Studies on γ-Lactams: Synthesis of some 3-Aryl-1,3a,4,9b-tetrahydrobenzo[*e*]indole-2,5-dione Derivatives and its Implication in the Total Synthesis of Functionalized 17-Azasteroids

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The γ-lactam esters **3** and **10**, prepared from anilinomalonates and 3-arylacryloyl chloride, are hydrolysed and selectively decarboxylated to the *trans*-acids **4** and **11**; further homologation and cyclization produce the tri- and tetra-cyclic γ-lactam derivatives **8** and **15** that simulate the B-C-D/A-B-C-D ring system of many azasteroids.

γ-Lactam moieties, fused to carbocyclic rings, are common in bioactive natural products[1,2] and consequently many synthetic strategies have been recorded.[3–6] We report here a novel sequence of reactions that synthesise γ-lactams with appropriate functionalities for further elaboration and thus construction of azasteroids (Schemes 1 and 2).

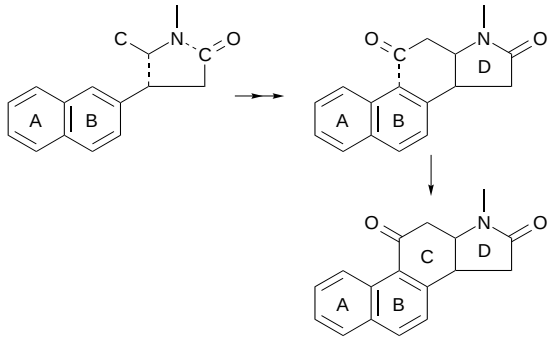
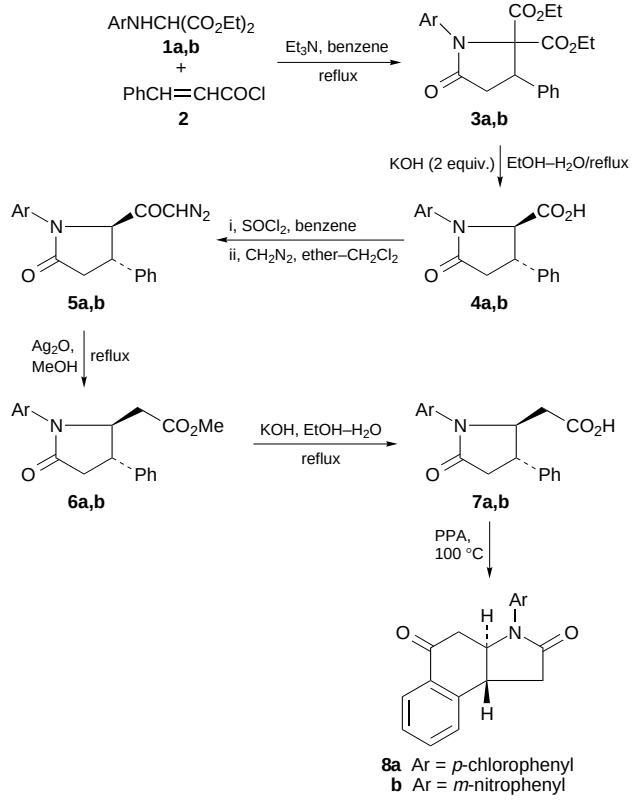


Fig. 1

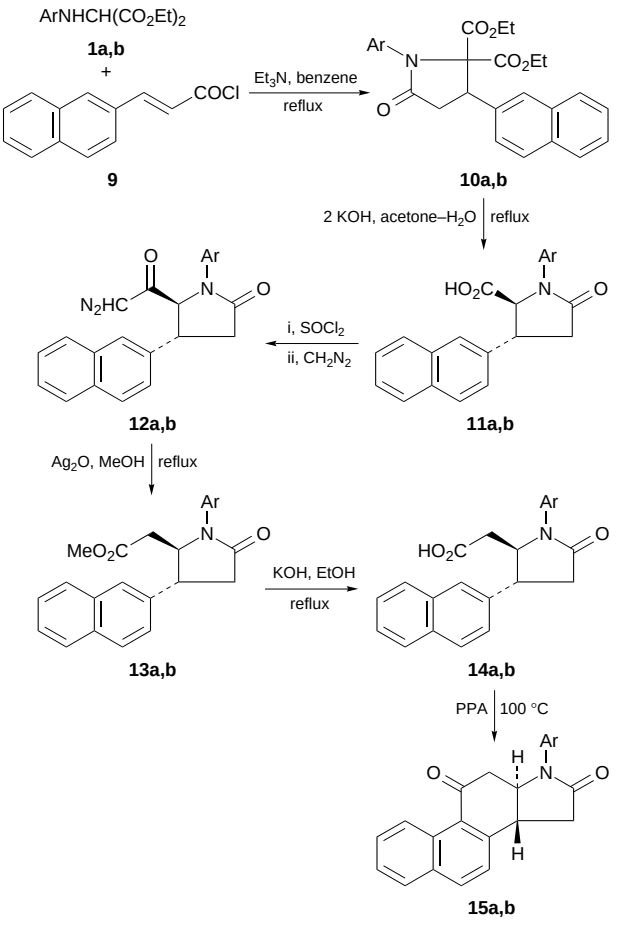


Scheme 1

Our strategy involved the construction of the γ-lactam moiety first, the starting materials already having rings B/A + B, followed by the construction of the ring C in the final stage to achieve model and target 17-azasteroids (Fig. 1).

Thus condensation of arylaminomalonates **1** with β-arylacryloyl chlorides **2** in the presence of triethylamine extensively produced the γ-lactam diesters **3** in good yields (Scheme 1).

Saponification with *in situ* decarboxylation of **3** with alcoholic KOH (2 equiv.) under reflux exclusively produced the *trans*-acid **4** in excellent yield. The structure was confirmed by spectral data (IR, NMR, MS) and elemental analysis. The *trans*-geometry was assigned by the coupling constants of 4-H and 5-H (*J ca*. 4–5 Hz). Annulation of the CO_2H side chain was achieved by the Arndt–Eistert method. Thus the γ-lactam monoacid **4** was converted into the acid chloride with $SOCl_2$ and subsequent treatment of the acid chloride with diazomethane gave the diazoketone **5** in excellent yield. The



Scheme 2

*To receive any correspondence.

diazoketone when refluxed with Ag_2O in MeOH produced the γ-lactam ester **6** in 50–70% yield. *Trans*-stereochemistry of the 4-H and 5-H was proved by X-ray crystallography[15] of **6a**. Alkaline hydrolysis of the ester **6** gave the acid **7** (78–82%) which when cyclised with PPA (at 100 °C) produced the B-C-D ring simulating an azasteroid, *i.e.* 3-aryl-1,3a,4,9b-tetrahydrobenzo[*e*]indole-2,5-dione in moderate to good yield.

Following a similar reaction sequence and starting from an anilinomalonate derivative and 2-(2-naphthyl)acryloyl chloride **9** the high yielding total synthesis of the functionalized 17-azasteroid was achieved (Scheme 2).

Anilinomalonates **1** on reaction with **9** in the presence of Et_3N produced the γ-lactam ester **10** in excellent yields. Compound **10** on hydrolysis (aq. acetone/KOH, 2 equiv., reflux), with decarboxylation followed by homologation of the CO_2H sidechain by the Arndt–Eistert method produced **13** in high overall yields. Saponification (KOH/EtOH–H_2O, reflux) of **13** afforded the acid **14** which when subjected to cyclization with PPA at 100 °C afforded the 17-azasteroid derivatives **15** in 59–63% yield in the final step of the reaction. The spectroscopic data as well as elemental analysis of the compounds gave satisfactory results.

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Techniques used: IR, ^1H and ^{13}C NMR, MS, elemental analysis

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