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REGIOSPECIFIC DIHYDROINDOLES DIRECTLY FROM β-ARYLETHYLAMINES BY PHOTO-INDUCED SET REACTION : ONE POT "WAVELENGTH SWITCH" APPROACH TO BENZO-PYRROLIZIDINES RELATED TO MITOMYCIN

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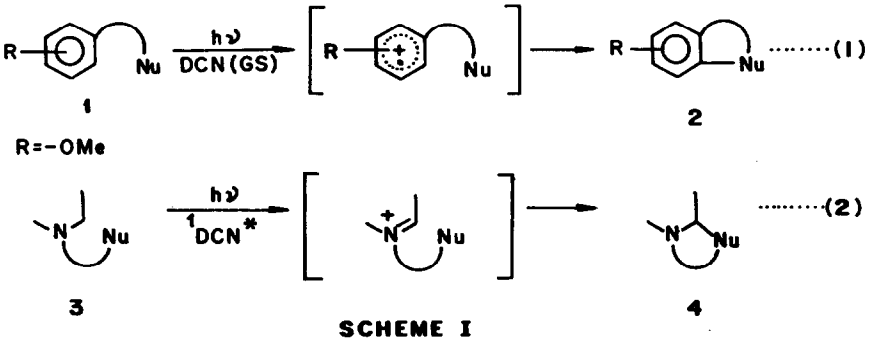
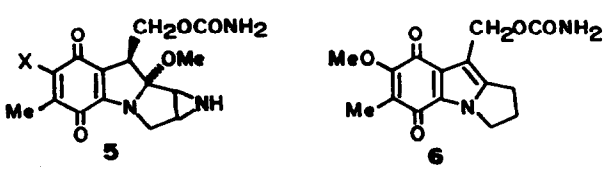
Abstract: Regiospecific highly substituted indole derivatives are synthesised by photoinduced SET initiated cyclisation of β-arylethylamines and development of sequential one pot approach to benzopyrrolizidines related to mitomycin at two different wavelengths under SET conditions is reported.

As part of our ongoing research interest in photoinduced SET reactions[1], we have reported two interesting reactions for effecting novel intramolecular nucleophilic cyclisation of great synthetic potential utilising 1,4-Dicyanonaphthalene (DCN) as electron acceptor in ground state (GS, Eq.1)[2] and in excited singlet state (Eq. 2)[3]. Subsequently, our attention was drawn to the utility of these methodologies for the construction of aromatic N-heterocyclic derivatives



SCHEME I

with a substitution pattern related to mitomycins, as the known methods for these classes of compounds often result in low yields after employing multiple step route[4]. Mitomycins,



X = OMe Mitomycin A
= NH_2 Mitomycin C

especially mytomycin C, are potent antineoplastic agents used currently in combination chemo-

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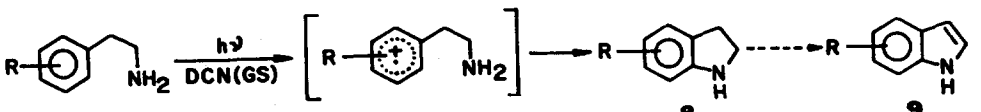
therapy, particularly for the treatment of adenocarcinoma of stomach and pancreas[5].

We have initiated studies directed towards the development of photoinduced SET approaches to the synthesis of mitomycin analogues and in the course of these studies a general method for the synthesis of highly functionalised indole derivatives have been developed which is described herein along with concurrent demonstration of combining the two reactions (Scheme I) for the one pot "wavelength switch" approach for the synthesis of benzopyrrolizidine (24) related to mitomycins.

The regiospecificity achieved in the intramolecular nucleophilic cyclisation to SET generated arene radical cation and pertinent explanation advanced based on FMO theory considering the HOMO of the arene radical cation[2c] led us to reason a direct and unprecedented route for the synthesis of dihydroindoles from β-arylethylamines (Scheme II). From a synthetic view



7 8 9

SCHEME II

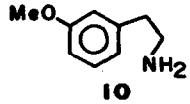
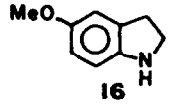
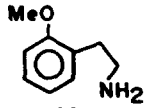
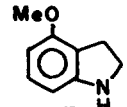
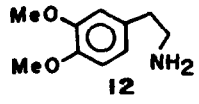
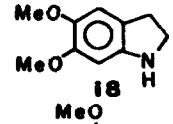
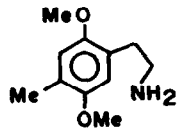
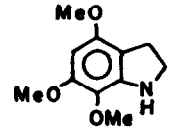
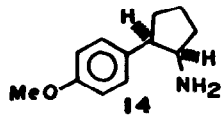
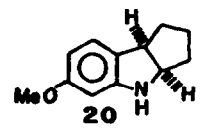
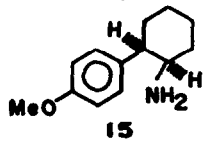
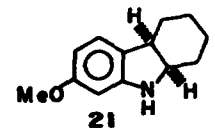
point, this offers a convergent and mild approach to highly substituted indole system[6].

Photolysis (> 280 nm, 8-10h) of β-arylethylamines (6mM), easily obtained by catalytic reduction of corresponding nitrostyrenes[7], in the presence of DCN (0.8mM)[8] in methanol or acetonitrile gave corresponding dihydroindole (8) with less than 5% cleavage product[9] following the identical mechanistic path as described earlier[2]. The dissolved air present in the solvent was enough to complete the final oxidation step[2a]. The representative examples of this reaction are listed in Table 1. Particularly, the transformation of (15) to the corresponding indole derivative (21) is considerably significant as this provides a newer methodology for the synthesis of stereospecific hexahydrocarbazole alkaloids[10,11].

In this general context it was, therefore, conceived that sequential generation and cyclisation of arene radical cation and iminium cation from substrate (22), obtained by selective excitation of substrate (22) and 9,10-Dicyanoanthracene (DCA) respectively at two different wavelengths would realise the one pot synthesis of benzopyrrolizidine (24) related to mitomycin skeleton (Scheme III). To this end a mixture of 22 (6 mM) and DCA (0.2mM)[12] in MeOH:H_2O(8:2) was first irradiated by 450 W medium pressure Hannovia lamp using pyrex sleeve (> 280 nm, 8h, all light absorbed by 22) and then pyrex filter was replaced by uranium yellow filter (> 350 nm, all light absorbed by DCA) and photolysis was continued for additional 10h. Removal of the solvent and normal chromatographic purification gave 24(62%) and DCA was recovered (92%) as such. Overman et al.[13] and our own work have shown that intramolecular cyclisation of iminium cation

by non-activated olefin takes place only in highly nucleophilic environment (MeOH: H_2O, Bu_4NBr, KI, etc.)[14] (24) could be easily converted to corresponding indoloquinone (25) by the reported procedure[15].

TABLE I: Dihydroindoles from β-arylethylamines

ENTRY	SUBSTRATE[a,b]	PRODUCT[c]	YIELD (%)[d]
1	 10	 16	80
2	 11	 17	78
3	 12	 18	80
4	 13	 19	82
5	 14	 20	76
6	 15	 21	70

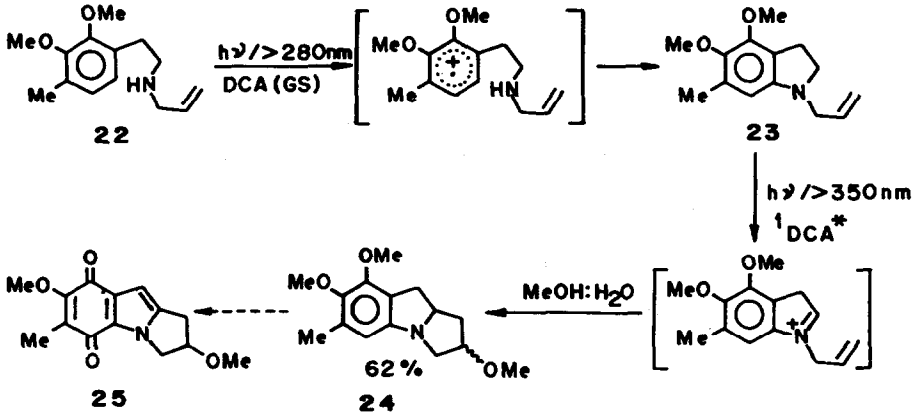
a) Substrate 10-13 were prepared by catalytic reduction of corresponding nitrostyrene;

b) Compounds 14-15 were prepared by Grignard reaction of bromoanisole and corresponding ketone followed by hydroboration and usual amination;

c) All products gave satisfactory spectral (^1H NMR and mass) data;

d) Isolated yields but not optimised.

In conclusion, this offers a new method for the synthesis of highly substituted indole derivatives and a one pot concise and efficient route to mitomycin skeleton just by irradiating at



SCHEME III

two different wavelengths. Further work is in progress.

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2. a) Pandey, G., Krishna, A. and Rao, J.M., **Tetrahedron Letters, 27,** 4075 (1986); b) Pandey, G. and Krishna, A., **J.Org.Chem., 53,** 2364 (1988); c) Pandey, G. and Krishna, A., **Tetrahedron Letters, 30,** 1867 (1989).
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8. Use of 9, 10-dicyanoanthracene (DCA) gives equally good result.
9. This difference from corresponding β-arylethylalcohol could be attributed to significant nucleophilicity difference of amino group.
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11. A total synthesis of (±)-Aspidospermine based on this approach is in progress.
12. DCA is used to avoid any absorption overlap.
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