

Unexpected Thorpe Reaction of an α -Alkoxy nitrile

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Abstract: α -Alkoxy nitrile **1** in the presence of tris(methylthio)methyl lithium **2** at -78°C gave the dimer **5** instead of the expected C_1 -elongated product **3**. The formation of compound **5** is explained in terms of anion formation and self-condensation, a variant of the Thorpe reaction. Scrutinizing the ^1H NMR spectra revealed that the enamine tautomer **5b** is predominant over the imine **5a** in the solvents investigated.

Keywords: Thorpe reaction, self-condensation.

Introduction

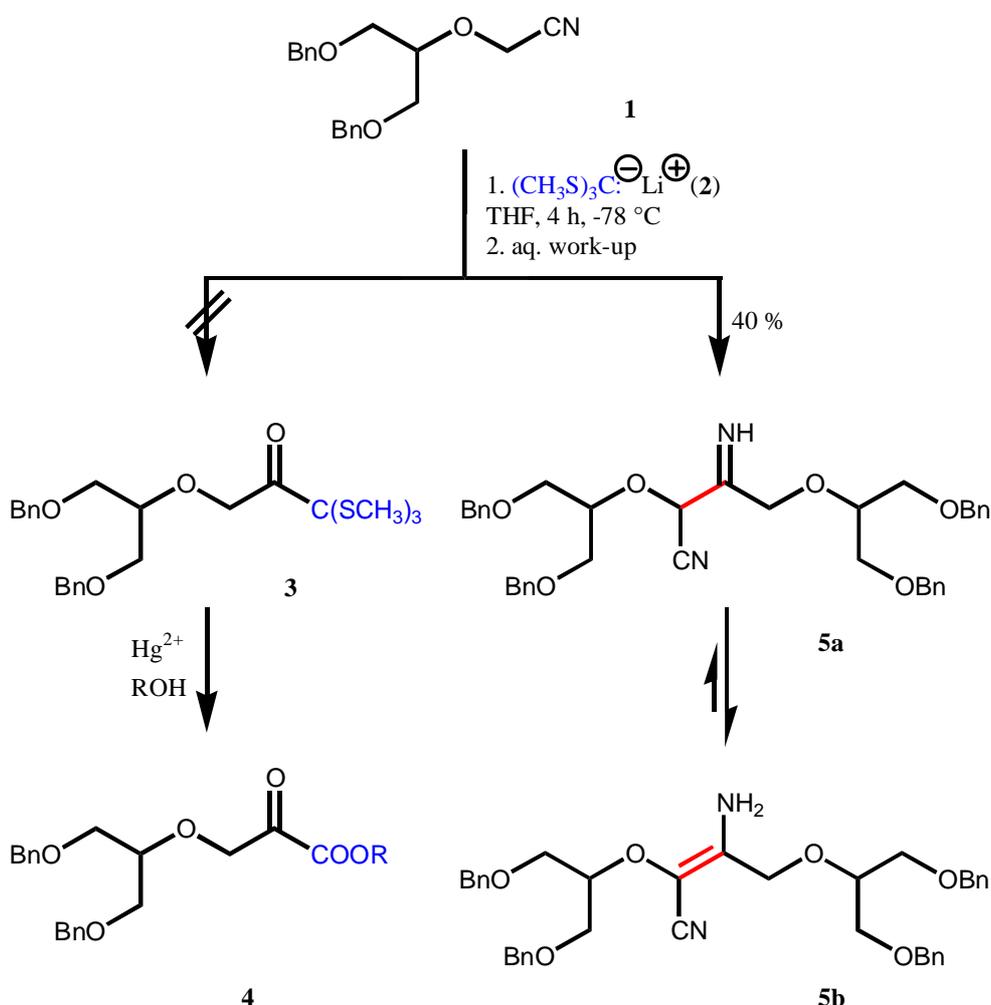
Nitrile **1** (*Scheme 1*) was obtained *en route* to acyclic analogues of the C-nucleoside tiazofurin [1]. This compound was deemed to be a good starting material for the synthesis of α -keto ester **4** via intermediate **3**. This assumption was based on analogy with the Grignard reaction of nitriles giving rise to ketones [2] or the Blaise reaction (Reformatsky reaction of nitriles affording β -keto esters) [3].

For the required carboxylate anion synthon different tris(alkylthio or arylthio)methyl lithiums, derived from tris(alkyl or arylthio)methanes [4], were used successfully in the C_1 elongation of ketones [5] and lactones [6]. Most often [tris(methylthio)methyl]lithium (**2**) was applied which is stable up to -40°C [7]. The obtained trithioorthoesters can be transformed into the corresponding esters using the common mercury(II) salt-assisted demercaptalisation procedure. In principle, alkyl chloroformates could also be employed as C_1 synthons. However, in the single reported Reformatsky-type reaction of ethyl chloroformate with ethyl acetoacetate in the presence of a zinc-copper couple leading to diethyl

2-hydroxy-2-methylsuccinate, the yield was rather low (20%) [8]. In a recent application, ethyl chloroformate was allowed to react with methyl phenylglyoxylate in a titanium(IV)-promoted reaction to afford ethyl methyl 2-hydroxy-2-phenylmalonate in 60% yield [9].

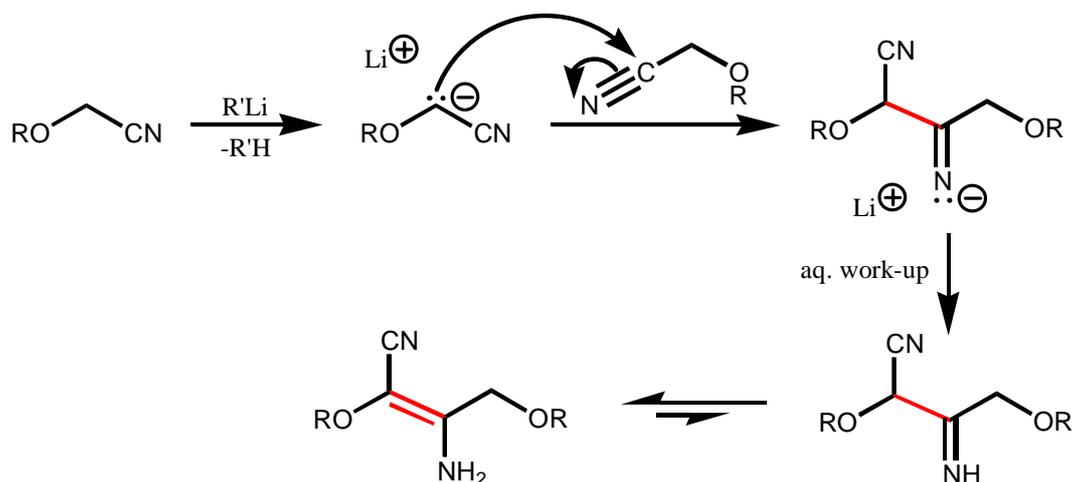
Results and Discussion

Nitrile **1** was allowed to react with compound **2** at -78°C for 4 h. Contrary to our expectations, compound **3** was not obtained. The isolated substance exhibited surprisingly complicated ^1H NMR spectra in different solvents, according to the microanalysis it contained no sulfur and its elemental composition was identical with that of nitrile **1**. Its low-voltage (15 eV) EI mass spectrum showed a molecular ion at m/z 622 (the molecular mass of the starting nitrile is 311) and a fragmentation pattern compatible only with the dimeric structures **5a** and **5b**. Scrutiny of the ^1H NMR spectrum revealed that the substance exists as an enamine (**5b**) rather than an imine (**5a**). The IR spectrum also confirmed the presence of a nitrile group ($\nu_{\text{CN}} 2180\text{ cm}^{-1}$).



Scheme 1.

The literature search for precedents (Beilstein's CrossFire 4.0, release BS9902PRPR using Beilstein Commander 4.0) showed that α -alkoxynitriles react normally with Grignard reagents [10] while organolithium [11] and organosodium compounds [12,13] provoke self-condensation. This can be explained by the strong basicity of organolithiums and the result is, just as in the above instance, the special case of the well-known Thorpe reaction [14] (Scheme 2).



Scheme 2.

It is noteworthy that even acetonitrile tends to react abnormally with Grignard reagents, *e.g.* with phenylmagnesium bromide, only 42% of the expected acetophenone has been obtained along with 32% of benzene [15]. Nitriles lacking α -hydrogens react normally and afford ketones.

Experimental

General

To tris(methylthio)methane [4] (0.927 g, 6.0 mmol) dissolved in anhydrous THF (2.0 mL) was added butyllithium (1.26 M solution, 5.20 mL, 6.60 mL) at -78°C under nitrogen. Nitrile **1** [1] (1.40 g, 4.5 mmol) dissolved in anhydrous THF (10.0 mL) was added dropwise to this solution after 20 min and kept at -78°C for 4 h. The reaction mixture was quenched at -60°C with satd. NH_4Cl solution. After allowing to warm up to room temperature, the mixture was diluted and extracted with chloroform (25 mL). The aqueous phase was extracted with chloroform (2×50 mL). The combined organic phases were dried (MgSO_4) and evaporated *in vacuo*. Chromatographic purification using 20% (v/v) ethyl acetate in hexanes afforded 3-amino-2,4-bis{2-(benzyloxy)-1-[(benzyloxy)methyl]-ethoxy}-2-butene-nitrile (**5**, 0.56 g, 40%) as a yellow oil.

Spectral Data

IR (KBr, ν , cm^{-1}): 3450m, 3330m, 3020m, 2910s, 2860s, 2180m, 1680m, 1493m, 1450m, 1090m.

^1H NMR (CDCl_3 , 200 MHz, δ , ppm): 3.55 (d, J 6 Hz, 4 H, 2 x CH_2); 3.65 (d, J 6 Hz, 4 H, 2 x CH_2); 3.71 (m, 1 H, CH); 3.94 (m, 1 H, CH); 4.37 (s, 2 H, 4- CH_2); 4.49 (s, 4 H, 2 x PhCH_2); 4.52 (s, 4 H, 2 x PhCH_2); 5.45 (br s, exchangeable with D_2O , 2 H, NH_2); 7.30 (m, 20 H, 4 x C_6H_5).

^1H NMR (DMSO-d_6 , 200 MHz, δ , ppm): 3.52 (d, J 5 Hz, 4 H, 2 x CH_2); 3.65 (d, J 5 Hz, 4 H, 2 x CH_2); 3.72 (m, 1 H, CH); 3.88 (m, 1 H, H); 4.20 (s, 2 H, 4- CH_2); 4.45 (s, 8 H, 4 x PhCH_2); 6.00 (br s, exchangeable with D_2O , 2 H, NH_2); 7.30 (m, 20 H, 4 x C_6H_5).

EI-MS (15 eV, m/z , %): 622 (5, M^+); 531 (1, $\text{M}-91$); 418 (4); 387 (4); 367 [4, $\text{M}-\text{CH}(\text{CH}_2\text{OBn})_2$]; 331 (6); 292 (9); 278 (24); 220 (14); 181 (75); 102 (88); 91 (100, C_7H_7^+).

Anal. calcd. for $\text{C}_{38}\text{H}_{42}\text{N}_2\text{O}_6$ (622.750): C, 73.29; H, 6.80; N, 4.50; found: C, 73.49; H, 6.71; N, 4.18.

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Samples Availability: not available.