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## Photocyclization of 1-(2-halophenyl)-3,4-dihydro-6,7-dimethoxyisoquinolines: a short and new synthesis of triclisine

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Abstract—A short and new synthesis of the non-phenolic azafluoranthene alkaloid triclisine utilizing the photocyclization of 1-(2-halophenyl)-3,4-dihydro-6,7-dimethoxyisoquinolines as a key step has been described. © 2005 Elsevier Ltd. All rights reserved.

Azafluoranthenes constitute a small group of isoquinoline derived alkaloids consisting of the non-phenolic bases triclisine, imeluteine and rufescine, and the phenolic bases norrufescine and telitoxine. Synthetic approaches towards these alkaloids involve either Pschorr or Pschorr-type cyclizations<sup>1–3</sup> of the appropriate arenediazonium precursors to build ring D, or selective controlled introduction of the azafluoranthene aryl D ring by an inverse electron demand Diels-Alder reaction of 3-carbomethoxy-2-pyrones.<sup>4</sup> The Snieckus approach,<sup>5</sup> which allowed the simultaneous formation of the B and C rings, is based on a metallation (ortho and remote)-cross coupling process. Herein, we wish to report a short synthesis of the non-phenolic azafluoranthene alkaloid triclisine utilizing the photocyclization of 1-(2-halophenyl)-3,4-dihydro-6,7-dimethoxyisoquinolines as a key step.

Towards this end, the photocyclization of 1-(2-halophenyl)-3,4-dihydro-6,7-dimethoxyisoquinolines 1a,b was explored. Irradiation of a benzene solution of 1acontaining sodium thiosulfate with Vycor-filtered light (~254 nm) for 12 h led to the formation of two products identified as the desired cyclized and photoreduced compounds 2 and 3 in yields of 42% and 19%, respectively. Photolysis of the iodo aromatic isoquinoline 1b under

Table 1.	Photolysis of 1-(2-halophenyl)-3,4-dihydro-6,7-dimethoxyiso-
quinolin	es 1a,b

Entry	Substrate	Time (h)	2 (%)	3 (%)
1	1a	12	42	19
2	1b	7	40	24

these conditions for 7 h proceeded in an identical fashion to give the cyclized product 2 in a 40% yield along with the photoreduced product 3 in a 24% yield. The results obtained from these photolysis reactions of 1a,b are summarized in Table 1. To the best of our knowledge, this photolysis of 1-(2-halophenyl)-3,4-dihydro-6,7-dimethoxyisoquinolines 1a,b has been utilized for the synthesis of 2,3-dihydroazafluoranthene 2 for the first time. Dehydrogenation of 2 with 5% Pd–C at 250 °C for 15 min gave the azafluoranthene alkaloid triclisine 4 in a 52% yield (Scheme 1).

In conclusion, this work provides a new synthesis of the azafluoranthene alkaloid triclisine 4, which involves photocyclization of 1a,b to give 2,3-dihydroazafluoranthene 2 as a key step and the subsequent dehydrogenation of 2.

Typical procedure for Vycor-filtered irradiation of 1-(2-halophenyl)-3,4-dihydroisoquinolines 1a,b: A solution of 1a,b (0.5 mmol) and Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (100 mg) in benzene (75 mL) and H<sub>2</sub>O (1 mL) was irradiated for 7–12 h (Table 1). The benzene was evaporated under reduced pressure and the residue obtained was made alkaline

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Scheme 1. Synthesis of the non-phenolic azafluoranthene alkaloid triclisine.

with 10% aqueous ammonium hydroxide solution (10 mL). It was then extracted with CHCl<sub>3</sub> ( $3 \times 15$  mL). The combined CHCl<sub>3</sub> layers were washed with water ( $2 \times 10$  mL) and then dried (anhydrous Na<sub>2</sub>SO<sub>4</sub>). Evaporation of the solvent gave a brown residue, which was purified by column chromatography [alumina (neutral), hexane–CHCl<sub>3</sub> (70:30)] to furnish the photoreduced product **3** (Table 1). Further elution with hexane–CHCl<sub>3</sub> (50:50) followed by recovery of the solvents gave the dihydroazafluoranthene **2** (Table 1).

<sup>1</sup>H NMR data of 2,3-dihydro-5,6,-dimethoxyazafluoranthene **2** were in agreement with the reported data.<sup>6</sup>

Typical procedure for the dehydrogenation of 2: Dihydroazafluoranthene 2 (100 mg) was heated with 5% Pd–C (50 mg) at 250 °C for 15 min then extracted with hot EtOAc ( $4 \times 50$  mL). The combined EtOAc extract was filtered to remove catalyst traces. Evaporation of the solvent gave a brown residue, which was purified by column chromatography [alumina (neutral), hexane–  $CHCl_3$  (50:50)] to afford the azafluoranthene alkaloid triclisine 4.

The MP, IR and <sup>1</sup>H NMR data of triclisine **4** were in agreement with the reported data.<sup>7</sup>

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