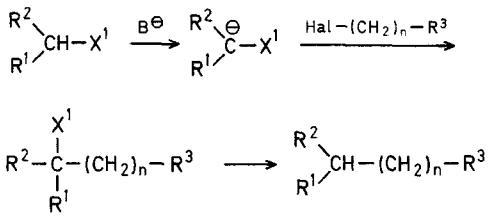
Activation by a Cyano Group: II[1]; A New Synthesis of Substituted Primary Alcohols

A. Debal, T. Cuvigny*, M. Larchevêque

Laboratoire de Synthèse Organique, Laboratoire associé au CNRS, Tour 44–45, Université Pierre et Marie Curie, 4, place Jussieu, 75230 Paris, Cédex 05, France

Recently the use of an activating function (X^1) to promote α-carbanion formation has been frequently reported[2]. Such functions allow temporary inversion of the normal polarity of the carbon atom and thus permit introduction of various substituents *via* nucleophilic substitution. The critical factor is however the ease with which the function X^1 can be subsequently eliminated.



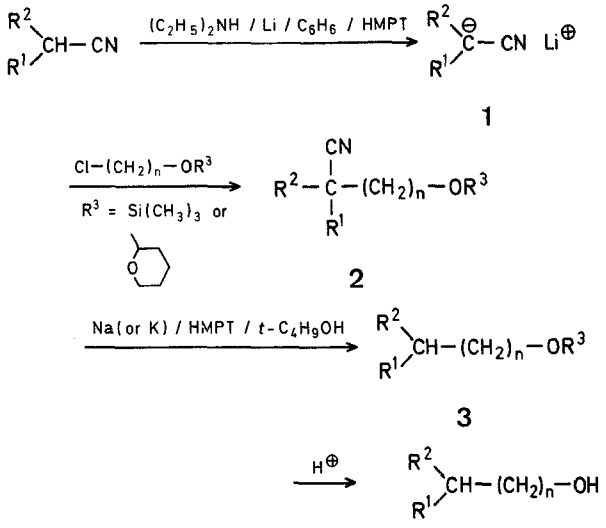
Scheme **A**

When the substituent introduced bears another functional group, cleavage of the X^1 group leads to a substituted functional compound. We now report an application of this principle for the lengthening of a carbon chain by two or more carbon atoms and the simultaneous introduction of a primary alcohol function ($R^3 = OH$ in Scheme **A**).

We have previously shown that the cyano is a suitable X^1 function[1] which gives rise to very reactive carbanions[3,4] and can subsequently be cleaved by reduction in hexamethylphosphoric triamide[5].

The hydroxy function (R^3 in Scheme **A**) must be protected during the synthesis. Various methods are available[6] and the 2-tetrahydropyranyl ethers are often satisfactory. The reaction sequence is shown below in Scheme **B**.

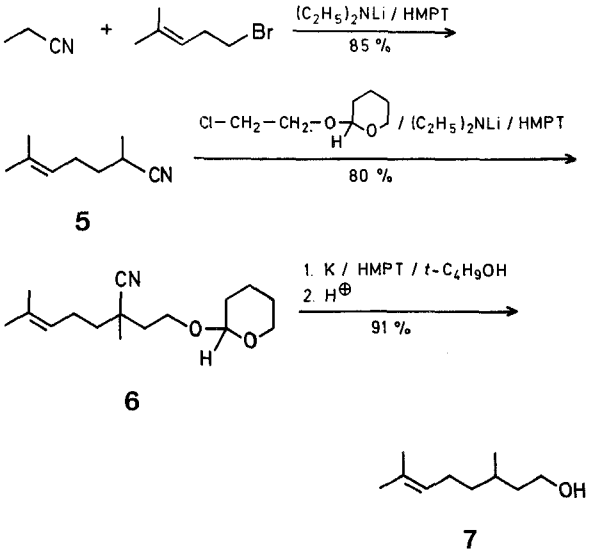
The compound **2** is isolated from reaction of the protected chlorohydrin with the anion **1** generated from the nitrile and an "activated amide"[3]. The reaction can be carried out by normal addition of the halogen compound to the carbanion or by inverse addition of the lithium amide to a mixture of the nitrile and the protected halohydrin. The latter process should be avoided when n = 2 as the corresponding halohydrins readily undergo dehydrohalogenation in basic media. In such cases the use of a trimethylsilyl protecting group gives better results, possibly due to the electronic effect of the silicon atom. Furthermore, the silyl group is cleaved by alkali metal/hexamethylphosphoric triamide solution[7] simultaneously with the cyano group.



Scheme **B**

The elimination of the cyano group is achieved by reduction. We have used sodium or potassium in hexamethylphosphoric triamide in the presence of *t*-butyl alcohol as a protic cosolvent. Results are usually better with potassium and the reaction is more rapid. The protected alcohol **3** is then warmed with a catalytic amount of *p*-toluenesulfonic acid and affords the substituted alcohol **4** in good yield.

To illustrate our method, we have prepared (±)-citronellol; 1-bromo-4-methyl-3-pentene (prepared according to the Julia's method[8] from the cyclopropyl methyl ketone) is reacted with the carbanion derived from propanenitrile and gives the nitrile **5** in 85% yield. The carbanion of this nitrile is condensed with the protected chlorohydrin to give the nitrile **6** in 80% yield. This is then treated with a solution of potassium in hexamethylphosphoric triamide and distillated from a small amount of *p*-toluenesulfonic acid to give citronellol **7** in 62% overall yield.



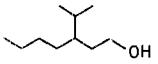
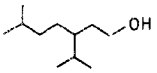
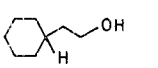
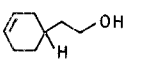
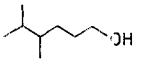
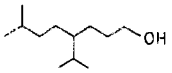
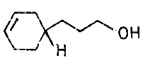
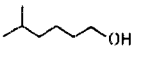
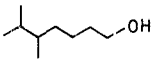
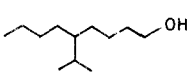
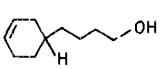
Further examples are given in the Table.

The hydroxy groups of chlorohydrins are protected as tetrahydropyranyl or trimethylsilyl ethers according to the methods of Corey[9] and Langer[10].

Preparation of the Nitrile 2:

A mixture of diethylamine (3.65 g, 0.05 mol), hexamethylphosphoric triamide (11 ml), benzene (11 ml), and hammer wrought lithium

Table. Preparation and Physical Data for Substituted Primary Alcohols

	Intermediate **3**									
	R^1	R^2	R^3	n	Yield[a] (%) of **3**	Alcohol **4**	Yield[a] (%) of **4**	b.p./torr (lit. b.p./torr)	n_D^{23} (lit. n_D/temp.)	Empirical formula[b]
a	H_3C	H_3C		2	76		95	125–127°/760 128°/760[13]	1.4120 1.4053/20°	$C_5H_{12}O$ (88.1)
b	H_3C	i-C_3H_7		2	73		89	77°/13 159–162°/760[13]	1.4247 1.4261/23°	$C_7H_{16}O$ (116.2)
c	n-C_4H_9	i-C_3H_7		2	66		92	107°/13	1.4412	$C_{10}H_{22}O$ (158.3)
d	i-C_5H_{11}	i-C_3H_7	$-Si(CH_3)_3$	2	75		85	114°/13	1.4416	$C_{11}H_{24}O$ (172.3)
e	$-(CH_2)_5-$			2	67		89	97°/14 97–100°/12[14]	1.4660 1.4647/20°	$C_8H_{16}O$ (128.2)
f	$-CH_2-CH=CH-(CH_2)_2-$			2	50		90	102°/13	1.4807	$C_8H_{14}O$ (126.2)
			$-Si(CH_3)_3$	2	67		85		1.4809/25°[15]	
g	H_3C	i-C_3H_7		3	98		90	88°/13	1.4322	$C_8H_{18}O$ (130.2)
h	i-C_5H_{11}	i-C_3H_7		3	86		87	76–78°/0.2	1.4449	$C_{12}H_{26}O$ (186.3)
i	$-CH_2-CH=CH-(CH_2)_2-$			3	85		73	79°/0.5 118°/21[16]	1.4720 1.4853/26°	$C_9H_{16}O$ (140.2)
j	H_3C	H_3C		4	68		90	86°/13 168°/760[13]	1.4237 1.4251	$C_7H_{16}O$ (116.2)
k	H_3C	i-C_3H_7		4	77		91	98°/14	1.4325	$C_9H_{20}O$ (144.2)
l	n-C_4H_9	i-C_3H_7		4	65		89	127°/13	1.4448	$C_{10}H_{18}O$ (186.3)
m	$-CH_2-CH=CH-(CH_2)_2-$			4	61		98	127°/13	1.4767	$C_{10}H_{18}O$ (154.2)

[a] Yield of isolated product.

[b] All alcohols **4** gave satisfactory elemental analyses (C ±0.25%, H ±0.38%).

(0.35 g, 0.05 mol) is stirred under nitrogen until the metal is completely dissolved. The temperature is held at 20–25° as soon as the blood-red colour appears. A mixture of nitrile (0.05 mol), ω-chloroalkyl tetrahydropyranyl ether (0.05 mol) in ether (70 ml) is cooled at −75° under nitrogen. The lithium diethylamide solution is then slowly added; the mixture is kept for 1 h at −75° after the addition and then allowed to warm up to 10° slowly. The mixture is poured into water and extracted four times with ether. The organic phases are combined, washed with crushed ice to remove hexamethylphosphoric triamide and dried over magnesium sulfate. The solvents are evaporated and the residue is distilled under reduced pressure.

On account of the cleavage of the Si-O bond by lithium diethylamide in hexamethylphosphoric triamide[11], with 2-chloroethyl trimethylsilyl ether, the nitrile is first metallated by direct dropwise addition into the amide diluted with ether cooled at −75°, 0.5 h later the protected chlorohydrin is slowly added at −65°. The subsequent procedure is similar to that described previously.

Preparation of the Alcohol 4:

To a mixture of potassium (1.18 g, 0.03 mol) in hexamethylphosphoric triamide (2.5 ml), ether (2.5 ml) under nitrogen, a solution of the nitrile **2** (0.01 mol) in *t*-butyl alcohol (2.9 ml) and ether (20 ml) is added dropwise at 0–5° with stirring. The mixture is then refluxed for 4 h. After the metal is completely dissolved, the mixture is cooled to 0° for hydrolysis under nitrogen. The subsequent procedure is similar to that described previously.

The tetrahydropyranyl protective group is removed by distillation from *p*-toluenesulfonic acid under atmosphere pressure; the alcohol is then distilled under reduced pressure. The trimethyl silyl protective group is removed by reduction[7] and the alcohol is directly distilled under reduced pressure.

Preparation of (±)-Citronellol (7):

2,6-Dimethyl-5-heptenenitrile (**5**): b.p. 91°/14 torr; $n_D^{23} = 1.4422$; *(±)-citronellol* (**7**): b.p. 109–113°/14 torr; $n_D^{23} = 1.4550$ (lit.[12]: b.p. 107–108°/12 torr; $n_D^{12} = 1.4515$).

All new compounds exhibited spectral data in agreement with the proposed structures.

Received: January 19, 1975

[1] M. Larchevêque, T. Cuvigny, *Tetrahedron Lett.* **1975**, 3851.
[2] M. Julia, D. Arnould, *Bull. Soc. Chim. Fr.* **1973**, 743.
D. Seebach, D. Enders, *Angew. Chem.* **87**, 1 (1975); *Angew Chem. Int. Ed. Engl.* **14**, 15 (1975).
K. Kondo, D. Tunemoto, *Tetrahedron Lett.* **1975**, 1007.

[3] T. Cuvigny, H. Normant, *Organomental. Chem. Synth.* **1,** 237 (1971).
M. Larchevêque, A. Debal, T. Cuvigny, *Bull. Soc. Chim. Fr.* **1974,** 1710.
[4] D. S. Watt, *Tetrahedron Lett.* **1974,** 707.
[5] T. Cuvigny, M. Larchevêque, H. Normant, *Bull. Soc. Chim. Fr.* **1973,** 1174.
[6] C. B. Reese in *Protective Groups in Organic Chemistry*, J. F. W. McOmie, Ed., Plenum Press, London, 1973 chap. 3.
[7] H. Normant, T. Cuvigny, *Bull. Soc. Chim. Fr.* **1966,** 3341.
[8] M. Julia, S. Julia, R. Guegan, *Bull. Soc. Chim. Fr.* **1960,** 1072.
[9] E. J. Corey, K. Achiwa, J. A. Katzenellenbogen, *J. Am. Chem. Soc.* **91,** 4318 (1969).
[10] S. H. Langer, S. Connell, I. Wender, *J. Org. Chem.* **23,** 50 (1958).
[11] T. Cuvigny, H. Normant, *J. Organometal. Chem.* **38,** 217 (1972).
[12] V. Grignard, R. Escourrou, *Bull. Soc. Chim. Fr.* (4) **37**, 543 (1925).
[13] R. C. Huston, A. H. Agett, *J. Org. Chem.* **6,** 128 (1941).
[14] N. Zelinsky, *Ber. dtsch. chem. Ges.* **41,** 2628 (1908).
[15] S. Winstein, P. Carter, *J. Am. Chem. Soc.* **83,** 4485 (1961).
[16] J. Colonge, R. Falcotet, R. Gaumont, *Bull. Soc. Chim. Fr.* **1958.** 211.