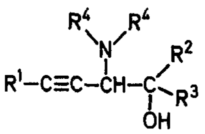
A General Method for the Synthesis of α-Amino-β,γ-acetylenic Alcohols

R. Epsztein, F. Mercier

C.N.R.S., IRCHA, F-91710 Vert-Le-Petit, France

A generally applicable method for the synthesis of α-amino-β,γ-acetylenic alcohols (2-amino-3-alkynols)



has to our knowledge hitherto not been reported, although these compounds are interesting from several points of view. They may be used as intermediates in the synthesis of oxiranes and furans[1]. On the other hand it may be expected that some of them possess useful pharmacological properties in analogy to other aminoalcohols such as ephedrine.

We report here a simple procedure which can be applied to the synthesis of a great variety of the above 2-amino-3-alkynols (**11–16**) starting from 2-alkynamines (**1–6**).

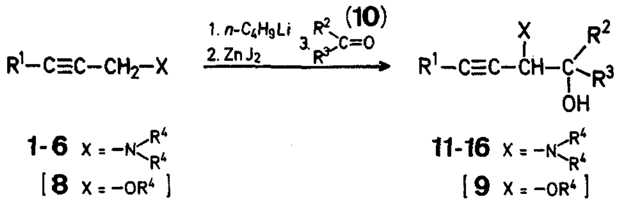
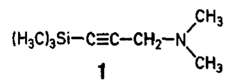
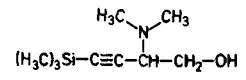
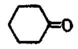
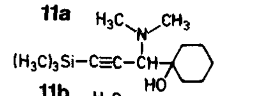
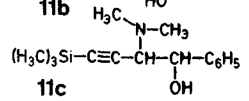
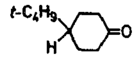
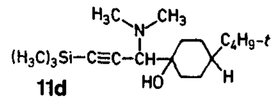
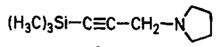
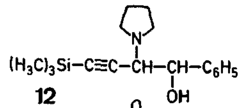
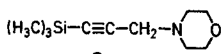
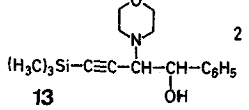
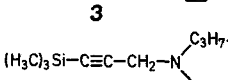
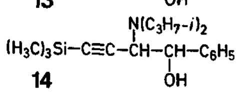
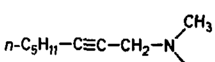
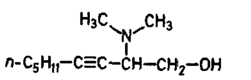
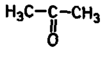
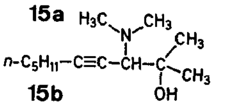
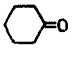
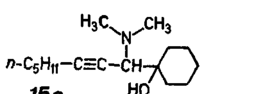
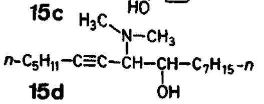
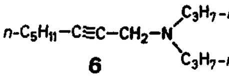
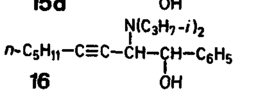


Table 1. Conversion of 2-Alkyn-1-amines to 2-Amino-3-alkynols

2-Alkyn-1-amine	Carbonyl Compound **10**	Product	Yield [%]	m.p. or b.p.	n_D^{20}	Molecular formula[a]
 **1**	$H_2C=O$	 **11a**	50	b.p. 99°/17 torr; m.p. 43°		$C_9H_{19}NOSi$ (185.3)
		 **11b**	73	m.p. 42–43°		$C_{14}H_{27}NOSi$ (253.4)
	C_6H_5-CHO	 **11c**	79	b.p. 95°/0.1 torr		$C_{15}H_{23}NOSi$ (261.4)
		 **11d**	80	b.p. 93°/0.1 torr; m.p. 96°[b]	1.4720	$C_{18}H_{35}NOSi$ (309.5)
 **2**	C_6H_5-CHO	 **12**	82	b.p. 110°/10^{-4} torr[c]; m.p. 123°[d]		$C_{17}H_{25}NOSi$ (287.5)
 **3**	C_6H_5-CHO	 **13** [2]	80			
 **4**	C_6H_5-CHO	 **14**	60	b.p. 114°/0.1 torr	1.4960	$C_{19}H_{31}NOSi$ (317.5)
 **5**	$H_2C=O$	 **15a**	50	b.p. 63°/0.1 torr	1.4630	$C_{11}H_{21}NO$ (183.3)[e]
		 **15b**	50	b.p. 72°/0.2 torr	1.4560	$C_{13}H_{25}NO$ (211.3)
		 **15c**	57	b.p. 98°/0.1 torr	1.4795	$C_{16}H_{29}NO$ (251.4)
	$n-C_7H_{15}-CHO$	 **15d**	70	b.p. 108°/0.05 torr	1.4620	$C_{18}H_{35}NO$ (281.5)
 **6**	C_6H_5-CHO	 **16**	53	b.p. 110°/10^{-4} torr[c]	1.5100	$C_{21}H_{33}NO$ (325.5)

[a] The microanalyses showed the following maximum deviations from the calculated values: C, ±0.52; H, ±0.26; N, ±0.26; O, ±0.17; Si, ±0.20.

[b] Isomer having OH on ring in axial position.

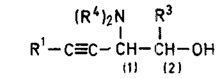
[c] Bath temperature.

[d] *erythro* diastereoisomer.

[e] Oxalate: m.p. 74° (from acetone/ether).

$C_{13}H_{23}NO_5$	calc.	C 57.12	H 8.48	N 5.13
(273.3)	found	57.16	8.26	5.21

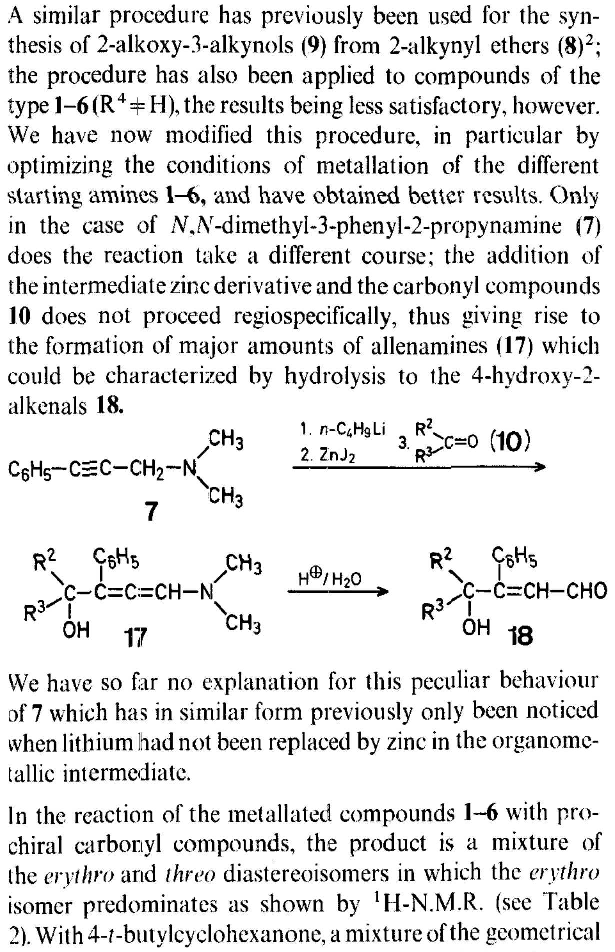
Table 2. ^{1}H-N.M.R. Spectra of Compounds **11–16** (R^2=H)



Compound	Solvent	δ(H-1) [ppm] e^a	t^a	δ(H-2) [ppm] e	t	$J_{1,2}$ [Hz] e	t	δ[$(H_3C)_3Si$] [ppm] e	t
11c	pyridine	3.83	3.48	5.07	4.72	7.2	9.7	0.23	0.18
11d	benzene	3.08[b]	3.55[c]						
12	pyridine	4.0	3.81	5.11	4.77	5.9	9.3	0.20	0.14
	$CDCl_3$	3.68	3.60	4.85	4.57	4.5	10.0	0.22	0.08
14	pyridine	3.85	3.43	5.01	4.56	7.5	9.3	0.21	0.14
15a	$CDCl_3$	3.49		3.49					
	pyridine	3.70		3.70					
15c	$CDCl_3$	3.08							
16	$CDCl_3$	3.67	—	4.55	4.36	7.1	9.2		

[a] *e* = *erythro*; *t* = *threo*. [b] OH axial. [c] OH equatorial.

A similar procedure has previously been used for the synthesis of 2-alkoxy-3-alkynols (**9**) from 2-alkynyl ethers (**8**)[2]; the procedure has also been applied to compounds of the type **1–6** ($R^4 \neq H$), the results being less satisfactory, however. We have now modified this procedure, in particular by optimizing the conditions of metallation of the different starting amines **1–6**, and have obtained better results. Only in the case of *N*,*N*-dimethyl-3-phenyl-2-propynamine (**7**) does the reaction take a different course; the addition of the intermediate zinc derivative and the carbonyl compounds **10** does not proceed regiospecifically, thus giving rise to the formation of major amounts of allenamines (**17**) which could be characterized by hydrolysis to the 4-hydroxy-2-alkenals **18**.



We have so far no explanation for this peculiar behaviour of **7** which has in similar form previously only been noticed when lithium had not been replaced by zinc in the organometallic intermediate.

In the reaction of the metallated compounds **1–6** with prochiral carbonyl compounds, the product is a mixture of the *erythro* and *threo* diastereoisomers in which the *erythro* isomer predominates as shown by ^{1}H-N.M.R. (see Table 2). With 4-*t*-butylcyclohexanone, a mixture of the geometrical stereoisomers is obtained, the main isomer being the one with the hydroxy group in axial position.

Preparation of 2-Amino-3-alkynols (11–16); General Procedure: To a 2 molar solution (28 ml) of butyllithium in hexane under an argon atmosphere, tetrahydrofuran (50 ml) is added with stirring at −80°, followed by the dropwise addition of the amine **1–6** (0.05 mol). Stirring is continued for 1 h at −70° to −80° for amines **1**, **2**, **3**, for 2 h at −50° for amine **4**, for 2 h at −20° for amine **5**, and for 20 h at −10° for amine **6**. Then, a solution of zinc iodide [prepared by adding a solution of iodine (10 g) in tetrahydrofuran (50 ml) to zinc dust (5 g) with exclusion of moisture] precooled with running water is added dropwise to the stirred mixture. Stirring is continued for 1 h; then, the carbonyl compound **10** (0.055 mol) is added and the mixture stirred for 2 h (in the case of **10** = paraformaldehyde, the mixture is stirred for 24 h). The whole reaction solution is then poured onto a mixture of crushed ice and solid potassium carbonate. The solid product is removed by filtration (or decantation) and washed with ether. The filtrate is washed with water, shaken with solid potassium carbonate for 1 h, and again filtered. The solvent is evaporated from the filtrate and the residue is purified by distillation or recrystallization from petroleum ether (for compound **12**, from cyclohexane).

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[1] R. Epsztein, unpublished results.
[2] F. Mercier, R. Epsztein, S. Holand, *Bull. Soc. Chim. Fr.* **1972**, 690.
H. Chwastek, R. Epsztein, N. LeGoff, *Tetrahedron* **29**, 883 (1973).
[3] J. Cousseau, L. Gouin, *Bull. Soc. Chim. Fr.* **1974**, 2955.
[4] E. Lukevits, A. E. Pestunovich, V. A. Pestunovich, M. G. Voronkov, *Zh. Obshch. Khim.* **40**, 624 (1970); *J. Gen. Chem. USSR* **40**, 595 (1970).
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