

CONVENIENT SYNTHESSES OF 2,2'-BIINDOLE

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Abstract

Two new syntheses for 2,2'-biindoles are reported. The first uses a palladium catalyzed annulation of a bis(*o*-iodophenyl)- α,β -diimine. The method employs mild conditions, gives good yields, and is potentially tolerant of a variety of substituent groups. The second method uses a Wittig reaction between a 2-nitrobenzylphosphonium salt and 2-nitrocinnamaldehyde to form 1,4-bis(2-nitrophenyl)butadiene, which followed by triethylphosphite cyclization to give the biindole.

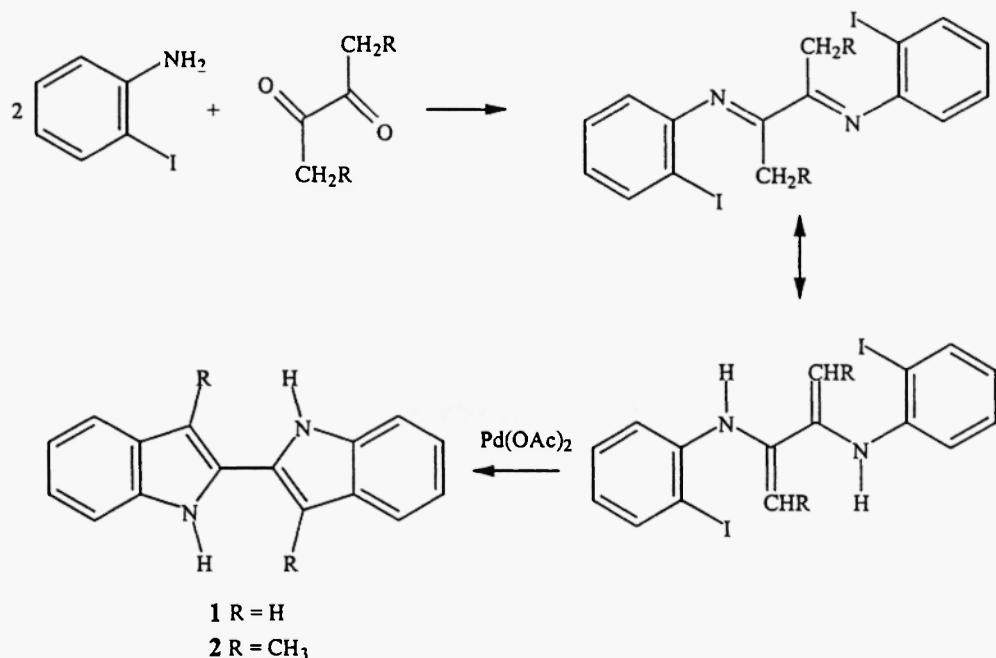
Introduction

Recently, 2,2'-biindole has received attention as a number of natural products containing the biindole moiety have been isolated (1). 2,2'-Biindole and simple derivatives are relatively inaccessible compounds with the few routes available for their synthesis employing harsh conditions and correspondingly low yields. Indoles substituted at the 2-position, particularly 2,2'-biindoles, are a formidable synthetic challenge due to the low inherent electron density of the 2-position. The Madelung synthesis of 2,2'-biindole from oxaryl *o*-toluidine is one of the few routes available for the synthesis of this compound and numerous modifications have been reported (2-6) but this method requires high temperatures. Metal mediated coupling of 2-haloindoles (7-9) does not require high temperatures but the inherent instability of 2-haloindoles limits the usefulness of these reactions. Finally, a butyllithium initiated ring closure of a substituted butyne has been reported (10). These syntheses preclude the incorporation of sensitive functional groups in the product and generally do not allow for substitution at the 3-position.

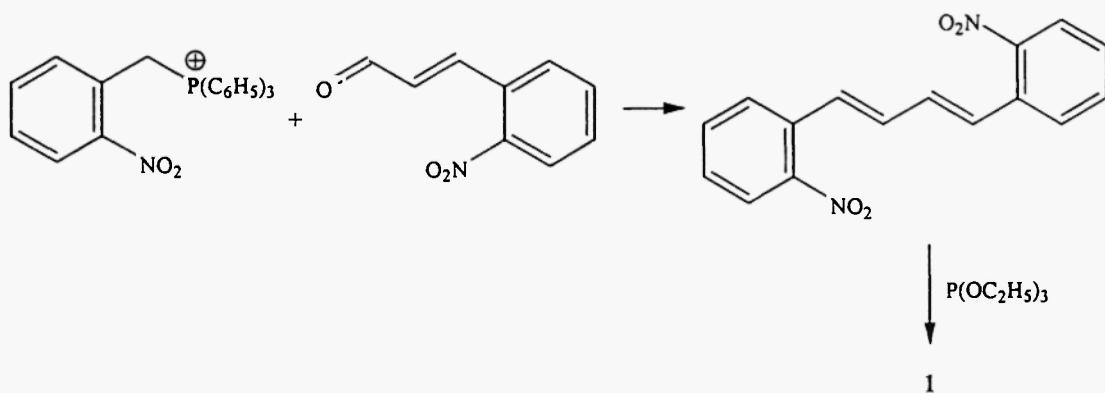
Given the difficulties of the known synthetic procedures for 2,2'-biindoles, we developed two new methods to this molecule. Recently, the palladium catalyzed coupling of aldehydes and ketones with *o*-haloanilines has become a mild alternative to traditional Fischer indole cyclizations. This straightforward approach for the synthesis of substituted indoles has been successfully applied for the synthesis of a wide variety of indole derivatives (11). In this paper, we report the synthesis of 2,2'-biindole (1) and 3,3'-dimethyl-2,2'-biindole (2) using the palladium catalyzed annulation. The second route uses a Wittig reagent to form a substituted 1,3-butadiene that is subsequently cyclized with triethylphosphite. This latter method provides the possibility of synthesizing 2,2'-biindoles asymmetrically substituted on the benzene rings.

Results

The two new strategies used to form **1** are shown in the Scheme. Method 1 uses a palladium catalyzed annulation. This reaction proceeds through by enamine formation followed by an intramolecular Heck reaction (12). The utility of this reaction is readily apparent in the synthesis of symmetric 2,2'-biindoles. Selection of the appropriate α -diketone gives the corresponding 2,2'-biindole in high yield and under very mild conditions. The coupling of 2-iodoaniline with 2,3-butanedione afforded 2,2'-biindole in 68% yield in the absence of significant side products. This scheme potentially could provide for the incorporation of acetals and carbamate functionalities, groups that are unstable under Madelung (2-6) conditions.



Method 1



Method 2

Method 2 uses the triethylphosphite promoted cyclization of 1,4-(2-nitrophenyl)-1,3-butadiene to achieve **1**. The Wittig reaction for these types of materials proceeds nearly quantitatively and would allow the facile synthesis of a 2,2'-biindole unsymmetrically substituted on the benzene rings, although we did not pursue such a structure.

Experimental

2,2'-Biindole (1) Method 1: 2-iodoaniline (1.07 g, 5 mmol), 2,3-butanedione (0.215 g, 2.5 mmol), DABCO (0.28 g, 2.5 mmol), and 0.01 g of $\text{Pd}(\text{OAc})_2$ are placed in a 50 mL round bottom flask. 25 mL of degassed DMF is added and the temperature raised to 105 °C with stirring for 6 hours. The reaction mixture is cooled to room temperature and partitioned between methylene chloride and water. The organic layer is extracted, dried over sodium sulfate, and concentrated under vacuum to dryness. The residue was chromatographed on silica by elution with chloroform and concentrated *in vacuo*. The residue was recrystallized from ethanol to afford 0.40g of 2,2' biindole in 68% yield as light brown crystals. Method 2: 1,4-(2-nitrophenyl)-1,3-butadiene. 2-nitrobenzyltriphenylphosphonium bromide (2.00 g, 4.19 mmol) and 2-nitrocinnamaldehyde (0.743 g, 4.17 mmol) are dissolved in 10 mL of dry methylene chloride. Saturated aqueous NaOH is added with stirring until the solution turns deep purple. After 30 min the solution becomes brown and an additional 20 mL of dry methylene chloride is added and the solution is placed in a separatory funnel. Water is added and the mixture is shaken. The organic layer is separated and the aqueous layer is extracted three more times with 50 mL aliquots of methylene chloride. The organic layers are combined, dried over sodium sulfate, and run through a column with 100 g of silica by elution with methylene chloride. The yellow eluent is rotary evaporated to dryness and the solid recrystallized from ethanol to yield 1.24 g (100%) of the bright yellow product. mp 142-148 °C as a mixture of the *cis* and *trans* isomers. 1,4-(2-nitrophenyl)-1,3-butadiene (1.00 g, 3.4 mmol) is placed in a 50 mL round bottom flask and 20 mL of triethylphosphite is slowly added. The mixture is heated to reflux with stirring as the solution turns from yellow to dark brown. After 3 hr the solution is allowed to cool to room temperature. The solution is dried under vacuum and the resulting solid chromatographed on silica by elution with chloroform. The first brown fraction was rotary evaporated to dryness and the residue crystallized from ethanol to afford 0.58 g of **1** in 74 % yield. Both synthetic methods for **1** gave the same characterization: mp 316-318 °C (Lit. (4) 308-310 °C). IR (KBr) 3400 (NH), 1661, 1583, 1516, 1455, 1394, 750 cm^{-1} . ^1H NMR (DMSO-d6) δ 6.93 (s, 2H, C3H), 7.02 (t, J = 8.1 Hz, 2H, C5H), 7.11 (t, J = 8.1 Hz, 2H, C6H), 7.40 (d, J = 8.6Hz, 2H, C7H), 7.55 (d, J = 8.6Hz, 2H, C4H), 10.71 (s, 2H, NH); ^{13}C NMR (DMSO-d6) δ 137.46 (C3a), 131.64 (C2), 129.17 (C7a), 122.00 (C6), 120.21 (C4), 119.73 (C5), 111.00 (C7), 98.70 (C3). UV-Vis λ_{max} = 354, 324, 275, 238 nm.

3,3'-Dimethyl-2,2'-biindole (2): 2-iodoaniline (1.07 g, 5mmol), 3,4-hexanedione (0.301 g, 2.5 mmol), DABCO (0.28 g, 2.5 mmol), and 0.01 g of $\text{Pd}(\text{OAc})_2$ are placed in a 50 mL round bottom flask. 25 mL of degassed DMF is added and the temperature raised to 105 °C with stirring for 12 hr. The reaction

mixture was cooled to room temperature and partitioned between methylene chloride and water. The organic layer was extracted, dried over sodium sulfate, and concentrated under vacuum to dryness. The residue was chromatographed on silica by elution with methylene chloride and concentrated in vacuo. The residue was recrystallized from ethanol/water giving 0.28 g (43%) of **2** as white crystals. mp 162 °C. IR (KBr) 3381, 2818, 1503, 1460, 1338, 1003, 738 cm⁻¹. ¹H NMR (DMSO-d6) δ 2.71 (s, 3H, methyl), 7.17 (t, J = 8.0 Hz, 1H, C5H), 7.30 (t, J = 8.1 Hz, 1H, C6H), 7.56 (d, J = 8.0 Hz, 1H, C7H), 7.95 (d, J = 8.0 Hz, 1H, C4H), 10.17 (s, 1H, NH). UV-Vis λ_{max} = 249, 281, 425 nm.

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