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# A short and efficient synthesis of furo[2,3-*b*]indoles

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ABSTRACT

Application of Wittig olefination–Claisen rearrangement protocol for the short synthesis of furo[2,3-*b*]indoles is described.



## 1. Introduction

Fused heterocyclic rings are present as partial structures in diverse natural products. For this and other reasons, since long ago, synthesis of fused heterocyclic ring systems such as pyrrolo-indoles,[1] carbazoles,[2] furo-indoles, etc. is a matter of interest for chemists.

The furo[2,3-*b*]indole ring system is at the core of many natural products.[3–8] Due to the biological activity[9–13] associated with this ring system and its derivatives and its use as a synthetic intermediate in the synthesis of numerous alkaloids, several methods have been reported for the synthesis of this ring system.[14–47] In spite of this voluminous work, even today construction of this ring system is an attractive goal for demonstrating the efficacy of newer synthetic protocols. The Wittig olefination–Claisen rearrangement protocol developed in our laboratory[48,49] has been applied extensively in the total syntheses of natural products[50–52] and heterocyclic compounds.[53–57] We herein describe the successful application of Wittig olefination–Claisen rearrangement protocol[58] in a four-step synthesis of furo[2,3-*b*]indoles.

Reaction of *o*-nitro benzaldehyde **(1a)** with allyloxymethylene triphenylphosphorane, under optimized reaction conditions[50] gave allyl vinyl ether **(2a)** in good yield (Scheme 1). The $^1$H NMR spectrum showed that the allyl vinyl ether **(2a)** was an inseparable mixture of *E*- and *Z*-isomers. All attempts to separate the *E*- and *Z*-isomers did not materialize, but the ratio of these isomers was determined from NMR spectrum (Table 1).

The Claisen rearrangement of the allyl vinyl ether **(2a)** was effected by heating it in refluxing anhydrous xylene to give the corresponding 4-pentenal **(3a)** in good yield. Double bond of 4-pentenal **(3a)** was ozonolyzed to get the di-aldehyde. This di-aldehyde, being found to be unstable and acid sensitive, was used as such for the next step. The attempted reduction of the nitro group in **(3a)** to the amine using Ra–Ni/$H_2$ or Pd/C–$H_2$ in methanol ended up in the formation of a complex mixture of products. Most likely the sensitive 1,4-di-aldehyde functionality is getting affected under the reaction conditions. Reduction of the nitro group under basic conditions using NaSH,[59] generated from the mixture of sodium sulfite and sodium bicarbonate in the presence of methanol, was carried out, which avoided the side reactions. From this reaction, furo[2,3-*b*]indole **(4a)** was isolated directly in good yield (Table 1).

After the successful preparation of furoindole (**4a**), the generality of this method was studied. For this purpose, substituted *o*-nitro benzaldehydes were used. All these compounds smoothly reacted under the above reaction conditions to give the corresponding furo[2,3-*b*]indoles (**4b–g**) in good yields (Table 1).

In conclusion, herein we have developed a short and efficient synthesis of furo[2,3-*b*]indole, with good overall yield, by using Wittig olefination–Claisen rearrangement methodology.

## 2. Experimental section

### 2.1. General procedure for the Wittig reaction

To a stirred and cooled (0 °C) suspension of allyloxy methylenetriphenylphosphonium salt (1.2 equiv) and aldehyde (1.0 equiv) in dry THF was added potassium tertiary butoxide (1.2 equiv) in a dropwise manner. After addition, the mixture was further stirred for 40–45 min at 0 °C (TLC check). Then it was diluted with water and extracted with ether (3 × 50 ml). The combined ether layer was washed with water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by column chromatography using hexane/ethyl acetate (98:1) solvent system to get allyl vinyl ethers **(2a–g)** in good yields. The *E*- & *Z*-isomers were inseparable and hence were carried forward for further reactions as such.

### 2.2. General procedure for the Claisen rearrangement

The inseparable mixture of *E*- and *Z*-allyl vinyl ethers **(2a–g)** was dissolved in dry xylene and the resulting reaction mixture

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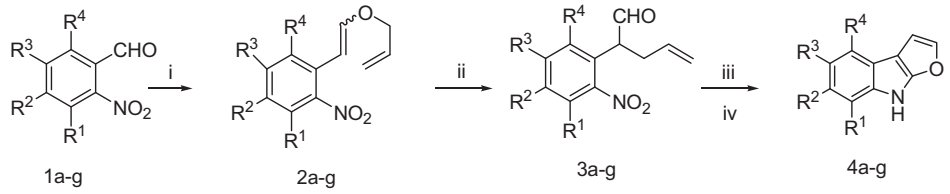



**Scheme 1.** Reagents and conditions: (i) $Ph_3P^+CH_2OCH_2CH{=}CH_2Cl^-$ (1.2 equiv), *t*-$BuO^-Na^+$ (1.2 equiv), dry THF, 0 °C, 40–45 min; (ii) dry xylene, reflux, 5–7 h; (iii) $O_3$, Dry DCM, $Me_2S$, 0 °C 20 min; (iv) $Na_2S$ (2 equiv), $NaHCO_3$, methanol, reflux 12 h.

was heated at 144 °C for 5–7 h (TLC check). Xylene was removed under reduced pressure; the crude product was directly loaded on a silica gel column using 1–2% of ethyl acetate/hexane system as an eluent to get pure 4-pentenals (**3a–g**).

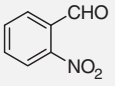
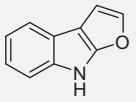
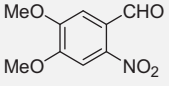
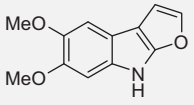
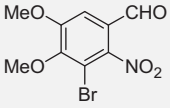
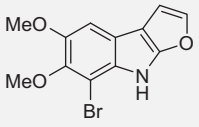
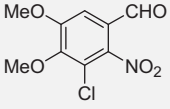
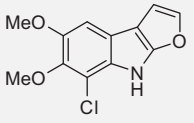
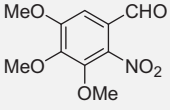
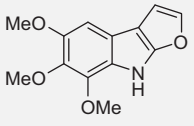
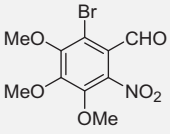
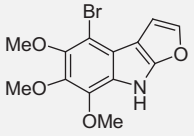
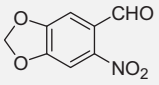
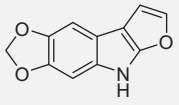
### 2.3. General method for the ozonolysis

The 4-pentenals (**3a–g**) were dissolved in dry DCM and the reaction mixture was cooled at 0 °C. Through a stirred and cooled reaction mixture, ozone gas was passed for about 20 min (TLC check). After completion of the reaction, excess of $Me_2S$ was added to effect the reduction of intermediate ozonoide to get di-aldehyde. As the di-aldehyde was found to be unstable it was used as such for the next reaction without purification.

### 2.4. General method for the reductive cyclization

Two equivalents of sodium sulfide was dissolved in a minimum amount of water then sodium bicarbonate was added to it until the solution became saturated. The reaction mixture was cooled at 0 °C and methanol was added slowly to the reaction mixture, sodium carbonate got precipitated. The reaction mixture was filtered. To

**Table 1**
Wittig olefination–Claisen rearrangement protocol for the synthesis of furo[2,3-*b*]indoles

| Sr. No. | Aldehydes | Allyl vinyl ethers % Yield (*Z*:*E*) **2a–g** | 4-Pentenals % Yield **3a–g** | Furo[2,3-*b*]indoles % Yield **4a–g** |
|---|---|---|---|---|
| **1a** |  | 75 (1:2.03) | 83 |  79 |
| **1b** |  | 70 (1:1.04) | 84 |  78 |
| **1c** |  | 71 (1:0.78) | 84 |  75 |
| **1d** |  | 80 (1:0.45) | 80 |  77 |
| **1e** |  | 71 (1:0.85) | 85 |  76 |
| **1f** |  | 72 (1:1.04) | 83 |  78 |
| **1g** |  | 72 (1:1.56) | 82 |  78 |

a stirred solution of di-aldehyde in methanol, the freshly prepared solution of NaSH was added and the reaction mixture was refluxed for 12 h to get tricyclic furo[2,3-*b*]indoles (**4a–g**) in good yields.

### 2.5. Spectral data for 8*H*-furo[2,3-*b*]indole

IR (Neat): $\nu$ = 3409.9, 2920.0, 1602.7, 1452.3, 1234.4 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz): $\delta$ = 7.15–7.21 (m, 2H), 7.25–7.34 (m, 2H), 7.92–8.15 (m, 3H); $^{13}C$ NMR ($CDCl_3$, 75 MHz): $\delta$ = 111.8, 118.0, 119.3, 120.3, 122.7, 123.7, 125.5, 126.2, 128.2, 139.2; GC–MS (relative intensity): $m/z$ = 157. Anal. Calcd for $C_{10}H_7NO$ (157.17): C, 76.41; H, 4.48; N, 8.91. Found: C, 76.57; H, 4.55; N, 8.85.

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