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

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A CONVENIENT SYNTHESIS OF TRICYCLIC GAMMA-LACTAMS, SIMULATING B-C-D RINGS OF AZASTEROIDS VIA MICHAEL ADDITION REACTION

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Cinnamoylchloride Abstract treatment with on arylaminomalonates produced γ−lactam diester the Highly stereoselective hydrolysis of the derivatives. 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.

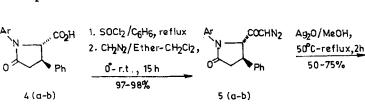
Synthesis of azasteroids have been the subject of much interest by many group of workers due to the important biological properties displayed by these compounds^{1,2}. A number of azasteroids have been synthesised in last few decades with variation of position of 'N' in the molecule³. However, so far only a few report of aza-steroid molecule has come out containing γ -lactam

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moiety as ring D of the aza- steroid and even in all these compounds the N atom is located in the ring juncture⁴. 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 azasteroid 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.

ArNHCH (CO_2Et)₂ 1 (a-b) + Ph-CH=CH-COCI 2



*"*0

3 (а-ь)

0

CO2Et

-CO₂Et

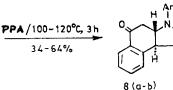
EtaN / CGHG, AT

Reflux, 6h

71-75%

Ar N _____CO₂Me KOH / EtOH - H₂O Ph Reflux , 4h 78-81%

5(a-b)





KOH /EtOH-H2O,

Reflux, 4h

71-93%

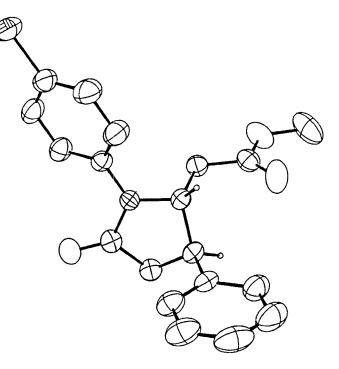
. .

a. Ar=p-chlogophenyl b. Ar=m-nitrophenyl The suitably substituted γ -lactam derivatives 3 were prepared through an intermolecular Michael addition followed by intramolecular amidification of arylaminomalonate (1) and cinnamoyl chloride in presence of Et₃N. However the alternative mechanisms that the intermolecular 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. Pachally⁶ for analogous system. The annulation of -CO₂H side chain was achieved in excellent yields by subsequent treatment of 4 with i) $SOCl_2$, ii) CH_2N_2 , iii) Ag₂ O/MeOH to produce 6. X-ray crystallographic data of $6a^7$ absolutely proved the trans stereochemistry of C₄-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 8a⁸8b in moderate to very good yield.

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



ORTEP diagram of 6a

the total synthesis of the functionalized azasteroid are in progress.

Acknowledgement

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- 7. 6a, m.p. $101-102^{\circ}C$, IR (CHCl₃) ν_{max} 1740, 1695 cm⁻¹;¹H-NMR (CDCl₃ 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. ¹³C-NMR (CDCl₃, 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. $189-190^{\circ}$ C, IR (Nujol) ν_{max} 1700, 1675 cm⁻¹, ¹H-NMR (CDCl₃, 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. ¹³C-NMR Spectrum (CDCl₃, 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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