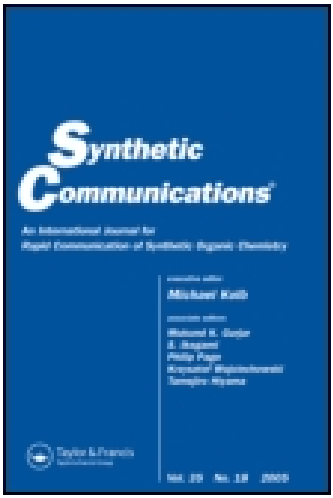

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An Expedient Synthesis of 5,11-Dimethylindolo[3,2-b]-carbazole, A Potent Ligand for the Receptor for TCDD

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AN EXPEDIENT SYNTHESIS OF 5,11-DIMETHYLINDOLO[3,2-*b*]-CARBAZOLE, A POTENT LIGAND FOR THE RECEPTOR FOR TCDD

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Abstract. A new and efficient synthesis has been developed for the title indolocarbazole which has been indicated by a recent computer-aided study to be a potent ligand for the receptor for the naturally occurring carcinogen, TCDD.

The well known tumour promoter, TCDD or 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, is ubiquitous in nature and poses serious health hazards. Its toxicity is thought to be mediated by a receptor, a thorough study of which necessitates the use of an alternative, efficient but non-carcinogenic ligand for it. A recent piece of work employing the *CASE* (*c*omputer-*a*utomated *s*tructure *e*valuation) programme has strongly suggested that 5,11-dimethylindolo[3,2-*b*]-carbazole (**1**) should be an efficient candidate-ligand of choice[1]. This fact underscores the need for the availability of a convenient and

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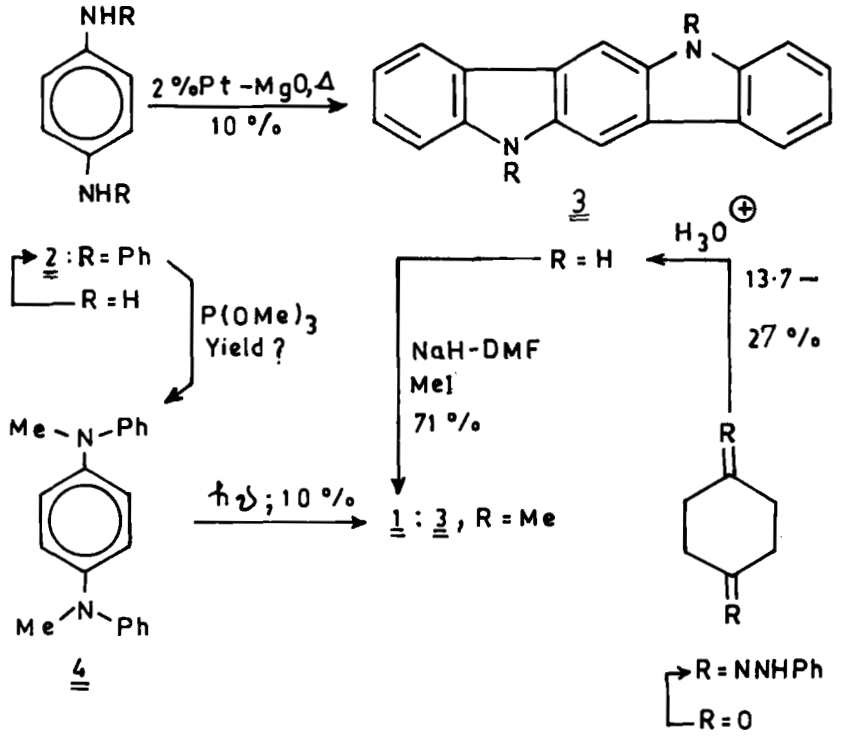

FIG 1

Reported Syntheses of 1

high-yielding synthesis of this ligand for its use in the study of the receptor for TCDD.

The title IC (1) is reported to have been prepared by three routes (FIG 1), all of which suffer from serious disadvantages. One of these routes, comprising the sequence, p-$C_6H_4(NH_2)_2$ to the diphenyl deriv., 2 to the parent IC, 3 to 1, required the use of very high temp. (560+5°C) and the yield at the cyclisation step was only 9.6%[2]. In the second

approach[3-6], viz. cyclohexane-1,4-dione to the bis(phenylhydrazone) to 3 to 1, the yields at the crucial bis-indolisation step were again low : 13.7%[3], 27%[4] and 20%[5]. The more recent third approach encompassed the sequence : *p*-$C_6H_4(NH_2)_2$ to 2 to 4 to 1[7]. Here also the yield at the cyclisation step (4 to 1) was only 10% and, more regrettably, the report contains no experimental details about the formation and no data whatsoever, including the yield, of 4. The overall yields of 1 were obviously still lower in all the cases.

These shortcomings of the extant syntheses of 1 prompted us to try to develop an expedient synthesis of this IC with improved overall yield. Our idea was to try the photochemical cyclisation of 9-methyl-3-(*N*-methylanilino)carbazole, 8 as the crucial step, as this mode of cyclisation has not been tried before. Accordingly, the known substrate, 9-methyl-3-aminocarbazole (5)[8] was prepared from the corresponding 3-nitrocarbazole[9] by reduction with $NH_2NH_2.H_2O$ and Pd-C. By increasing the proportions of the reagents we could increase the yield of 5 appreciably, from 66% to 78%. The yield of 5 was further improved, but only marginally, by the use of tin and conc. HCl. *N*-Phenylation was next accomplished by the application of Goldberg reaction[10,11] (FIG 2). Thus, the derived (Py/Ac_2O) acetate, (6) was allowed to react with bromobenzene in the presence of copper bronze and potassium carbonate, and the resulting *N*-acetyl-*N*-phenyl derivative, formed *in situ*, was hydrolysed by aq. alc. alkali to furnish

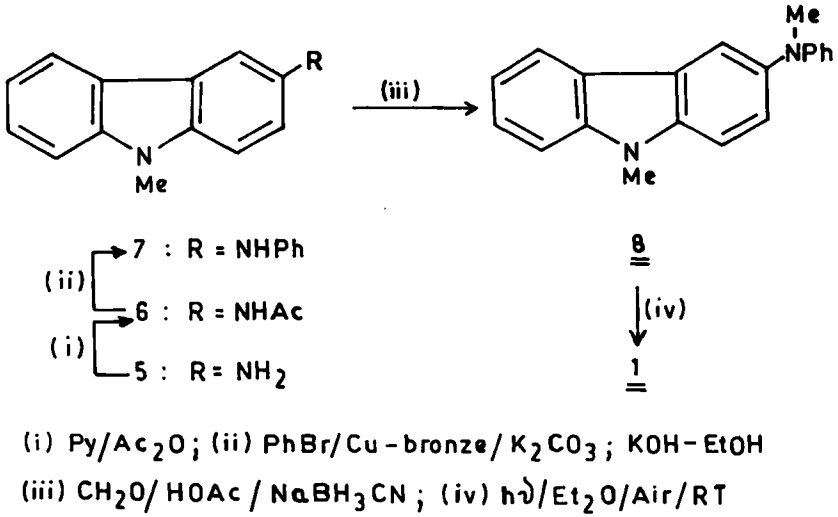

FIG 2

Our Syntheses of 1

the anilinocarbazole, **7** in excellent yield. The classical Eschweiler-Clarke reaction (CH_2O-HCO_2H) and reductive methylation in alkaline condition[12] then failed to provide the desired *N*-methylated product in good yield. It was, however, obtained smoothly and in exceedingly high yield by the application of reductive methylation in acidic medium[13]. Thus, the cyanoborohydride reduction of the imine salt, formed *in situ* by the reaction of **7** with formaldehyde and acetic acid, resulted in the formation of the penultimate substrate, **8**. An ambient temp. photocyclisation of the latter in ethereal solution produced the target IC, **1** in 51% yield. All the compounds were characterised properly - the known compounds

by comparison of their data with the reported ones and the unknown ones by microanalytical and sufficient spectral analyses.

Our method constitutes a new, expedient synthesis of **1**, in which all the steps are easy to perform and the yields are high. The overall yield (*ca*. 40% from **5**, as against <<10%, 9-18% and <<10% in three earlier syntheses) and the yield at the crucial cyclisation step (51% in contrast to 9.6%, 13.7-27% and 10% in the three previous reports) was markedly improved in our method. But the most significant advantage that our method offers is that, though developed for **1**, the approach can be applied to the synthesis of any unsymmetrically substituted IC of [3,2-*b*] type, whereas the existing routes lead only to symmetrical IC's. The advantage of our method stems from the fact that the crucial anilino-carbazole is prepared by the Goldberg reaction of two different arenes.

Experimental

M.ps. are uncorrected. Ir spectra (KBr) were recorded on a Perkin-Elmer IR-782 spectrophotometer, mass spectra (EI) on Kratos-AEI MS9 and VG TRIBID mass spectrometers and ^1H NMR spectra ($CDCl_3$ + TMS) on JEOL FX-100 and Bruker AC-200 spectrometers. Photoreaction was carried out on a SAIC 400 Watt medium pressure mercury lamp fitted with a pyrex filter of M/s. Applied Photophysics, U.K. All column chromatographies (CC) were performed over silica gel (60-120 mesh; Qualigens,

India). Microanalyses were carried out on a Dr. Hans Hoesli Analyser, Bischofszell, Switzerland. Petrol refers to petroleum ether, b.p. 60-80°C.

Preparation of **5**. *Method A*.- Following the reported procedure but using 2 equiv. of $NH_2NH_2.H_2O$ and 10% Pd-C (20 mg/mmol), **5** was obtained as greyish crystals, m.p. 170-171°C (EtOH) (lit.[8] 173-175°C) in 78% yield.

Method B.- An alcoholic solution (10 ml) of **4** (0.226 g, 1 mmol) was refluxed with tin (0.475 g, 4 mmol) and conc. HCl (4 ml) for 2 h to furnish, after usual work-up, the amine, **5** in 80% yield (0.16 g).

Preparation of **7**.- **5** (1.96 g, 10 mmol) in dry Py (7 ml) was treated with Ac_2O (14 ml) in cold, left overnight and then diluted with benzene. The resulting solid was filtered to furnish **6**, m.p. 198-200°C (dec.) (EtOH) in 92% yield (2.19 g); ν_{max} 1668 (amide CO), 1598, 1502, 1480 (Ar) cm^{-1}.

A mixture of **6** (1.19 g, 5 mmol), fused K_2CO_3 (0.7 g), copper bronze (0.16 g, 2.5 mmol) and distilled PhBr (2.6 ml, 25 mmol) was refluxed in an oil bath (~ 200°C) in N_2 atm. for 28 h. After distilling off excess PhBr, hydrolysis of the residue by refluxing with 20% KOH/aq. EtOH for 4.5 h, usual work-up and purification by CC over SiO_2 afforded in 10% EtOAc/petrol eluates the product, **7** (1.26 g, 93%) as colourless crystals, m.p. 158-159°C (petrol) (Found : C, 83.42; H, 5.85; N, 10.35. $C_{19}H_{16}N_2$ requires C, 83.82; H, 5.88; N, 10.29%); ν_{max} 3380 (NH), 1600, 1508, 1490 (Ar) cm^{-1}; EI-MS : *m/z* 272

(M^+; 100%), 257 (20), 256 (10), 195 (3), 136 (M^{++}; 19), 128 (10), 127 (10).

Reductive methylation of **7** .- $NaBH_3CN$ (0.19 g, 3 mmol) was added in portions with stirring to a solution of **7** (0.55 g, 2 mmol) in CH_3CN (20 ml) containing 37% aq. CH_2O (3.2 ml). Glacial HOAc (0.2 ml) was then added and the solution was stirred till (2.5 h) **7** was consumed (tlc). An usual work-up, followed by CC, furnished in 5% EtOAc/petrol eluates the product, **1a** (0.52 g, 91%) as colourless prisms, m.p. 114-115°C (petrol-CH_2Cl_2) (Found : C, 83.99; H, 6.33; N, 9.72. $C_{20}H_{18}N_2$ requires C, 83.81; H, 6.29; N, 9.79%); ν_{max} 1590, 1560, 1493 (Ar) cm^{-1}; EI-MS : *m/z* 286 (M^+; 100%), 271, 256, 180, 179, 143 (M^{++}), 77; δ_H (100 MHz, $CDCl_3$) 3.38 and 3.84 (3H, s each, side chain Me and 9-Me, respectively), 6.78 (3H, m), 7.08-7.52 (7H, m) and 7.99 (2H, br d, *J* <7 Hz, all Ar-H).

Photocyclisation of **1a** .- A solution of **1a** (0.28 g) in ether (200 ml) was irradiated by a 400 Watt Hg lamp at RT for 8 h in presence of air and the residue from the solution was purified by CC. 10% Benzene/petrol eluates furnished **1** (0.1 g, 51%) as light yellow crystals, m.p. 250-252°C (petrol-CH_2Cl_2) (lit. 258°C, from EtOH[2]; 295-296°C, from CH_3NO_2 [3]); ν_{max} 1592, 1450, 1360, 1305, 1230, 732, 705 cm^{-1}; EI-MS : *m/z* 284 (M^+; 100%), 269, 254, 180, 142 (M^{++}); δ_H (200 MHz, $CDCl_3$) 3.95 (6H, s, 2 x *N*Me), 7.35-7.50 (2H, m) and 7.50-7.70 (6H, m, all Ar-H), 8.92 (2H, d, *J* 8 Hz, 2 x *peri* -H).

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