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Synthesis of 2,2'-Biindole: Formal Synthesis of Arcyriaflavin-A and Staurosporinone (K-252c)

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A convenient four-stage synthesis of 2,2'-biindole, the immediate precursor of arcyriaflavin A and staurosporinone *via* double Wittig-double reductive cyclization reactions is described.

Key Words: 2,2'-Biindole, Indolocarbazole, Reductive cyclization, Wittig reaction.

INTRODUCTION

The indolocarbazole alkaloids, arcyriaflavin-A (**1**) and staurosporinone (K-252c) (**2**) (Fig. 1), metabolites of a marine ascidian, *Eudistoma* sp.[1] collected off the coast of West Africa exhibit a wide range of biological properties, *viz*., inhibition of protein kinase C, platelet aggregation, cytotoxicity, antimicrobial, antitumor activities, *etc*.[2,3]. These alkaloids **1** and **2** had also been previously reported from the fungi *Arcyrai denudata*[4] and *Nocardiopsis* sp.[5], respectively.

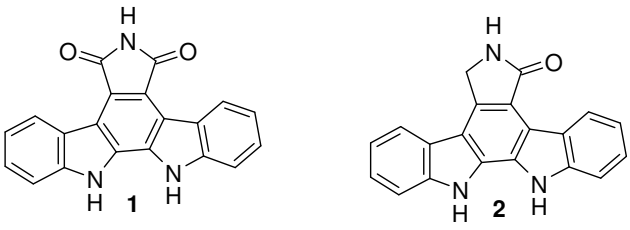


Fig. 1

Continuing our interest[6] in natural products containing indole moiety, we report herein a simple approach to synthesis 2,2'-biindole from easily and cheaply available starting materials. 2,2'-Biindole is a core structural motif of several biologically active indolocarbazole alkaloids[7,2b] like staurosprine, staurosporinone, arcyriaflavin, rebeccamycin and tjipanazole. 2,2'-Biindole as a structural unit[8] is present in the dyes indigo and tyrian purple (6,6'-dibromoindigo) known from ancient times and is also exploited in the construction of various ligand systems[9].

EXPERIMENTAL

General procedures: Commercial reagents were purchased from Sigma-Aldrich and used without further purification. Solvents were distilled prior to use. Reactions were monitored by thin layer chromatography (Kieselgel Merck 60) purchased from Merck. Column chromatography were performed on silica gel (60-120 mesh). Infrared spectra were recorded on Shimadzu FT-IR spectrophotometer. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) were recorded on a Brucker 300 instrument using DMSO-d_6 and $CDCl_3$ as solvent and TMS as an internal standard. HRMS were recorded on a MicroMass ES-QTOF. Melting points are recorded using Thiele apparatus and are uncorrected.

Preparation of 1,4-*bis*-(*o*-nitro-phenyl)-1,3-butadiene (4): A mixture of *o*-nitro-benzaldehyde (**7**) (0.5234 g, 3.46 mmol) and (triphenylphosphoranylidene)-acetaldehyde (**8**) (1.0540 g, 3.46 mmol) was refluxed in chloroform (10 mL) for 3 h. The reaction mixture was allowed to cool to room temperature and to this was added *o*-nitro-benzyl-triphenyl phosphonium bromide (**5**) (1.6582 g, 3.46 mmol), Et_3N (1 mL) and stirred at room temperature for 1 h. The chloroform was removed under reduced pressure and to this was added methanol. The yellow solid *i.e*., product (**4**) precipitated out was filtered through Buchner funnel (0.8517 g, 83 % overall yield). m.p. 102-104 ºC. IR (KBr, ν_{max}, cm^{-1}) 1518, 1341, 1142, 952, 858, 748; ^{1}H NMR (300 MHz, $CDCl_3$) showed complex multiplets between δ 6.60-7.82 ppm; HRMS m/z $[M + Na]^+$ 319.0692 (calculated for $C_{16}H_{12}N_2O_4Na$, 319.0695).

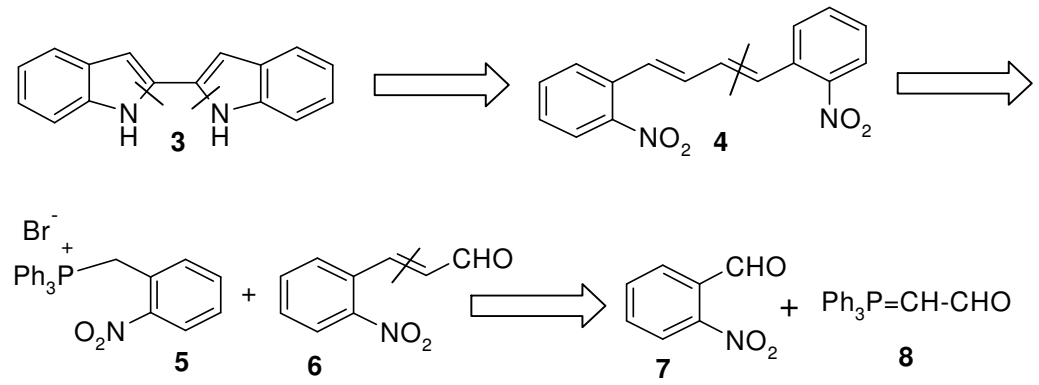
Preparation of 2,2'-biindole (3): A mixture of nitro-dimer (**4**) (0.5086 g, 1.72 mmol) and triphenyl phosphine (1.8028 g,

6.87 mmol) was refluxed in Ph_2O (15 mL) for 3 h under N_2 atmosphere. After cooling, reaction mixture was chromatographed on silica gel column (60-120 mesh) and diphenyl ether was removed using hexanes as an eluent. Further elution with 20 % ethyl acetate in hexanes afforded 2,2'-biindole (**3**) (0.0.1797 g, 45 %) as a grey coloured solid. m.p. > 300 ºC (Lit.[10] m.p. 311-314 ºC). IR (KBr, ν_{max}, cm^{-1}) 3398, 1442, 1396, 1340, 1261, 1070, 931, 800, 625; ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.93 (s, 2H), 7.01 (t, 2H, *J* = 7.5 Hz), 7.11 (t, 2H, *J* = 7.5 Hz), 7.41 (d, 2H, *J* = 7.5 Hz), 7.56 (d, 2H, *J* = 7.5 Hz), 11.57 (s, 2H, -NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 98.9 (2 × -CH), 111.5 (2 × -CH), 119.8 (2 × -CH), 120.5 (2 × -CH), 122.1 (2 × -CH), 128.9 (2 × -CH), 131.9 (2 × -C), 137.4 (2 × -C); HRMS m/z $[M + K]^+$ 271.0839 (calculated for $C_{16}H_{12}N_2K$, 271.0838).

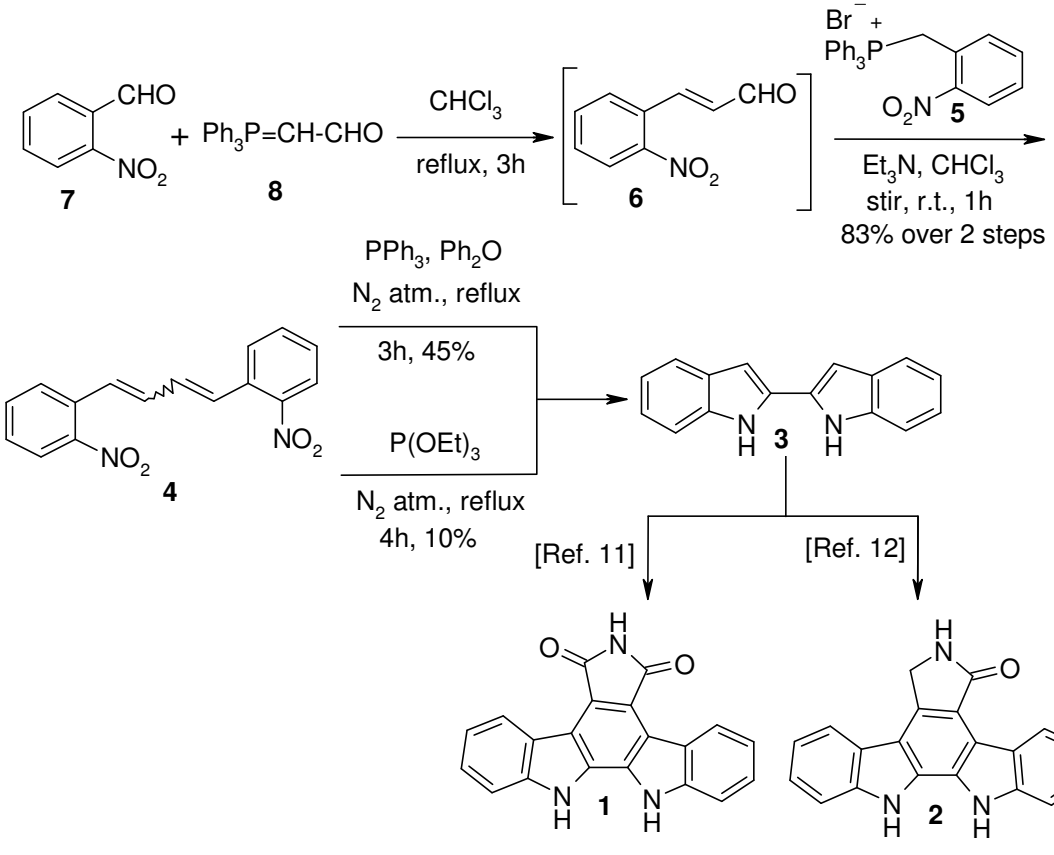
RESULTS AND DISCUSSION

Our approach to the synthesis of 2,2'-biindole (**3**) was based on the retrosynthetic analysis depicted below (**Scheme-I**), through the preparation of 1,4-*bis*-(*o*-nitro-phenyl)-1,3-butadiene (**4**), which in turn can be obtained by Wittig reaction.

To begin with, *o*-nitro-benzaldehyde (**7**) was condensed with (triphenylphosphoranylidene)-acetaldehyde (**8**) and the resultant product *i.e.*, *o*-nitro-cinnamaldehyde (**6**) without isolation was treated with *o*-nitro-benzyl-triphenylphosphonium bromide (**5**) in presence of triethyl amine to give 1,4-*bis*-(*o*-nitro-phenyl)-1,3-butadiene (**4**) in 83 % overall yield over two steps. When the compound (**4**) was refluxed in triethyl phosphite (TEP) under nitrogen atmosphere, 2,2'-biindole (**3**) was obtained in only 10 % yield *via* nitrene insertion. Replacement



Scheme-I



Scheme-II

of TEP with triphenyl phosphine (TPP) in diphenyl ether at reflux temperature furnished the product (**3**) in 45 % yield. The formation of 2,2'-biindole (**3**) constitutes the formal synthesis of naturally occurring indolocarbazole alkaloids-arcyriaflavin-A (**1**) and staurosporinone (K-252c) (**2**), respectively (**Scheme-II**).

Conclusion

We have developed a new approach for the synthesis of 2,2'-biindole, a precursor to arcyriaflavin-A and staurosporinone (K-252c) using consecutive Wittig reactions and double reductive cyclization which can be extended to prepare derivatives of 2,2'-biindole.

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