

## REGIOSELECTIVE SYNTHESIS OF CARBAZOLE PRECURSOR TO OLIVACINE

Santosh G. Tilve\*, Anita S. Tilve and Vidya G. Desai

Department of Chemistry, Goa University  
Taleigao Plateau, Goa, 403 203, India.

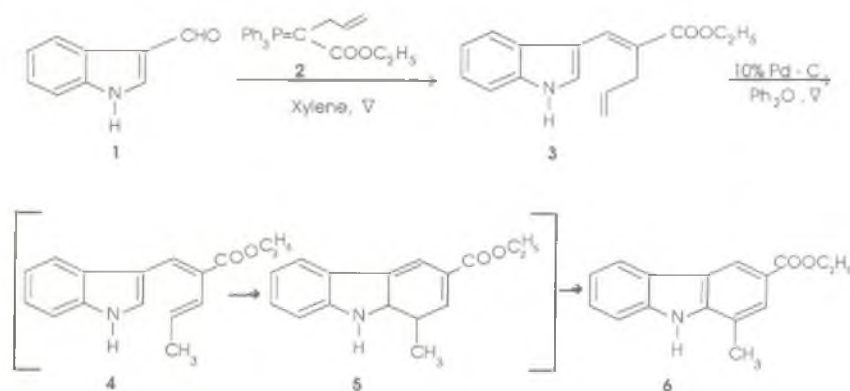
**ABSTRACT:** A short regioselective synthesis of ethyl 1-methyl-9H-carbazole-3-carboxylate is described from 3-formylindole which utilizes Wittig reaction and Pd-C catalysed ring annulation reaction.

Synthesis of biologically active carbazoles and pyridocarbazoles<sup>1</sup> continues to be an area of great importance to organic chemists. One of the most efficient routes for the synthesis of the pyridocarbazole ring system was devised by Cranwell and Saxton<sup>2</sup> and modified by Birch et al<sup>3</sup>. This route employs a Pomerantz-Fritsch reaction on a 3-functionalised carbazole derivative.

The major limitation of the above method is the preparation of suitably functionalised carbazoles and particularly the carbazole required for the synthesis of olivacine, as in most cases it leads to the formation of regioisomers<sup>4</sup>. In one approach<sup>5</sup> gramine has been regiospecifically converted in a few steps to the required 3-functionalised carbazoles for the syntheses of olivacine and ellipticine.

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\* To whom correspondence should be addressed



We report herein a regioselective synthesis of ethyl 1-methyl-9H-carbazole-3-carboxylate (**6**) from 3-formylindole (**1**). Thus 3-formylindole was condensed with Wittig reagent **2** in refluxing xylene for 6h to give *E*-ester **3**. Attempted ring annulation using sulphuric acid, PPA and  $\text{AlCl}_3$  gave complex mixtures. Refluxing **3** with diphenyl ether in the presence of 10% Pd-C, however gave ethyl 1-methyl-9H-carbazole-3-carboxylate **6** directly. The product **6** can also be obtained in a one pot experiment by carrying out the reaction of **1** and **2** in refluxing diphenyl ether and adding 10% Pd-C after 1h and refluxing further. The likely steps involved in the formation of product **6** could be isomerization of double bond leading to **4** followed by intramolecular Diels-Alder reaction leading to **5**, followed by dehydrogenation to **6**. Extension of this methodology for the synthesis of carbazole precursor to ellipticine failed, as the Wittig reaction on 3-acetyl- or *N*-benzenesulphonyl-3-acetylindole did not take place under a variety of conditions.

#### Experimental :

All melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer 337 IR spectrophotometer and  $^1\text{H-NMR}$  spectra on Varian (300 MHz) instrument. Chemical shifts are expressed in  $\delta$ (ppm) downfield from TMS as an internal standard.

#### Preparation of **3** :

A mixture of **1** (0.145g, 1mmol), phosphorane **2** (0.389g, 1mmol) and xylene (5ml) was refluxed for 6h under nitrogen atmosphere. Chromatography using pet. ether (60-80) - ethyl acetate as an eluent furnished **3** as a colourless solid. Recrystallisation from dichloromethane - pet. ether furnished **3** (0.230g, 90%); m.p.

132°C; IR (nujol): 3340, 1680  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ): 1.36 (3H, t,  $J = 7.7\text{Hz}$ ,  $-\text{CH}_2-\text{CH}_3$ ), 3.48 (2H, m,  $-\text{CH}_2-\text{CH}=\text{CH}_2$ ), 4.28 (2H, q,  $J = 7.7\text{Hz}$ ,  $-\text{CH}_2-\text{CH}_3$ ), 5.12 (2H, m,  $-\text{CH}_2-\text{CH}=\text{CH}_2$ ), 6.00 (1H, m,  $-\text{CH}_2-\text{CH}=\text{CH}_2$ ), 7.25 (2H, m, C-5&6H), 7.4 (1H, m, C-7-H), 7.52 (1H, m, C-2-H), 7.80 (1H, m, C-4-H), 8.16 (1H, s,  $\text{CH}=\text{C}$ ), 8.54 (1H, s, exchangeable with  $\text{D}_2\text{O}$ , NH).

#### Preparation of 6 from 3 :

A mixture of **3** (0.255g, 1mmol), 10% Pd - C (0.025g) and diphenyl ether (5ml) was refluxed for 6h under nitrogen atmosphere. Chromatography using pet. ether (60-80) - ethyl acetate as an eluent furnished **6** (0.228g, 90%) as a colourless solid; m.p. 151°C (lit<sup>4a</sup> m.p. 151°C); IR (nujol): 3440, 1680  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ): 1.45 (3H, t,  $J = 7.7\text{Hz}$ ,  $-\text{CH}_2-\text{CH}_3$ ), 2.57 (3H, s,  $-\text{CH}_3$ ), 4.43 (2H, q,  $J = 7.7\text{Hz}$ ,  $-\text{CH}_2-\text{CH}_3$ ), 7.28 (1H, m, C6 - H), 7.46 (2H, m, C7&8-H), 7.95 (1H, m, C3-H), 8.09 (1H, m, C5-H), 8.12 (1H, s, exchangeable with  $\text{D}_2\text{O}$ , NH), 8.67 (1H, m, C4-H).

#### Preparation of 6 from 1 :

A mixture of **1** (0.145g, 1mmol), phosphorane **2** (0.389g, 1mmol) and diphenyl ether (5ml) was refluxed for 1h under nitrogen atmosphere, 10% Pd - C (0.025g) was added and refluxing continued for 7h more. Chromatography using pet. ether (60-80) - ethyl acetate as an eluent furnished **6** (0.202g, 80%).

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