Alkylation of pyrrolidine-2,5-dione with 2-(3,4-dihydro-1-naphthalenyl)ethyl-4-methylphenylsulfonates: a new and general approach to 13-aza-8,9-dehydro-3-desoxy-18-norestrone analogs

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M.M.V. Ramana*, J.A. Parihar and M.M. Jaiswar

Department of Chemistry, University of Mumbai, Vidyanagari, Santacruz (E), Mumbai-400098, India

Pyrrolidine-2,5-dione was *N*-alkylated with five different 2-(3,4-dihydro-1-naphthelenyl)ethyl-4-methylphenylsulfonates to afford the corresponding imides, which on reduction with $NaBH_4$ in MeOH at –10°C followed by intramolecular cyclisation in $POCl_3$ afforded the corresponding title compounds.

Keywords: *N*-Alkylation, imide reduction, 13-aza-3-desoxy-9-hydroxy-18-norestrone, intramolecular cyclisation, 13-aza-8,9-dehydro-3-desoxy-18-norestrone

Azasteroids are known to exhibit a number of biological properties such as analgesic,[2] antiandrogenic,[8] antiphlogistic,[9] antimicrobial,[10] antileukemia,[11] antifungal,[12] bactericidal,[13] antiestrogenic,[14] antifertility,[15] and cardiotonic and hypotensive activity.[16] These observations and our interest in the synthesis of azasteroids led us to investigate a new synthesis of the title compounds.

Towards this end pyrrolidine-2,5-dione **1** was *N*-alkylated with different 2-(3,4-dihydro-1-naphthalenyl)ethyl-4-methylphenylsulfonates[17] **2a–e** using K_2CO_3 in dry DMF under reflux for 45 min to afford the corresponding seco-azasteroids **3a–e** (68–78%). Seco-azasteroid **3a** was reacted with $NaBH_4$ in MeOH[18] at –10°C under N_2. This resulted in the selective reduction of one of the carbonyl groups to give the corresponding 5-hydroxy-2-pyrrolidone **4a** (39-64%) along with 13-aza-3-desoxy-9-hydroxy-18-norestrone **5** (20%). The formation of **5** could be rationalised on the basis of reductive cyclisation.[19] This is the first reported synthesis of 13-aza-3-desoxy-9-hydroxy-18-norestrone. The reduction of the other seco-azasteroids **3b–e** with $NaBH_4$ in MeOH under the same conditions gave exclusively the corresponding 5-hydroxy-2-pyrrolidones **4b–e**. The intramolecular cyclisation of **4a–e** was achieved with $POCl_3$ at 50°C under N_2 in 8 h to afford the corresponding title compounds **6a–e** (50–62%). It is important to notice that only **6a–e** and not the corresponding Δ9,11 isomers[19] are formed in the intramolecular cyclisation of **4a–e**. The structures of **6a–e** were ascertained from their elemental and spectroscopic data. The PMR spectrum of **6a** was consistent with the reported data[20] and the absence of vinylic protons in the PMR spectra of **6b–e** ruled out the possibility of the corresponding Δ9,11 isomers. Moreover, the mass spectra of **6a, 6b** and **6e** showed the corresponding molecular ion peaks and base peaks at M^+-1 for the loss of H radical.

In conclusion, the present work describes a new synthesis of the title compounds **6a–e** starting from 4-methylphenylsulfonates **2a–e** which involves *N*-alkylation of **1** with **2a–e** followed by selective reduction of one of the carbonyl groups of **3a–e** and finally intramolecular cyclisation of **4a–e** in $POCl_3$. Moreover, 9-hydroxy-13-azasteroid **5** has been isolated as a minor product during selective reduction of **3a** for the first time. Thus the method is short, general and utilises easily accessible materials.

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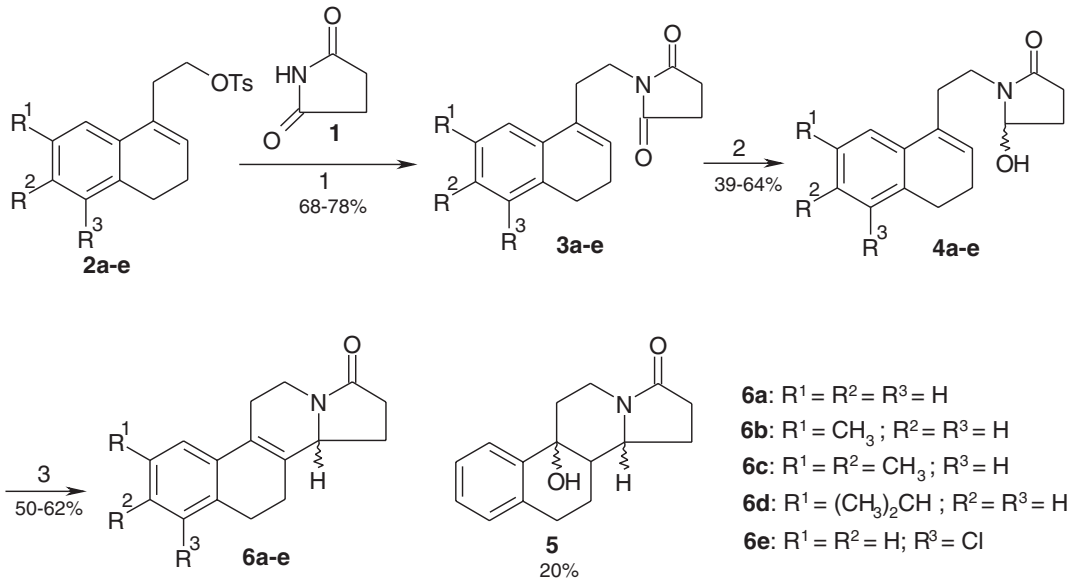

Scheme 1 Reagents and conditions: (1) K_3CO_3, dry DMF, reflux, 45 min. (2) $NaBH_4$, dry MeOH, –10°C, N_2. (3) $POCl_3$, 50°C, 8 h.

* To receive any correspondence. Email: mmvramana@indiatimes.com

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