Tetrahedron Letters,Vol.25,No.16,pp 1659-1660,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

REDUCTION OF α - SUBSTITUTED SUCCINONITRILES WITH DIISOBUTYLALUMINUM HYDRIDE: A FACILE METHOD FOR THE SYNTHESIS OF 3-SUBSTITUTED PYRROLES

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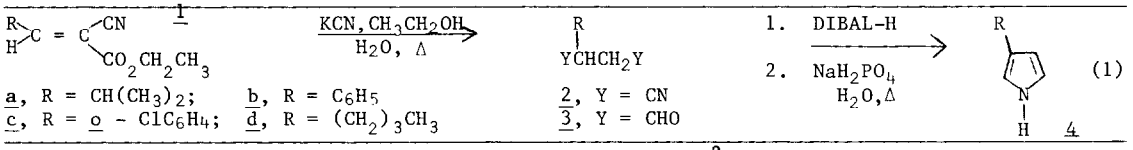
SUMMARY: Treatment of four representative α-substituted succinonitriles (2) with diisobutylaluminum hydride, followed by hydrolysis of each reaction mixture with aqueous sodium dihydrogen phosphate, afforded 3-substituted pyrroles (4) in approximately 50% yield.

A research project that we were about to initiate required efficient access to α-substituted succinaldehydes (3). Since a facile route (equation 1) to the corresponding bisnitriles (2) is now available,[1] the reductive transformation of 2 to 3 using diisobutylaluminum hydride (DIBAL-H) was investigated.



(1)

1
a, R = $CH(CH_3)_2$; b, R = C_6H_5
c, R = o - ClC_6H_4; d, R = $(CH_2)_3CH_3$

2, Y = CN
3, Y = CHO

4

To test this methodology, isopropylsuccinonitrile (2a)[2] was selected as a representative substrate. The latter was conveniently prepared in 47% overall yield from isobutyraldehyde via a Knoevenagel condensation[3] to obtain unsaturated cyanoester 1a[4], followed by a tandem Michael addition - decarbalkoxylation[5] involving the latter substrate (1a) and potassium cyanide. Subsequent treatment of bisnitrile 2a with Dibal-H, followed by hydrolysis using an aqueous solution of sodium dihydrogen phosphate[6] at 20°C for 10 minutes, afforded a product mixture whose spectral properties were inconsistent with those of the expected bisaldehyde (3a) or any cyclized material derived from it. To our amazement, an attempt to purify the initial product mixture by distillation[7] afforded a known compound[8], 3-isopropylpyrrole (4a), as the major volatile product.[9] Only trace amounts of the latter (4a) could be detected by NMR analysis[10] of the crude reaction product. More conveniently, pyrrole 4a was obtained in 50% yield by heating the hydrolysis mixture at reflux for 30 minutes prior to isolation of the product.

Since the preparation of 3-substituted pyrroles is one of the more difficult tasks in heterocyclic chemistry,[11] the methodology outlined above was further explored utilizing a representative arylsuccinonitrile (2b)[12]. This compound was obtained in 83% yield from the Knoevenagel adduct (1b)[13] derived from benzaldehyde and ethyl cyanoacetate after treatment of the latter (1b) with potassium cyanide in aqueous ethanol at reflux. As had been anticipated, subsequent reduction of bisnitrile 2b with Dibal-H, followed by hydrolysis as outlined in this communication, afforded 3-phenylpyrrole (4b)[14] in 51% yield.

To illustrate further the utility of this methodology, bisnitrile 2c[15] was converted in 57% yield to pyrrole 4c, a compound which has recently been reported[16] to exhibit potent antiinflammatory activity. In a similar manner, Knoevenagel adduct 1d[4] was converted in two

steps (34% overall yield) to 3-butylpyrrole (4d)[17]. In view of the few steps involved and the facility with which these reactions can be conducted, this methodology should prove useful in the synthesis of 3-substituted pyrroles.[18] In particular, it complements several elegant routes to this class of compounds that have been recently developed,[11] but which cannot provide direct access to β-arylpyrroles such as 4c.

Conversion of Bisnitriles (2) to 3-substituted Pyrroles (4) - - To a solution of bisnitrile 2 (1.15 mmol) in anhydrous benzene (8.0 ml) was added 2.00 ml of a 1.5 M solution of Dibal-H in toluene.[19] This mixture was stirred under a nitrogen atmosphere at 20°C for 3 hours, after which 20 ml of 1.5 M aqueous $NaH_2PO_4 \cdot H_2O$ was added to destroy the excess hydride and hydrolyze the reaction intermediate. This mixture was subsequently heated at reflux for 30 minutes, after which it was cooled to room temperature, diluted with 40 ml of ether, and filtered to remove any insoluble salts. The filtrate was then diluted with 50 ml of 15% aqueous NaCl and the layers were separated. The organic layer was washed in successive order with 15% aqueous NaCl (1x50ml) saturated brine (1x50ml), dried over anhydrous magnesium sulfate, and filtered. Removal of the solvent in vacuo, followed by evaporative (Kugelrohr) distillation, afforded a 3-substituted pyrrole (4).

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4. For previous syntheses of cyanoesters 1a and 1d see: F.D. Popp and A. Catala, J. Org. Chem., 26, 2736 (1961).
5. This transformation was accomplished by heating a solution of cyanoester 1 (4.9 mmol) and potassium cyanide (575 mg. 8.82 mmol) in 90% aqueous ethanol (8.5mL) at reflux for 4h. The product was isolated by dilution of the cooled reaction mixture with 5 mL of 1 M aqueous NaOH and 80mL of 15% (w/v) aqueous NaCl, followed by extraction with CH_2Cl_2.
6. Similar results were obtained using saturated aqueous ammonium chloride for this hydrolysis.
7. Decomposition of the product mixture to afford pyrrole 4a occurred only at a bath temperature greater than 100°C (2.5 mm). During a subsequent evaporative (Kugelrohr) distillation, 4a was collected at 55° - 78°C (bath temperature, 2.5mm).
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9. Pyrrole 4a prepared in this manner could be obtained in ~45% yield after redistillation to separate it from unidentified higher-boiling impurities.
10. Pyrrole 4a ($CDCl_3$ solution) exhibited the following NMR spectral properties: δ8.1 (broad m, NH), 6.73 (m, ring H_5), 6.60 (m, ring H_2), 6.17 (m, ring H_4), 2.88 {septet, J=7Hz, $CH(CH_3)_2$}, 1.23 {d, J=7Hz, $CH(CH_3)_2$}. This data is fully consistent with that previously reported for 3-n-propylpyrrole. See: P.S. Skell and G.P. Bean, J. Am. Chem. Soc., 85, 4655 (1962).
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14. The properties of this compound were fully consistent with the assigned structure. For a previous synthesis of 4b, see: K. Kondo and M. Matsumoto, Chem. Lett., 701 (1974).
15. Satisfactory elemental analysis (C,H,N,Cl) was obtained for this novel compound, which was prepared in 68% yield from cyanoester 1c in the usual manner.[5] For a previous synthesis of 1c see: F.D. Popp, J. Org. Chem., 25, 646 (1960).
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(Received in USA 3 October 1983)