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A FACILE ROUTE TO α-IMINO ACETALS AND THE CORRESPONDING MONOACETAL DERIVATIVES OF α-DIKETONES WITH COMPLETE REGIOCHEMICAL CONTROL

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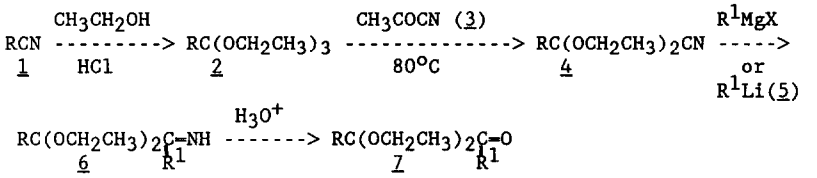
ABSTRACT: Treatment of representative orthoesters (2) with pyruvonitrile (3) afforded the corresponding α, α-diethoxynitriles (4) in 65-80% yields. Depending upon the conditions used to protonate the initial adduct, subsequent addition of an organolithium (5) or Grignard reagent to the latter (4) led to the obtention of either α-imino acetals (6) or the corresponding monoprotected α-diketones (7) in >90% yield.

In view of their utility in the preparation of various synthetic targets, including polyquinanes[1] and certain heterocycles, a host of methods have been developed[2] for the synthesis of α-diketones. Only a few[3] of these methodologies, however, lead to the obtention of monoprotected α-diketones (e.g., 7), which are attractive intermediates in the regiospecific synthesis of α, β- unsaturated ketones and 1, 3-dienes, derived from the latter by a subsequent Wittig reaction. With this in mind, we set out to develop a route to compounds of general structure 7, one that would offer both convenience and control of regiochemistry.



a, R = CH_2CH_3; R^1 = CH_3

b, R = CH_2CH_3; R^1 = $(CH_2)_3CH_3$

c, R = C_6H_5; R^1 = CH_3

The starting material selected for our methodology was an orthoester (e.g., 2, R = alkyl or aryl), which itself was either commercially available or readily prepared from the corresponding nitrile (1) via a Pinner reaction.[4] The former class of compounds (2) had previously[5] been converted to the corresponding α, α-dialkoxynitriles (4) by treatment with liquid hydrocyanic acid. More conveniently, we were able to effect this same transformation (2 --> 4) in 65-80% yield by use of pyruvonitrile (3) in slight molar excess. We anticipated that subsequent treatment of nitrile 4 with either an organolithium (5) or Grignard reagent,[6] after addition of water to the reaction mixture, would afford the desired monoprotected α-diketone (7).

To test this methodology, 2,2-diethoxybutanenitrile (4, R = CH_2CH_3), readily obtained from triethyl orthopropionate (2, R = CH_2CH_3; available from Aldrich Chemical Co., Milwaukee, WI, USA) and pyruvonitrile (3), was treated with methyllithium (1.4 M solution in ether, halide content 0.05 M, available from Aldrich Chemical Co.) as outlined in the experimental procedure given below. Subsequent addition of aqueous methanol to the reaction mixture afforded α-imino acetal 6a[7] in 92% yield rather than ketone 7a. However, imine 6a could be hydrolyzed[8] to the corresponding monoprotected α-dione (7a)[9,10] (75% yield) by use of one molar equivalent of pyridinium tosylate in 1:1 (v/v) methylene chloride : water at 20°C. More conveniently, this hydrolysis could be effected in a one-pot transformation by addition of methanol and aqueous acetic acid to the reaction mixture derived from addition of the organometallic reagent to the nitrile (4, R = CH_2CH_3).

To assess the scope of this methodology, nitrile 4 (R = CH_2CH_3) was also treated with n-butyllithium using the general procedure outlined below to afford monoprotected α-diketone 7b[11,12] with complete control of regiochemistry in 95% yield. Likewise, nitrile 4 (R = C_6H_5), readily prepared from triethyl orthobenzoate (2, R = C_6H_5, available from Aldrich Chemical Co.), could be converted to monoprotected α-diketone 7c[13] after treatment with methyllithium and aqueous acetic acid in successive order.

The methodology reported in this communication takes on added significance since the functionality in both of these products (6 and 7) can be elaborated[14] in a variety of ways. For example, it should be feasible to reduce α-imino acetals (6) to the corresponding α-amino acetals, useful in the synthesis of heterocycles.

Conversion of Orthoesters (2) to α, α-Dialkoxynitriles (4). A mixture of 10 mmol of orthoester 2 and 1.00 mL (14.1 mmol) of pyruvonitrile (3, available from Aldrich Chemical Co.) was heated at 80°C (external bath temperature) for 20 hours. After cooling the solution to room temperature, the product was isolated by diluting the mixture with 20 mL of ether and washing the organic layer with 1:1 (v/v) 1M aqueous NaOH: brine (1x20 mL) and saturated brine (1x20mL) in successive order. The organic layer was then dried (anhydrous Na_2SO_4), filtered, and the solvent removed at reduced pressure. The crude product was further purified by filtration through Florisil (60-100 mesh, 60 mL/g of crude nitrile, elution with 300 mL of hexane -10% ether) to afford the α, α-diethoxynitriles (4)[15] in 65-80% yield.

Preparation of Monoprotected α-Diketones (7). A mixture of 0.65 mmol of nitrile 4 and 1.0 mmol of the organolithium reagent in 1.2 mL of 1:1 (v/v) hexane : anhydrous ether was stirred at room temperature for 2 hours. After cooling the mixture to 10°C in a cold water bath, 2.75 mL of 8:2:1 (v/v/v) methanol:water:acetic acid was added, and the mixture was stirred at 20°C for an additional 15 hours to hydrolyze the imine.[16] The product was

then isolated by dilution of the mixture with 25 mL of 4:1 (v/v) ether:dichloromethane and washing with saturated brine (1x25 mL) and 4:1 (v/v) brine:saturated aqueous $NaHCO_3$ (1x25 mL) in successive order. The organic layer was then dried over Na_2SO_4, filtered, and the solvent removed at reduced pressure to give the monoprotected α-diones (7) [IR:ν_{max} (film) 1730 cm^{-1} (C=O)] in 90-95% yield after simple evaporative distillation.

REFERENCES AND NOTES

1. α-Diketones have been shown to be useful starting materials in the synthesis of polyquinanes. See: M. Venkatachalam, M.N. Deshpande, M. Jawdosiuk, G. Kubiak, S.. Wehrli, J.M. Cook, and U. Weiss, Tetrahedron, 42, 1597 (1986) and references therein.

2. For methodologies used to synthesize α-diketones, see: R. Conrow and P.S. Portoghese, J. Org.Chem., 51, 938 (1986); J. Verlhac, E. Chanson, B. Jousseaume, and J. Quintard, Tetrahedron Lett., 26, 6075 (1985); M.C. Carre and P. Caubere, Tetrahedron Lett.,26, 3103 (1985); J. Souppe, J.-L. Namy, and H. B. Kagan, Tetrahedron Lett., 25, 2869 (1984); K.S. Petrakis, G. Batu, and J. Fried, Tetrahedron Lett., 24, 3063 (1983); I.T. Harrison and S. Harrison (Vol. 2), L.S. Hegedus and L.G. Wade, Jr. (Vol. 3), L.G. Wade, Jr. (Vol. 4 and 5) "Compendium of Organic Synthetic Methods," Wiley: New York, 1974, 1977, 1980, 1984, Vol. 2: pp. 405-407, Vol. 3: pp. 458-461, Vol. 4: pp. 465-467, Vol. 5: pp. 516-517.

3. For previous routes to monoprotected α-diketones, see: B. Gregoire, M.-C. Carre and P. Caubere, J. Org. Chem., 51, 1419 (1986); S. Raucher and L.M. Gustavson, Tetrahedron Lett., 27, 1557 (1986); F. Huet, A. Lechevallier and J.M. Conia, Synth. Commun., 10, 83 (1980).

4. For a review, see: R. Roger and D.G. Neilson, Chem. Rev., 61, 179 (1961).

5. J.G. Erickson, J. Am. Chem. Soc., 73, 1338 (1951).

6. An attempt to convert nitrile 4 (R = CH_2CH_3) to ketone 7b using butylmagnesium chloride in ether-hexane solution was successful. However, the reaction was slow in comparison to an analogous one using butyllithium; and ^1H NMR analysis of the reaction product indicated the presence of minor amounts of by-products.

7. bp 65-83°C (bath temperature, 0.25 mm); IR, ν_{max} (film) 1650 (C=N) cm^{-1}; ^1H NMR δ ($CDCl_3$) 10.05 (br,NH), 3.37 and 3.35 (overlapping quartets, J = 7Hz, 2 x $OC\underline{H}_2CH_3$),

2.01 (s,$CH_3C=N$), 1.78 (quartet, J = 7Hz, $CC\underline{H}_2CH_3$), 1.21 (t, J = 7Hz, 2 x $OCH_2C\underline{H}_3$), 0.67 (t, J = 7Hz, CH_3). Satisfactory (± 0.10%) elemental analysis (C,H,N) was obtained for this novel compound.

8. This hydrolysis (6a -->7a) proved to be unexpectedly difficult to effect. Imine 6a was stable to saturated aqueous NH_4CL mixed with either tetrahydrofuran or ether at 20°C, as well as to K_2CO_3 in 3:1 (v/v) methanol:water at reflux. Attempts to hydrolyze 6a using dilute aqueous hydrochloric acid led to acetal decomposition.

9. S. A. Humphrey, J.L. Hermann, and R. H. Schlessinger, J. Chem. Soc. D., 1244 (1971).

10. ^1H NMR: δ3.47 and 3.44 (overlapping quartets, J = 7Hz, 2 x $OC\underline{H}_2CH_3$), 2.25 (s, $CH_3C=O$), 1.86 (quartet, J = 7Hz, $CC\underline{H}_2CH_3$), 1.21 (t, J = 7Hz, $OCH_2C\underline{H}_3$), 0.77 (t, J = 7Hz, CH_3).

11. F. Huet, M.Pellet, and J. M. Conia, Tetrahedron Lett., 3579 (1976).

12. ^1H NMR: δ 3.48 and 3.45 (overlapping quartets, J = 7Hz, 2 x $OC\underline{H}_2CH_3$), 2.62 (t, J = 7Hz, $CH_2C=O$), 1.83 [quartet, J = 7Hz,$C\underline{H}_2C(OCH_2CH_3)_2$], 1.21 (t, J = 7Hz, 2 x $OCH_2C\underline{H}_3$).

13. N. DeKimpe, R. Verhe, L. DeBuyck, and N. Schamp, J. Org. Chem., 45, 2803 (1980).

14. For conditions used to hydrolyze α-keto acetals (7), see Scheme C (p 523) in a review by G.A. Olah, P.S. Iyer, and G.K.S. Prakash, Synthesis, 513-531 (1986).

15. Nitrile 4 (R = C_6H_5) was contaminated with a small amount (~ 5%) of ethyl benzoate. The latter could be conveniently removed by either fractional distillation or chromatography on Florisil (gradient elution, hexane-ether).

16. The imine (6) can be isolated by quenching the reaction with methanol:water, followed by extraction with 4:1 (v/v) ether:dichloromethane as outlined in the experimental procedure.

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