An Efficient One-Step Synthesis of 3-Oxoalkanenitriles

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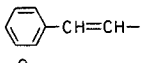
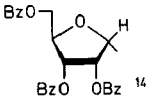
3-Oxoalkanenitriles (β-ketonitriles) have been used as the key starting materials in the synthesis of several heterocyclic ring systems, such as dihydropyrans[1], dihydrothiopyrans[1], tetrahydropyridines[2], pyridines[2], and pyrimidines[3,4]. We were in need of an efficient and mild procedure for the preparation of 3-oxoalkanenitriles **(4)** in connection with our efforts directed towards the synthesis of *C*-nucleosides. Available procedures

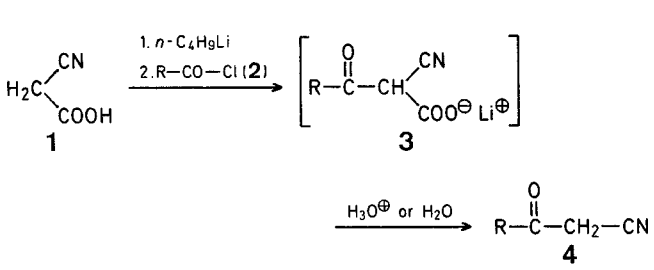
Table. 3-Oxoalkanenitriles **(4)** prepared

R	Work-up Procedure	Yield [%] obtained[a]	Yield [%] reported	m.p. [°C] (solvent)	Lit. m.p. [°C] or Molecular formula
	A	97	94[12]	82–83° (water)	81–82°[12]
	A	81	94[1]	97–98° (butanol)	96–97°[1]
	B	52	–[13]	75°[b]	74–75°[13]
	B	41		137.5–140°[b]	$C_{30}H_{25}NO_8$ (527.2)[c]
t-C_4H_9–	B	51	10[6]	70°[b]	59–60°[6]

[a] Yield of purified product.
[b] Isolated as a syrup which crystallized.
[c] calc. C 68.31 H 4.78 N 2.66; found 68.28 4.77 2.58

from the literature either produced acyclic compounds **4** in less than optimal yields[5–8] or involved harsh reaction conditions, i.e., sodium amide in liquid ammonia[2], or sodium hydride in tetrahydrofuran at reflux[1]. Procedures involving the electrophilic addition of a cyano group α to a carbonyl moiety such as in the cyanation of a ketone[8,9,10] were not adaptable to our needs, as these methods, in general, do not produce 3-oxoalkanenitriles unsubstituted at the 2-position. We now report a general and mild one-step method for the synthesis of a variety of 3-oxoalkanenitriles **(4)** unsubstituted at the 2-position.

The condensation of salts of substituted malonic monoesters with acid chlorides[11,12] has provided an excellent route for the preparation of 3-oxoalkanoic esters (β-ketoesters). We have now found that the condensation of an acid chloride **(2)** with the dilithium salt of cyanoacetic acid **(1)** affords 3-oxoalkanenitriles **(4)** in good yield, directly upon hydrolysis of the intermediate lithium 2-cyano-3-oxoalkanoate **(3)**.



The reaction is performed using a molar ratio **1**:n-C_4H_9Li:**2** = 2:4:1.

3-Oxoalkanenitriles (4); General Procedure:

A solution of cyanoacetic acid (0.91 g, 10.7 mmol; dried with magnesium sulfate in ethyl acetate) and 2,2′-bipyridine (1 mg; as an indicator) in tetrahydrofuran (60 ml, distilled from sodium) is cooled to −70 °C with stirring under a nitrogen atmosphere. The mixture is titrated dropwise with butyllithium in hexane (21.4 mmol, 13.4 ml) while allowing the reaction temperature to slowly rise to 0 °C. After the red color persists at 0 °C, the slurry is recooled to −70 °C and a solution of the acid chloride **2** in tetrahydrofuran (10 ml, distilled from sodium) is added dropwise. The slurry is stirred at −70 °C for 1 h and then allowed to gradually come to room temperature over a period of 1 h. The work-up of the mixture is accomplished using one of the following procedures.

Work-up A: Hydrochloric acid (25 ml) is added to the mixture. The solution is extracted with chloroform (2 × 50 ml) and the combined organic extracts are washed with saturated sodium hydrogen carbonate solution (1 × 25 ml) and then with saturated sodium chloride solution (1 × 25 ml). The organic layer is dried with magnesium sulfate, filtered, and evaporated in vacuo (bath temperature <40 °C). The residual crude product **4** is recrystallized from an appropriate solvent (see Table).

Work-up B: Water (25 ml) is added dropwise to the mixture. The mixture is evaporated (bath temperature <40 °C) in vacuo, and the residue is dissolved in chloroform (10 ml), filtered, and the filtrate applied to a silica column (2.5 × 25 cm, # 70–200 mesh). The column is eluted with hexane/ethyl acetate (3/1; v/v). The U.V. absorbing fractions are pooled, and the solvent is evaporated in vacuo (bath temperature < 40 °C) to yield the desired product **4** (Table).

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[1] M. Augustin, W. Jahreis, W. D. Rudorf, *Synthesis* **1977**, 472.
[2] C. R. Hauser, C. J. Eby, *J. Am. Chem. Soc.* **79**, 728 (1957).
[3] B. R. Baker, J. H. Jordaan, *J. Heterocyclic Chem.* **3**, 324 (1966).
[4] S. Kambe, K. Saito, H. Kishi, *Synthesis* **1979**, 287.
[5] C. Goasdoue, R. Couffignal, *Tetrahedron Lett.* **1979**, 1585.
[6] C. Rodriguez, A. Lamazouere, J. Sotiropoulos, *C. R. Acad. Sci.* [C] **291**, 179 (1980).
[7] D. Kahne, D. B. Collum, *Tetrahedron Lett.* **22**, 5011 (1981).
[8] J. K. Rasmussen, A. Hassner, *Synthesis* **1973**, 682.
[9] L. Claisen, R. Stock, *Ber. Dtsch. Chem. Ges.* **24**, 130 (1891).
[10] R. E. Ireland, J. A. Marshall, *J. Am. Chem. Soc.* **81**, 2907 (1959).
[11] W. Wierenga, H. I. Skulnick, *J. Org. Chem.* **44**, 310 (1979).
[12] C. J. Eby, C. R. Hauser, *J. Am. Chem. Soc.* **79**, 723 (1957).
[13] C. Musante, S. Fatutta, *Gazz. Chim. Ital.* **88**, 879 (1958).
[14] Starting material was a 1:1 α to β mixture; the product, however, possessed only the α configuration.