Tetrahedron Letters, Vol.32, No.10, pp 1363-1366, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

CARBANION ADDITION TO ACETYLENES : AN EFFICIENT STEREOSELECTIVE ROUTE TO α-METHYLENE-γ-LACTAMS

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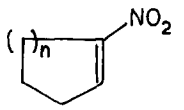
Abstract : Intramolecular addition of carbanions, derived from the acetylenic amides **(5b,d)**, **(7)** and **(9)** has been shown to be highly stereoselective leading to the α-methylene-γ-lactam derivatives **(6a,b)**, **(8a,b)** and **(10)**.

α-Methylene-γ-lactams have attracted the attention of many workers[1] in recent years. This is mainly due to their cytotoxic activity[1b] comparable to the related γ-lactones. The special feature is that the γ-lactams are much less toxic[1b] than the corresponding α-methylene-γ-lactones, and this probably makes them suitable for cancer treatment. We report here a new, efficient, and stereoselective procedure for the synthesis of the title compounds.

Each of the stereoisomeric amides **(2a,b)**[2], prepared as shown in Scheme 1, on Michael condensation with methyl acrylate, provided a 1:1 mixture of the adduct **(3)**[2], and interestingly, the pyrrolidine derivative **(4)**[2]. As expected, **(4)** was the only product (90%) when the above reaction was carried out in the absence of an electrophile.

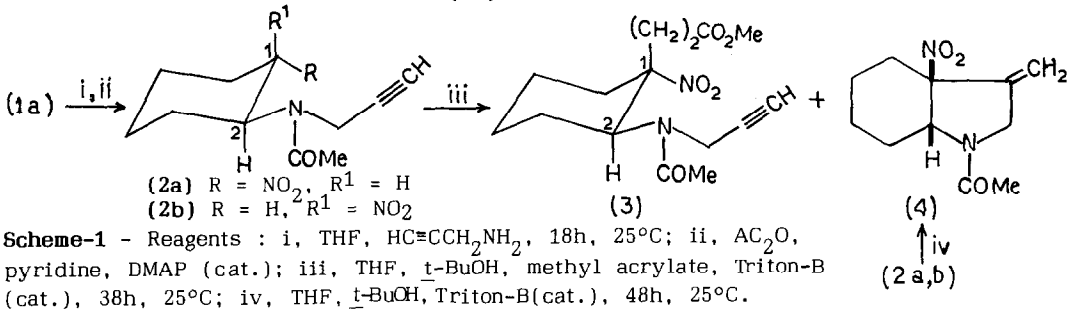
Encouraged by the above stereoselective intramolecular addition of carbanions (from **2a,b**) to acetylenes[3], we investigated similar cyclisation of the acetylenic amides **(5b,d)**, **(7)** and **(9)** as a route to α-methylene-γ-lactam derivatives (Scheme 2). The results are presented below.

Condensation of benzylamine with nitrocyclohexene **(1a)** furnished in good yield the crystalline nitroamine **(5a)** which on acylation with the acid chloride of phenyl propiolic acid provided the required crystalline amide **(5b)** (70%). Characteristic ^{1}H n.m.r. signals for C-1 and C-2 protons at δ5.51 (ddd, J12, 12 and 4Hz) and 3.90 (ddd, J12, 12 and 4Hz) respectively are quite in agreement with the assigned stereochemistry for **(5b)**. This amide on intramolecular cyclisation as before (Scheme 2) afforded a single[4] crystalline material (70%), characterised as the bicyclic γ-lactam derivative **(6a)**. The stereostructure **(6a)** is suppored from the following facts : (i) the ring-fusion hydrogen appeared as a triplet at δ 3.94 (J4-5Hz), (ii) the significant downfield shift of the olefinic proton singlet at δ 8.04 is probably due to its deshielding by the lactam carbonyl. The stereochemistry of the olefinic bond is also supported from other findings reported below.



(1a) n = 2

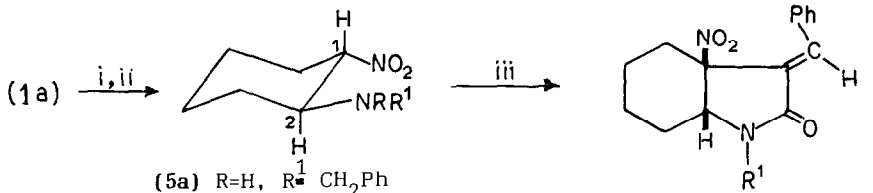
(1b) n = 1



(2a) R = NO_2, R^1 = H

(2b) R = H, R^1 = NO_2

Scheme-1 - Reagents : i, THF, $HC{\equiv}CCH_2NH_2$, 18h, 25°C; ii, AC_2O, pyridine, DMAP (cat.); iii, THF, t-BuOH, methyl acrylate, Triton-B (cat.), 38h, 25°C; iv, THF, t-BuOH, Triton-B(cat.), 48h, 25°C.



(5a) R=H, R^1 = CH_2Ph

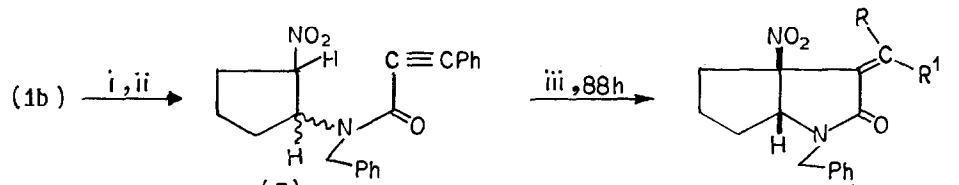
(5b) R=COC≡CPh, R^1=CH_2Ph

(5c) R=R^1=H

(5d) R=COC≡CPh, R^1=H

(6a) R^1=CH_2Ph

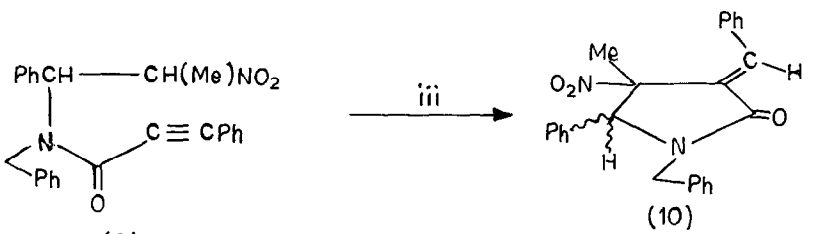
(6b) R^1=H



(7)

(8a) R=Ph, R^1=H

(8b) R=H, R^1=Ph



(9)

(10)

Scheme-2 - Reagents : i, THF, $PhCH_2NH_2$, 18h, 30°C; ii, THF, Et_3N, PhC≡C-COCl, 19h, 0-30°C; iii, THF, t-BuOH, Triton-B(cat.), 48h, 30°C.

The crystalline amide **(5d)**, prepared in low yield from the known trans-amine **(5c)**[5], was proved to be a mixture of stereoisomers (from ^1H n.m.r.). Usual cyclisation of this amide mixture furnished in very low yield the desired crystalline γ-lactam **(6b)**, δ 7.92 (1H, s), 4.22 (1H, t, J5-6Hz). The low yield of this lactam **(6b)** from the secondary amide **(5d)** is probably due to s-cis/s-trans conformational inversion[6] of the amide C-N bond.

The oily amide **(7)**[7], ν_{max} 2215 and 1550 cm^{-1}, δ 5.58-5.34 (1H) and 4.38-4.08 (1H), available from **(1b)**[5] in excellent yield, on usual cyclisation furnished two crystalline stereoisomeric γ-lactams (75%) in a ratio of ca. 6:1. The special features of the ^1H n.m.r. spectrum of the major isomer **(8a)** are the olefinic proton singlet at δ 7.80 and the ring-fusion hydrogen triplet at 4.04 (J5-6Hz); the corresponding protons of the minor isomer **(8b)** appeared at 7.20 (1H, s) and 4.80 (1H, t, J5-6Hz). The most important aspect of ^1H n.m.r. spectrum of **(8b)** is the appearance of a low field multiplet (δ8.20-8.02) accounting for two aromatic protons deshielded by the C=O of the lactam **(8b)**.

Extension of the above cyclisation procedure to the acyclic amide **(9)**[8] furnished (Scheme 2) in moderate yield the crystalline γ-lactam **(10)**, δ 8.08 (1H, s), 4.70 (1H, s) and 1.12 (3H, s). The stereochemistry of the two asymmetric centres in **(10)** remains unresolved.

The high stereoselectivity realised in the intramolecular addition of carbanions to acetylenes must be due to overlap control of the orbitals in the transition state. Axial conformation of the side chains will ensure better orbital overlap leading to the cis-products as observed. The stereochemistry of the olefinic bonds of the γ-lactams seems to be controlled by the protonation step of the intermediate vinyl carbanion from the less hindered side of the double bond.

Acknowledgement : We thank C.S.I.R. and U.G.C., New Delhi for financial assistance.

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2. All new compounds described herein are racemic and provided the expected spectral data and chemical analyses. The special features of the ^{1}H n.m.r. spectrum of **(2a)** : C-1 proton at δ 5.14 (ddd, J12, 12 and 4Hz) and C-2 proton at 4.74 (ddd, J12, 12 and 4Hz); **(2b)**: C-1 proton at 5.00 (m) and C-2 proton at 4.54 (ddd, J12,4 and 4Hz); **(3)**: C-2 proton at 4.90 (dd, J12 and 4Hz); **(4)**: homogeneous through g.l.c., two close singlets of equal intensity at 2.10 and 1.99 (amide Me, collapsed to a single peak at 100°C), ring-fusion proton as two separate multiplets between δ 4.50-5.00.

3. For other carbanion additions to acetylenes, see (a) G. Eglinton, and M.C. Whiting, J. Chem. Soc., 1953, 3052; (b) R. Epsztein, and N.L. Goff, Tetrahedron, 1985, **41**, 5347; (c) W.F. Bailey, T.V. Ovaska, and T.K. Leipert, Tetrahedron Lett., 1989, **30**, 3901; (d) W.F. Bailey, and T.V. Ovaska, ibid, 1990, **31**, 627; (e) J. Cossy and A. Thellend, ibid, 1990, **31**, 1427.

4. No six-membered lactam could be detected, regiospecific 5-exo-dig cyclisation is the most favoured path as expected.

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7. The stereochemistry of this amide remains undecided.

8. This amide (mixture of diastereomers) was used as a glassy material.

(Received in UK 22 October 1990)