lithium diethylamide and the metallation, the procedure is the same as that described previously[1].

Preparation of Aliphatic Nitriles (6):

After the solution of **5** has been allowed to stand for 1.5 h at +10°, a solution of the alkyl bromide (0.05 mol) in dry tetrahydrofuran (70 ml) is added drop-wise at −60°. The solution is discoloured and allowed to stir for 2 h at room temperature. After hydrolysis, it is extracted with ether. The ether layer is dried over K_2CO_3. The solvents are removed under reduced pressure and the residue distilled.

Preparation of β-Hydroxy Nitriles (7):

After the solution of **5** has been allowed to stand for 1.5 h at +10° a solution of the carbonyl compound (0.05 mol) in dry tetrahydrofuran (70 ml) is added drop-wise at −60°. The solution is discoloured and allowed to stir for two hours at room temperature. After the same work-up as above the residue is distilled.

Preparation of 2-Iminotetrahydrofurans (9):

After the solution of **5** has been allowed to stand for 1.5 h at +10°, a solution of the oxirane (0.05 mol) in dry tetrahydrofuran (70 ml) is added drop-wise at +5°. The solution is discoloured and is allowed to stir at room temperature for 0.5 h for isobutylene oxide and overnight for propylene oxide. After hydrolysis and the same work-up as above the residue is distilled.

Preparation of Lactones (10):

The procedure is the same as that described for the preparation of the iminotetrahydrofurans. The hydrolysis is made with a solution of tartaric acid (15 g) in water (100 ml). The solution is allowed to stir for five hours at room temperature.

Received: November 3, 1975

---

[1] T. Cuvigny, J. F. Le Borgne, M. Larchevêque, H. Normant, *Synthesis* **1976**, 237.

[2a] For a review see; H. F. Ebel, A. Lüttringhaus in Houben-Weyl *Methoden der organischen Chemie*, E. Müller, Ed., 4th Edit., Vol. XIII/1, Georg Thieme Verlag, Stuttgart, 1970, p. 225ff.
T. Cuvigny, H. Normant, *Organomet. Chem. Synth.* **1**, 237 (1971).
T. Cuvigny, P. Hullot, M. Larchevêque, *J. Organomet. Chem.* **57**, C36 (1973).
M. Larchevêque, A. Debal, T. Cuvigny, *Bull. Soc. Chim. Fr.* **1974**, 1710.

[3] D. Hoch, P. Karrer, *Helv. Chim. Acta* **37**, 397 (1954).

[4] D. Currell, C. A. Grob, S. W. Tam, *Helv. Chim. Acta* **50**, 349 (1967).