An Efficient General Synthesis of α-Amino Acetals

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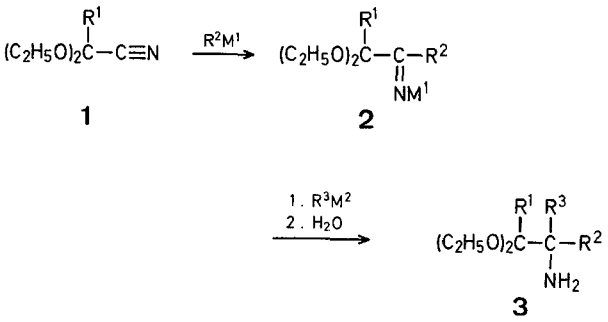
A recent paper[1] points out the interest in substituted α-amino acetals (protected forms of the unstable aminoaldehydes and aminoketones) for the preparation of various heterocycles and proposes an interesting route to such compounds via oxime tosylates. This method is, however, limited by the availability of starting materials and the nature of the substituents on the amino acetal. Alternatively, the catalytic hydrogenation of α,α-dialkoxynitriles affords aminoacetals[2], but the synthesis cannot be extended to compounds **3** with R^2 and $R^3 \neq H$.

We have shown that activated nitriles such as, for example, methoxyacetonitrile, permit a rather unexpected double addition of organometallic reagents and give primary



1 **2**

3

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Table. α-Amino Acetals **3**

Product	R^1	R^2M	R^3M	Yield [%][a]	m.p. [°C] or b.p. [°C]/torr	Molecular formula[b]	I.R. (film) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]	M.S. (70 eV) *m/e* (rel. intensity %)
3a	H	*n*-C_4H_9MgBr *n*-C_4H_9Li	*n*-C_4H_9Li *n*-C_4H_9Li	89 95	65°/0.05	$C_{14}H_{31}NO_2$ (245.4)	3380; 3350; 1150–1100	1.0 (m, 24H + NH_2); 3.7 (m, 4H); 4.05 (s, 1H)	200 (11); 188 (6); 142 (100)
3b	H	C_6H_5MgBr *n*-C_4H_9MgBr	*n*-C_4H_9Li C_6H_5Li	90 60[c]	87°/0.05	$C_{16}H_{27}NO_2$ (265.4)	3380; 3300; 3100–3000; 1160–1050	1.0 (m, 9H); 1.45 (s, NH_2); 4.25 (s, 1H); 7.4 (m, $5H_{arom}$)	220 (8); 208 (6); 162 (100); 103 (88); 75 (47)
3c	H	C_6H_5MgBr	C_6H_5Li	80	56–57° (40–60° PE)	$C_{18}H_{23}NO_2$ (285.4)	3350; 3270; 3100–3000; 1100–1020	1.20 (t, 6H); 1.90 (s, NH_2); 3.4 (m, 4H); 4.85 (s, 1H); 7.2 (m, $10H_{arom}$)	240 (7); 182 (97); 103 (100); 75 (50)
3d	C_6H_5	*n*-C_4H_9Li	$LiAlH_4$ (R^3=H in **3**)	82	107°/0.2	$C_{16}H_{27}NO_2$ (265.4)	3400; 3320; 3090–3000; 1100–1030	0.90 (t, 3H); 1.5 (m, 8H + NH_2); 1.25 (t, 6H); 3.2 (m, 1H); 3.55 (q, 4H); 7.45 (m, $5H_{arom}$)	220 (9); 179 (100); 151 (23); 123 (30); 86 (41)

[a] Yield of distilled or recrystallised product.
[b] The microanalyses were in satisfactory agreement with the calculated values (C ±0.34, H ±0.15, N ±0.08).
[c] 30% of pentanal diethylacetal also observed.

amines after hydrolysis[3,4]. In the case of α,α-diethoxynitriles **1** we employ here, a similar reaction occurs as shown in the scheme.

The first addition to the cyano-function of **1** can be carried out by an organomagnesium reagent or an organolithium reagent and leads exclusively to the intermediate ketiminate **2**. By then using an organolithium reagent or lithium aluminium hydride, a second total addition to **2** becomes possible and leads to the α-amino acetal **3** after hydrolysis.

The present method is a simple, one-pot synthesis giving excellent yields in compounds **3**. The starting material is easily synthesized according to Böhme and Neidlein[5] from the corresponding orthoesters[6] and a 2-oxoalkanenitrile. There is no major limitation as to the nature of the substituents R^2 and R^3 on **3** except in the case of hindered nitriles (product **3d**) where the second addition is possible only with the less voluminous lithium aluminium hydride (R^3=H), probably due to steric hindrance. When R^1=H, one could expect a deprotonation of **1** by the organometallic reagent and consequently a decrease in the overall yield of **3**. Surprisingly, this is not observed, nor is any other secondary reaction.

α-Amino Acetals 3; General Procedures:

Method A: Two different organometallic reagents: To a solution of the organometallic reagent (16 mmol; ~2 molar solutions of Grignard reagents in ether are prepared in the usual manner and the organolithium reagents are commercially available) is added under a nitrogen atmosphere the nitrile **1** (15 mmol) in diethyl ether (~20 ml) and the solution is stirred for ~12 h at room temperature. A solution of the second organolithium reagent (20 mmol) or a suspension of lithium aluminium hydride (20 mmol) in diethyl ether (~15 ml) is then added under a nitrogen atmosphere and the reaction mixture is stirred for 12–15 h at room temperature. After cooling at 0°C, the mixture is hydrolysed by addition of an approximately equal volume of saturated ammonium chloride solution and extracted with diethyl ether (4 × 50 ml). The combined extracts are washed with water (3 × 20 ml), dried with magnesium sulphate, and then the solution is concentrated and analysed.

Method B: Two identical organolithium reagents: The nitrile **1** (15 mmol) in diethyl ether (~20 ml) is added as above to the organolithium reagent (40 mmol). After 2–3 h at room temperature, the reaction mixture is treated as above.

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[1] J. LaMattina, R. T. Suleske, *Synthesis* **1980**, 329.
[2] J. Erickson, W. Montgomery, O. Rorso, *J. Am. Chem. Soc.* **77**, 6640 (1955).
[3] M. Chastrette, G. P. Axiotis, R. Gauthier, *Tetrahedron Lett.* **1977**, 23.
[4] R. Gauthier, G. P. Axiotis, M. Chastrette, *J. Organomet. Chem.* **140**, 245 (1977).
[5] H. Böhme, R. Neidlein, *Chem. Ber.* **95**, 1859 (1962).
[6] S. McElvain, J. W. Nelson, *J. Am. Chem. Soc.* **64**, 1852 (1942).

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