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A Convenient Synthesis of Tricyclic Gamma-Lactams, Simulating B-C-D Rings of Azasteroids Via Michael Addition Reaction

Gandhi K. Kar [a] , Basanta G. Chatterjee [a] & Jayanta K. Ray [a]
[a] Department of Chemistry , Indian Institute of Technology , Kharagpur, 721302, India
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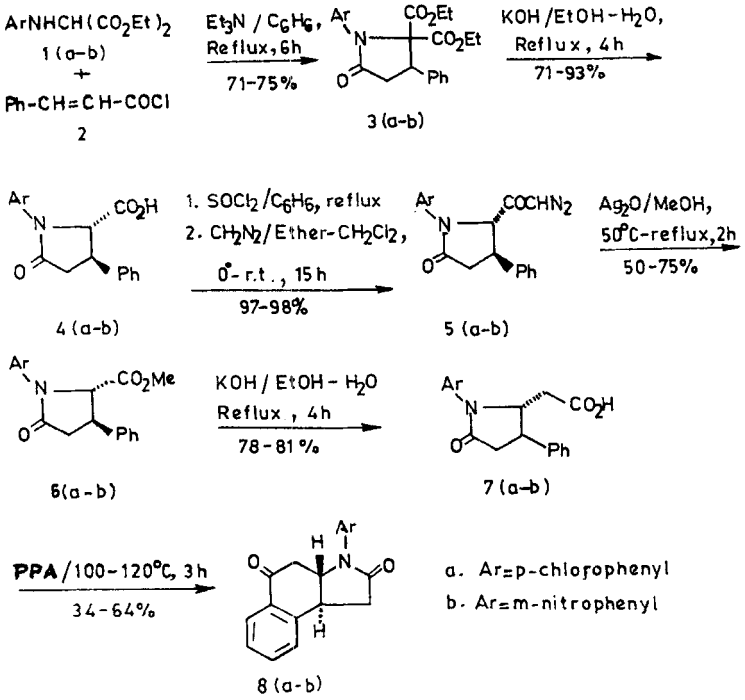
A CONVENIENT SYNTHESIS OF TRICYCLIC GAMMA-LACTAMS, SIMULATING B-C-D RINGS OF AZASTEROIDS VIA MICHAEL ADDITION REACTION

Gandhi K Kar, Basanta G Chatterjee & Jayanta K Ray*
Department of Chemistry, Indian Institute of Technology, Kharagpur 721302, India

Abstract *Cinnamoylchloride on treatment with arylaminomalonates produced the γ-lactam diester derivatives. Highly stereoselective hydrolysis of the diester, produced the trans acid, which on homologation by Arndt-Eistert's method followed by PPA cyclization generated the tricyclic γ-lactam derivatives simulating B-C-D ring of many azasteroids in good overall yield.*

Synthesis of azasteroids have been the subject of much interest by many group of workers due to the important biological properties displayed by these compounds[1,2]. A number of azasteroids have been synthesised in last few decades with variation of position of 'N' in the molecule[3]. However, so far only a few report of aza-steroid molecule has come out containing γ-lactam

moiety as ring D of the aza- steroid and even in all these compounds the N atom is located in the ring juncture[4]. In this communication, as a model study, we report the synthesis of some 9-aryl-9-aza-3,8-dioxo-4,5-benzobicyclo[4.3.0]- nonane derivatives simulating B-C-D ring of an aza- steroid and the methodology thus developed could be utilised for the total synthesis of a novel functionalized 17-azasteriod. Our strategy involves the construction of the γ-lactam moiety (i.e. ring D) first starting from materials already having the ring B followed by construction of the ring C at the final step.

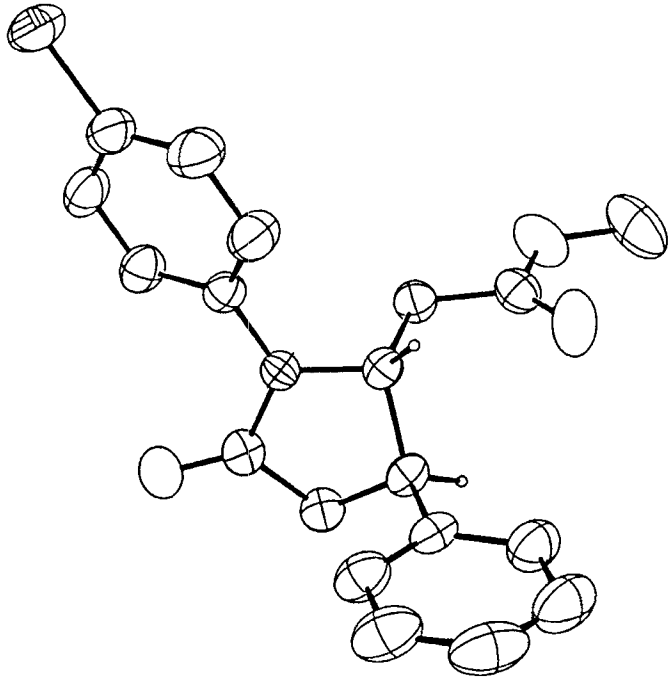


The suitably substituted γ-lactam derivatives 3 were prepared through an intermolecular Michael addition followed by intramolecular amidification of arylamino-malonate (1) and cinnamoyl chloride in presence of Et_3N. However the alternative mechanisms that the inter-molecular amide formation followed by intramolecular Michael addition is not possible in this type of system.[5]

Saponification cum in situ decarboxylation of 3 exclusively produced the trans acid 4 in very good to excellent yield. The trans geometry was assigned from the coupling constant value of C_4-H & C_5-H (~4.5 Hz). The results are consistant with the value reported by P. Pachally[6] for analogous system. The annulation of $-CO_2H$ side chain was achieved in excellent yields by subsequent treatment of 4 with i) $SOCl_2$, ii) CH_2N_2, iii) Ag_2O/MeOH to produce 6. X-ray crystallographic data of 6a[7] absolutely proved the trans stereochemistry of C_4-H and C_5-H.

Alkaline hydrolysis of 6 produced the acid which on cyclization with PPA revealed the desired 9-aryl-9-aza-3,8-dioxo-4,5-benzobicyclo[4.3.0]- nonanes 8a-8b[8] in moderate to very good yield.

Following a similar sequence of reactions, starting from arylaminomalonate and 3-(β-naphthyl) acryloyl chloride



ORTEP diagram of 6a

the total synthesis of the functionalized azasteroid are in progress.

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7. 6a, m.p. 101-102°C, IR ($CHCl_3$) ν_{max} 1740, 1695 cm^{-1}; ^{1}H-NMR ($CDCl_3$ 250 MHz) δ 2.54 (dd,1H,J_{Gem}= 17.7 Hz, J_{Vic}= 9.2 Hz), 3.41 (ddd,1H), 3.5 (s,3H), 4.5 (ddd,1H), 7.2-7.4 (m,9H) ppm. ^{13}C-NMR ($CDCl_3$, 62.5 MHz) 37.4, 38.7, 42.8, 51.6, 64.1, 125.2, 126.7, 127.4, 129.0, 129.2, 131.6, 135.4, 142.0, 170.2, 172.7. MS(m/e) 345(M+2), 343(M^+), 272, 270, 213, 211, 140, 138, 117. A satisfactory elemental analysis was also obtained.

8. 8a, m.p. 189-190°C, IR (Nujol) ν_{max} 1700, 1675 cm^{-1}, ^{1}H-NMR ($CDCl_3$, 200 MHz) : 2.6 (m,4H), 3.40 (m,1H), 4.30 (m,1H), 7.2-7.6 (m,6H), 8.0 (m,1H), 8.8 (d,1H) ppm. ^{13}C-NMR Spectrum ($CDCl_3$, 25 MHz) : 39.9, 42.8, 45.7, 63.2, 120.5, 126.9, 127.2, 127.9, 129.1, 129.6, 135.0, 137.8, 139.4, 172.0, 190.5, MS(m/e) 311(M^+). The compound gave satisfactory elemental analyses.

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