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PREPARATION AND REACTIVITY OF ACETOACETONITRILE DIANION

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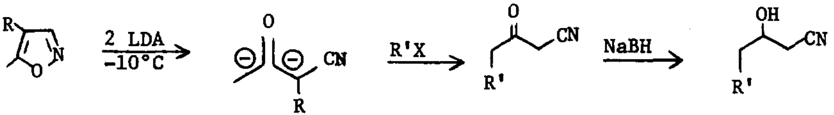
Dianions of 1,3-dicarbonyl and 1,3-dicarbonyl-like compounds[1,2] have become a valuable part of present day methodology in organic synthesis. We wish to report the preparation of a new reagent of this general type, acetoacetonitrile dianion (2a), and its reaction with a number of electrophiles.

After a preliminary investigation of various experimental conditions[3], it was found that 2a is most conveniently prepared by treatment of 5-methylisoxazole[4a] (1a) with two equivalents of lithium diisopropylamide (LDA) in THF at -10°C. When allyl bromide (1.1 equivalents) was added to this solution, compound 3a [IR (film) 2253, 1725 cm^{-1}; NMR ($CDCl_3$)[5] δ 2.20-2.93 (m, 4H), 3.62 (s, 2H), 4.87-6.18 (m, 3H)] was obtained in 60% yield following standard aqueous work-up.[6] Not unexpectedly, 3a, a derivative of cyanoacetone[7], rapidly polymerized to an orange glass upon standing at room temperature or upon attempted distillation.



1a (R=H)
1b ($R=CH_3$)

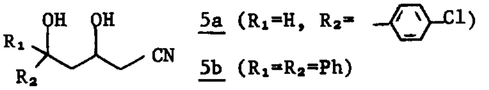
2a (R=H)
2b ($R=CH_3$)

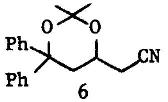
3a ($R'=CH_2CH=CH_2$)
3b ($R'=CH_2CH_2CH_3$)
3c ($R'=CH_2Ph$)

4a ($R'=CH_2CH=CH_2$)
4b ($R'=CH_2CH_2CH_3$)
4c ($R'=CH_2Ph$)

In order to circumvent the problem of the instability of 3a, this material was, upon isolation in crude form, immediately reduced with $NaBH_4$ and distilled to give cyano alcohol 4a [IR (film) 3425, 2240 cm^{-1}; NMR ($CDCl_3$)[5] δ1.20-2.50 (m, 4H), 2.50 (d, 2H, J = 4.5 Hz), 3.33-4.12 (m, 2H, 1 ex), 4.84-6.20 (m, 3H)] in 49% overall yield from 1a. Similarly, alkylation with n-propyl iodide and benzyl bromide yielded 4b (52%) and 4c (50%), respectively.

The reaction of 2a with aldehydes and ketones was next examined. Addition of 1.1 equivalents of p-chlorobenzaldehyde to 2a and subsequent reduction of the crude product as previously described afforded an 82% yield of the diastereomeric mixture 5a [IR (CH_2Cl_2) 3390, 2260 cm^{-1}; NMR ($CDCl_3$)[5] δ 1.67-1.98 (m, 2H), 2.47 (d, 2H, J = 4.5 Hz), 4.67-5.04 (m, 1H), 7.27 (s, 4H)]. Repetition of the same sequence with benzophenone as the electrophile gave a 44% yield of 5b [mp 114-117°C; IR (Nujol) 3290, 2260 cm^{-1}; NMR (DMSO-d_6)[5] δ 2.36-2.60 (m, 4H), 3.58-4.02 (m, 1H), 5.44 (bs, 1H, ex), 5.80 (bs, 1H, ex), 7.13-7.62 (m, 10H)] after recrystallization from ether/hexane.





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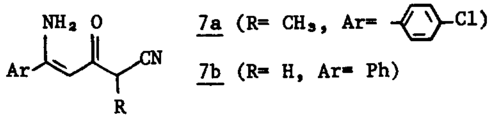
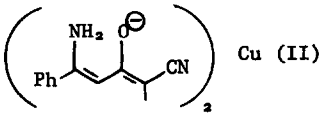
Compound 5b was further characterized by reaction with 2,2-dimethoxypropane and a catalytic amount of p-TsOH at 25°C to give a quantitative yield of 6 [mp 124-125°C; IR (Nujol) 2250 cm^{-1}; NMR ($CDCl_3$)^5 δ 0.94 (s, 3H), 1.53 (s, 3H), 1.89 (d, 1H, J = 10 Hz), 2.45 (d, 1H, J = 4.5 Hz), 2.76 (d, 2H, J = 10 Hz), 4.02-4.49 (m, 1H), 7.20 (s, 5H), 7.29 (s, 5H)].

Reaction of 2a or 2b (prepared from commercially available[4b] 4,5-dimethylisoxazole, 1b) with nitriles gave two types of products, depending on the reaction time. For example, addition of p-chlorobenzonitrile to 2b (-10°C, THF) followed by aqueous work-up after 30 min at 0°C afforded 7a [mp 100-102°C; IR (Nujol) 3330, 3165, 2245, 1622, 1616 cm^{-1}; NMR ($CDCl_3$)^5 δ 1.52 (d, 3H, J = 5.5 Hz), 3.44 (q, 1H, J= 5.5 Hz), 5.60 (s, 1H), 7.44 (s, 4H); MS m/e 234 (M^+), 180] in 32% isolated yield.





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In similar fashion, 2a and benzonitrile yielded 7b [24%; mp 95-96°C; IR (CH_2Cl_2) 3470, 2252, 1615, 1599 cm^{-1}; NMR ($CDCl_3$)^5 δ 3.35 (s) and 3.53 (s) (2H, keto and enol forms), 5.49 (s) and 6.33 (s) (1H, keto and enol forms), 7.24-7.96 (m, 5H); MS m/e 186 (M^+), 146]. It should be noted that 7b, a vinylogous amido nitrile, showed no tendency toward polymerization due to the decreased acidity of the methylene protons.

The vinylogous amido nitriles could be readily isolated from the crude reaction mixtures as their Cu(II) chelates. Specifically, 2b and benzonitrile yielded a dark oil, which, after treatment with $Cu(OAc)_2$ in aqueous methanol, gave 8 [56%; mp 175-177°C; IR (Nujol) 3330, 2232, 1580, 1555 cm^{-1}].

The chelates could be reconverted to the free vinylogous amido nitriles in modest yields by hydrolysis with 20% H_2SO_4 at room temperature for 30 min.

In contrast to the above results, 2a and p-anisonitrile, after 18 h at 25°C and careful neutralization of the reaction mixture, gave the cyclized product 9a[8,9], 2-amino-5-(p-anisyl)-4(1H)-pyridone [mp 280°C (dec); IR (Nujol) 3370, 3305, 3180, 1640 cm^{-1}; NMR (TFA-d)^5 δ 4.01 (s, 3H), 6.37 (d, 1H, J = 2 Hz), 6.75 (d, 1H, J = 2 Hz), 7.45 (AB q, 4H, J = 9 Hz); MS m/e 216 (M^+)]. Examples of this reaction are shown in Table I.

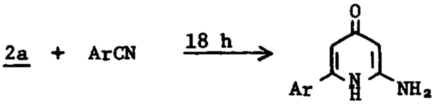

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TABLE I

ArCN	Product[b]	% yield (isolated)
p-anisonitrile	9a	62
p-chlorobenzonitrile	9b	65 (HCl salt)
o-toluonitrile[a]	9c	63
1-cyanonaphthalene[a]	9d	48 (HCl salt)
piperonylonitrile	9e	67

a) The nitrile and 2a were heated in THF at reflux for 16 h. In all other cases, reaction was carried out at 25°C for 18 h.

b) All products gave satisfactory elemental analyses and spectroscopic data in accordance with the assigned structure.

A number of nitriles failed to yield any characterizable products. 2,6-Dichlorobenzonitrile, perhaps due to steric hindrance, was unreactive toward 2a. Acetonitrile, pivalonitrile, and o-anisonitrile all gave complex unidentified products. It is felt that acetonitrile suffers deprotonation rather than nucleophilic attack.

A typical experimental procedure is as follows:

To a mechanically stirred solution of 21 ml (0.15 m) of diisopropylamine in 150 ml dry THF (-10°C, N_2 atmosphere) was added 67.6 ml (0.15 m) of 2.22 M n-BuLi. After 15 min, 6.16 ml (0.075 m) of 1a was added dropwise. The yellow-orange suspension was stirred at -10°C for 30 min and then 8.99 g (0.068 m) of p-anisonitrile in 15 ml THF was added dropwise. The reaction mixture was allowed to warm to 25°C and stirred at that temperature for 18 h. Water was added and the pH adjusted to 7 with glacial HOAc, whereupon 9a precipitated from solution. The product was collected by filtration, washed with water and ether, and decolorized by digestion in hot methanol. The yield of analytically pure 9a was 9.3 g (62%).

Further reactions of dianions 2a and 2b are currently being investigated.

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REFERENCES AND NOTES

1. a) β-keto aldehyde dianions: T. M. Harris, S. Boatman, and C. R. Hauser, J. Am. Chem. Soc., 87, 3186 (1965); S. Boatman, T. M. Harris, and C. R. Hauser, Org. Syn., 48, 40 (1968). b) β-diketone dianions: C. R. Hauser and T. M. Harris, J. Am. Chem. Soc., 80, 6360 (1958); K. G. Hampton, T. M. Harris, and C. R. Hauser, Org. Syn., 47, 92 (1967). c) β-keto ester dianions: L. Weiler, J. Am. Chem. Soc., 92, 6702 (1970); S. N. Huckin and L. Weiler, Tetrahedron Lett., 4835 (1971); S. N. Huckin and L. Weiler, Can. J. Chem., 52, 1379 (1974).

2. a) β-keto sulfoxide dianions: P. A. Grieco, D. Boxler, and C. S. Pogonowski, Chem. Comm., 497 (1974); P. A. Grieco and C. S. Pogonowski, J. Org. Chem., 39, 732 (1974); I. Kuwajima and H. Iwasawa, Tetrahedron Lett., 107 (1974). b) β-keto sulfone dianions: N. M. Carroll and W. I. O'Sullivan, J. Org. Chem., 30, 2830 (1965); W. I. O'Sullivan, D. F. Tavares, and C. R. Hauser, J. Am. Chem. Soc., 83, 3453 (1961). c) phenylacetone dianion: C. Mao, C. R. Hauser, and M. L. Miles, J. Am. Chem. Soc., 89, 5303 (1967); J. P. Bays, J. Org. Chem., 43, 38 (1978).

3. Other reaction conditions studied and the observed results are as follows: one equivalent NaH/THF/0°C, then one equivalent n-BuLi/0°C (no product isolated); two equivalents n-BuLi/THF/0°C (product obtained in significantly decreased yield); two equivalents LDA/THF/-78°C (mixture of regioisomeric monoalkylation products, suggesting incomplete dianion formation at this temperature).

4. a) Supplied by Aldrich Chemical Company, Inc.
   b) Supplied by Pfaltz and Bauer, Inc., 88% pure.

5. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad; ex, exchangeable with D_2O.

6. Polyalkylation of 2a was not observed.

7. L. Claisen, Chem. Ber., 25, 1776 (1892); L. Claisen, ibid., 42, 59 (1909); H. Lettré, G. Meiners, and H. Wichmann, Naturwiss., 33, 157 (1946).

8. For the reaction of a β-diketone dianion with a nitrile to give a 4(1H)-pyridone, see C. Kashima, M. Yamamoto, S. Kobayashi, and N. Sugiyama, Bull. Chem. Soc. Jap., 42, 2389 (1969).

9. For the reaction of a β-keto ester dianion with a nitrile to give a 4-hydroxy-2(1H)-pyridone, see S. N. Huckin and L. Weiler, Can. J. Chem., 52, 1343 (1974).

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