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# One-pot sequential multi-component reaction: Synthesis of 3-substituted indoles

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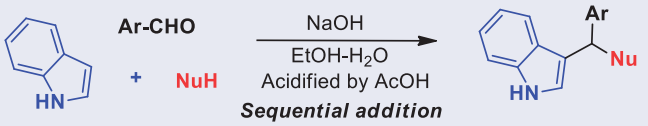
**ABSTRACT**

Here, we have developed a 3-component one-pot sequential approach to 3-substituted indoles. The main advantages of this process are step economy, reduced waste, and operational simplicity. The method involves *in situ* generation of 3-indolylalcohols from the reaction of indoles and aldehydes in the presence of base. Further, nucleophilic substitution of 3-indolylalcohols with various nucleophiles affords 3-substituted indole derivatives. The reaction does not requires any hazardous and expensive metal catalyst. In addition, the reaction is carried out in (1:1) ethanol–water which is considered as environmentally benign solvent. On the other hand, nonsequential 3-component reaction results in the formation of unwanted bisindolylmethanes.

**GRAPHICAL ABSTRACT**

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**KEYWORDS**
Alkylideneindolenine intermediate; 3-indolylalcohol; one-pot; sequential transformation; 3-substituted indole

## Introduction

Sequential transformation is one of the most powerful tools in modern day synthetic organic chemistry owing to its step economy.[1–3] Contrary to the traditional stepwise approach, this method offers easier access to the more complex molecules from simple and easily available starting materials. Some of the important examples of this method include cascade,[4,5] domino,[6–8] and tandem reactions.[9,10] Different reactions knitted into a sequence using one-pot process and multiple reagents and catalyst afford structurally complex molecules. Over the years multicomponent reactions (MCRs) have gained attention due to atom economy and found applications in combinatorial chemistry and diversity-oriented synthesis.[11–16] Numerous pharmaceuticals and natural products were synthesized through MCRs. The interest has also increased due to the replacement of

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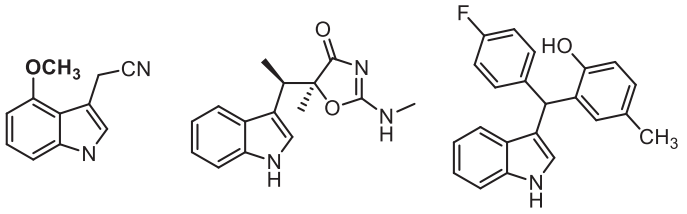



**[A]** Arvelexin

**[B]** Indolmycin

**[C]** 2-((4-fluorophenyl)(1*H*-indol-3-yl)methyl)-4-methylphenol

**Figure 1.** 3-Substituted indoles having biological activity.

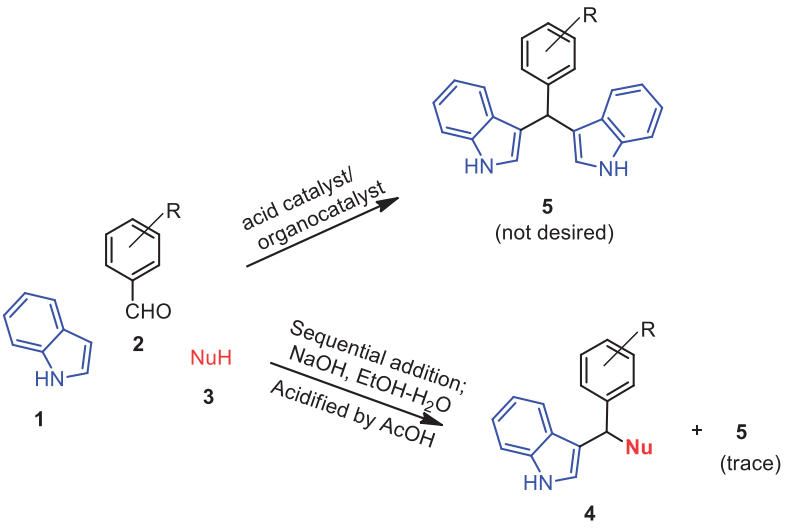
hazardous solvents with environment friendly solvents such as water, ethanol, PEG, etc.[17,18]

Nitrogen containing heterocyles are known to have wide biological activity. Indole derivatives are most important and naturally found in plants,[19] fungi,[20] and marine organism.[21] They also exhibit several pharmacological activities,[22–24] act as free radical scavengers and show a broad spectrum of antioxidant activity.[25–27] Furthermore, the indole nucleus plays a vital component in several drugs. 3-Substituted indoles are versatile intermediates for the synthesis of a wide range of indole compounds.[28–30] For example, some bioactive 3-substituted indole derivatives are shown in Figure 1. Arvelexin [**A**] shows potent activity against influenza virus A (H3N2).[31] Indolomycin [**B**] is a potent antibacterial drug which is effective against *Staphylococcus aureus* and *Helicobacter pyroli*.[32] 3-(α,α-Diarylmethyl)indole [**C**] which was synthesized in our laboratory is found to be active against Methicillin-resistant *S. aureus* bacteria.[33] Indole-3-carbinol has anticancer activity in many types of human prostate cancer cells.[34]

## Results and discussions

The compounds in Figure 1 show excellent biological activities. Inspired by this, we looked for an efficient method to synthesize such type of 3-substituted indole compounds (see Scheme 1). In the very beginning, we planned to isolate 3-indolylalcohols from the reaction of indole and aldehydes in the presence of a base in order to utilize them as electrophiles. However, due to low stability of 3-indolylalcohols, we could not isolate it. Therefore, it was decided to perform the nucleophilic substitution of 3-indolylalcohols generated *in situ* from the 3-component reaction of indoles, aldehydes, and various nucleophiles. We attempted to synthesize compound **4a** by using our reported method.[35] But we obtained bisindolylmethane (BIM). The use of Brønsted or Lewis acids also offered solely BIM **5a**. We then observed that the sequential addition of the substrates catalyzed by base and acidified by an acid gave us good yield of **4a**. Therefore, here we report a sequential 3-component approach to **4** *via* 3-indolyl alcohols.

We began our model experiment with the reaction of indole (**1a**) and benzaldehyde (**2a**) in the presence of base catalysts. After a careful screening of variety of bases/acids, we found that sodium hydroxide (1 equiv) in EtOH–$H_2O$ (1:1) as solvent at RT for 2 h and then adding acetic acid (up to pH 5), nucleophile 3-methyl-1-phenyl-1H-pyrazol-5-amine (**3a**, 1 eqv.) and heating at 90 °C for 1.5 h is the optimum condition for the synthesis of **4a** (Table 1, entry 6). Lowering the NaOH loading decreased the product yield since all the




**Scheme 1.** Synthesis of 3-substituted indoles.

**Table 1.** Optimization of the reaction condition.[a]

| Entry | Base (eq) | Acidification (pH) | Solvent | Temp. (°C) 1st step | Temp. (°C) 2nd step | Time (h) 1st step | Time (h) 2nd step | Yields (%) 4a | Yields (%) 5a |
|---|---|---|---|---|---|---|---|---|---|
| 1 | NaOH (1.3) | HCl (3) | EtOH | RT | 90 | 2 | 1.5 | – | 68 |
| 2 | NaOH (1.3) | HCl (4) | EtOH | RT | 90 | 2 | 1.5 | – | 52 |
| 3 | NaOH (1.3) | HCl (5) | DMF | RT | 90 | 2 | 1.5 | n.r.[b] | n.r. |
| 4 | NaOH (1.3) | HCl (5) | $H_2O$ | RT | 90 | 2 | 1.5 | n.d.[c] | 76 |
| 5 | NaOH (1.3) | AcOH (5) | EtOH–$H_2O$ (1:1) | RT | 90 | 2 | 1.5 | 80 | 11 |
| **6** | **NaOH (1.0)** | **AcOH (5)** | **EtOH–$H_2O$ (1:1)** | **RT** | **90** | **2** | **1.5** | **86** | **5** |
| 7 | NaOH (1.0) | AcOH (5) | EtOH–$H_2O$ (1:2) | RT | 90 | 2 | 1.5 | 70 | 18 |
| 8 | NaOH (0.7) | AcOH (5) | EtOH–$H_2O$ (1:1) | RT | 90 | 2 | 1.5 | 51 | 14 |
| 9 | NaOH (1.0) | AcOH (6) | EtOH–$H_2O$ (1:1) | RT | 90 | 2 | 1.5 | 76 | 16 |
| 10 | NaOH (1.0) | AcOH (5) | EtOH–$H_2O$ (1:1) | RT | 100 | 2 | 1.5 | 82 | 12 |
| 11 | NaOH (1.0) | AcOH (5) | EtOH–$H_2O$ (1:1) | RT | 80 | 2 | 2 | 75 | 10 |
| 12 | KOH (1.0) | AcOH (5) | EtOH–$H_2O$ (1:1) | RT | 90 | 2 | 1.5 | 82 | 8 |
| 13 | $K_2CO_3$ (1.0) | AcOH (5) | EtOH–$H_2O$ (1:1) | RT | 90 | 4 | 1.5 | 41 | 22 |
| 14 | $Et_3N$ (1.0) | AcOH (5) | EtOH–$H_2O$ (1:1) | RT | 90 | 5 | 1.5 | n.r. | n.r. |
| 15 | DABCO (1.0) | AcOH (5) | EtOH–$H_2O$ (1:1) | RT | 90 | 5 | 2 | n.d. | 10 |
| 16 | $Cs_2CO_3$ (1.0) | AcOH (5) | EtOH–$H_2O$ (1:1) | RT | 90 | 4 | 1.5 | n.d. | 12 |
| 17[d] | $Cu(OAc)_2{\cdot}H_2O$ (10 mol %) | | EtOH–$H_2O$ (1:1) | RT | | 5 | | – | 60 |
| 18[d] | $FeCl_3{\cdot}6H_2O$ (10 mol %) | | EtOH–$H_2O$ (1:1) | RT | | 4 | | – | 68 |

[a]Reagents and conditions: Indole (**1a**, 1.0 mmol, 117 mg), benzaldehyde (**2a**, 1.0 mmol, 106 mg), 3-methyl-1-phenyl-1H-pyrazol-5-amine (**3a**, 1.0 mmol, 173 mg). The 1st step was in RT and 2nd step was under heating. Products were purified by column chromatography and yields are for the isolated products.
[b]n.r.: no reaction.
[c]n.d.: not detected.
[d]Three component reaction using metal catalyst.

–NH proton of indole are not abstracted (Table 1, entry 8). On the other hand, increase of NaOH did not improve the yield due to the increased formation of bisindolylmethane (Table 1, entry 5). An increase in the ratio of water in the solvent mixture reduced the yield of **4a** (Table 1, entry 7). This is due to the increased formation of bisindolylmethanes.[36] We also performed the reaction at higher and lower temperature for the second step. But

no improvement in the yield was observed (Table 1, entries 10–11). Using stronger acids in the 2nd step favors bisindolylmethane formation. The KOH is almost as good as NaOH as base catalyst (Table 1, entry 12). Interestingly, the bases like $Et_3N$, DABCO, and $Cs_2CO_3$ did not produce our required product. We further used metal catalysts $Cu(OAc)_2.H_2O$ and $FeCl_3{\cdot}6H_2O$ for carrying out the reaction using nonsequential 3-component approach (Table 1, entries 17–18). However, the reaction afforded only bisindolylmethane.

Having identified the optimized conditions, we next investigated the substrate scope for the synthesis of **4** by subjecting various aldehydes and nucleophilic groups. When alononitrile and imidazole were used as nucleophile, we obtained relatively less yield of the product (**4g** and **4f**, Scheme 2). 1,3-Dimethyl-6-aminouracil also produced good yield (**4h**, Scheme 2). When *N*-substituted indoles were taken as nucleophiles we obtained excellent yield of unsymmetrical bisindolylmethanes (**4i** and **4l–4o**, Scheme 2). Naphthols also afforded excellent yield of the products (**4j–k**, Scheme 2). Compounds **4** containing a wide range of substituents were obtained in good to excellent yields, as summarized in Scheme 2. All the products were characterized by NMR spectroscopy as well as analyzing X-ray structure of **4d** (Figure 2). The compound was crystallized from 1:1 mixture of dichloromethane and petroleum ether by slow evaporation.

A plausible mechanism is proposed for the reaction based on the literature report (Scheme 3).[37] The N–H proton of indole is abstracted by the base (NaOH) and the indole anion thus formed attacks the aldehyde to generate the 3-indolylalcohol **[X]**. In presence of acid, **[X]** then gets converted to alkylideneindolenine intermediates **[Y]**. This intermediate was then attacked by various nucleophiles to give the desired product. Moreover, the intermediate **[Y]** also reacts with indole to furnish small amount of symmetrical bisindolylmethanes **5** as side product in some cases.

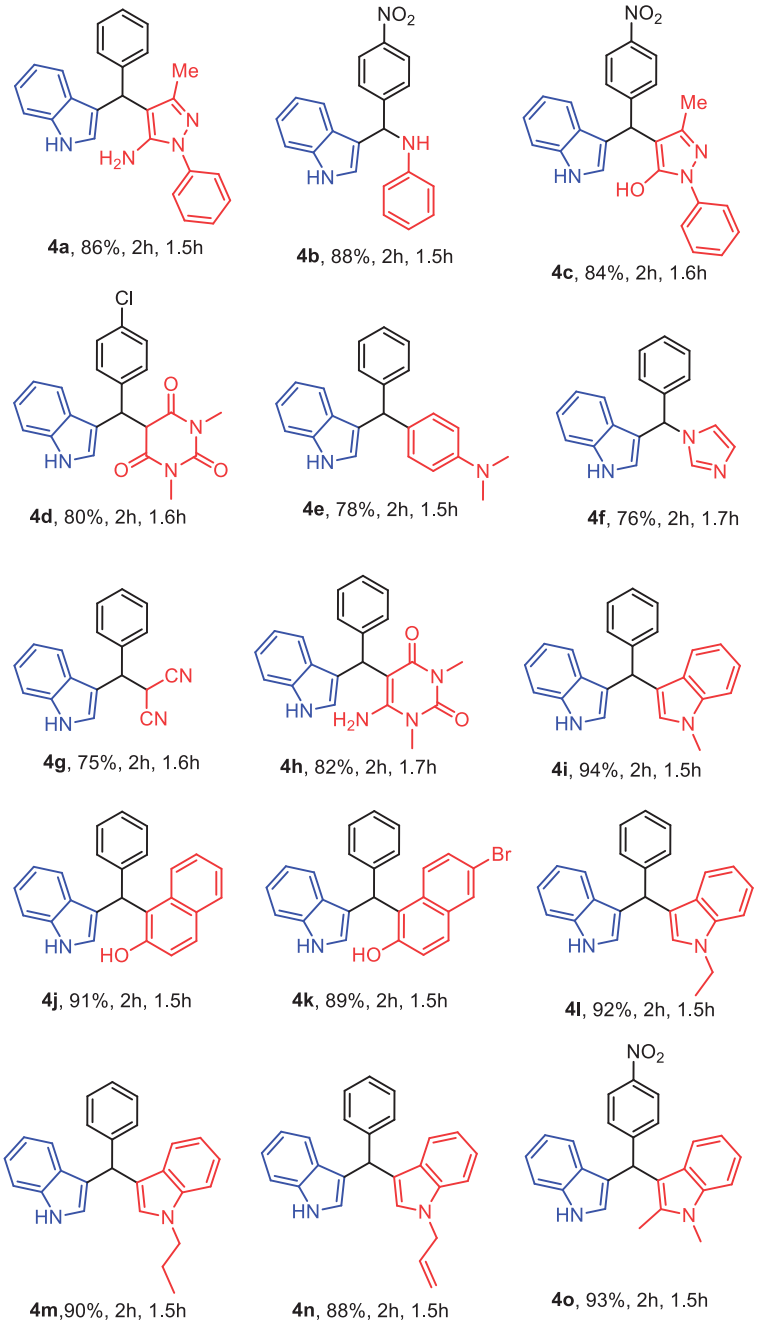
## Conclusion

We here developed a 3-component one-pot sequential approach to 3-substituted indoles. The reaction proceeds *via* the formation of 3-indolylalcohols. The reaction does not require any hazardous metal catalyst. A plausible mechanism is proposed for the reaction.

## Experimental

### *Representative procedure for the synthesis of compound 4a*

Indole (**1a**, 1 mmol, 117 mg), benzaldehyde (**2a**, 1 mmol, 106 mg), and NaOH (1 mmol, 40 mg) were taken in a round bottom flask. To this EtOH–$H_2O$ (1:1, 2 mL) as solvent was added. The reaction mixture was stirred for 2 h at room temperature. The progress of the reaction was monitored by TLC. After completion of the first step, the reaction mixture was acidified up to pH 5 by adding acetic acid, added 3-methyl-1-phenyl-1H-pyrazol-5-amine (**3a**, 1 mmol, 173 mg) and then heated at 90 °C for 1.5 h. Solvent was removed under vacuum and extracted with dichloromethane (DCM). The solvent was evaporated under vacuum and the crude product was purified by column chromatography to obtain the desired product **4a**[38] in the pure form. White solid, (325 mg, 86%); $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 8.48 (bs, 1H, indole –N**H**), 7.51–7.49




**Scheme 2.** The substrate scope for the synthesis of compound **4**. Reagents and conditions: **1** (1 mmol), **2** (1 mmol), **3** (1 mmol). The first mentioned time indicates the reaction at room temperature and the second one is under heating.

(m, 2H), 7.40–7.31 (m, 8H), 7.27–7.24 (m, 2H), 7.19 (t, $J = 7.9$ Hz, 1H, Ar–H of indole $C_6\mathbf{H}$ benzene ring), 7.04 (t, $J = 7.8$ Hz, 1H, Ar–H, indole $C_5\mathbf{H}$ benzene ring), 6.62 (s, 1H, indole $-C_2\mathbf{H}$, heterocyclic ring), 5.53 (s, 1H, aliphatic $-C\mathbf{H}$(Indole)(Ph)), 3.26 (bs, 2H, $-N\mathbf{H_2}$), 2.18 (s, 3H, $-C\mathbf{H_3}$); 13C NMR (125 MHz, $CDCl_3$): $\delta$ 148.2

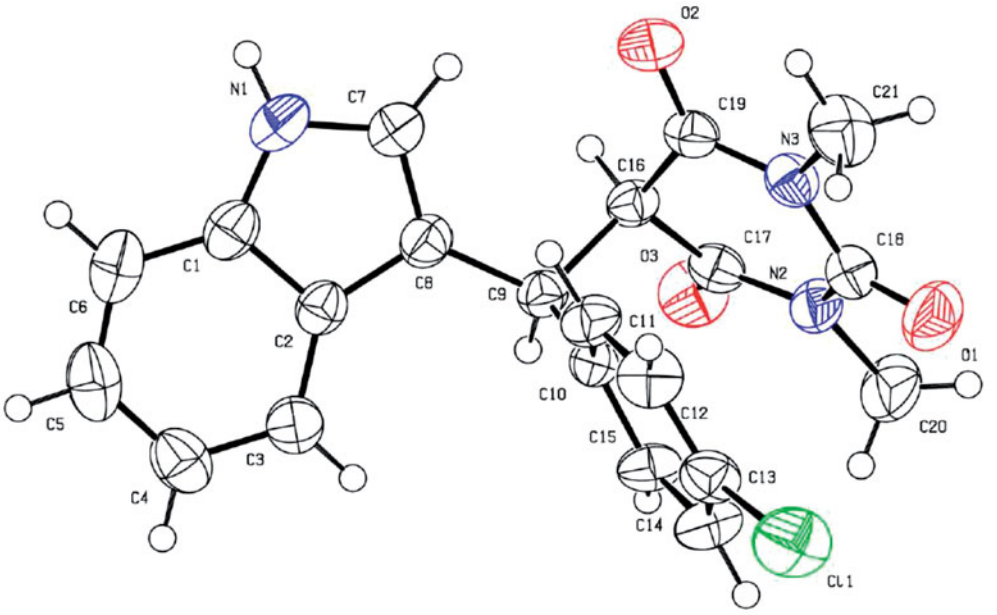
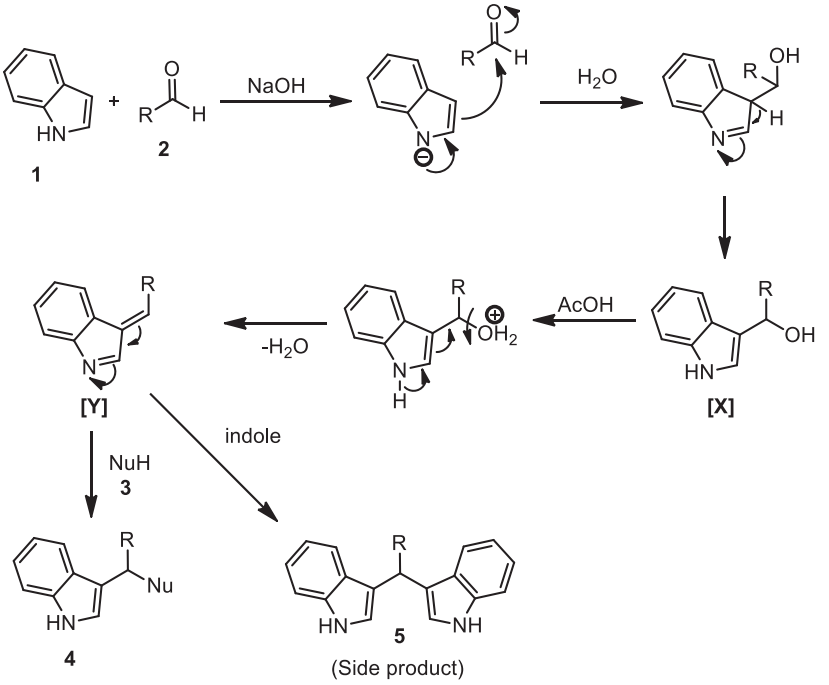



**Figure 2.** ORTEP of compound **4d** with 35% polarizability ellipsoids (CCDC 1815249).




**Scheme 3.** A plausible mechanism for the reaction.

(pyarozole **C**$NH_2$), 142.9 (pyarozole **C**$CH_3$), 142.7 (**C**$_1$Ph(pyrazole)), 138.4, 136.7, 129.3, 128.6, 128.5 (2C), 128.4, 126.8, 126.6, 126.4, 123.8, 123.7, 122.2, 119.6, 119.4, 117.5 (Indole **C**$_6$H or **C**$_3$H), 111.2 (Indole **C**$_6$H or **C**$_3$H), 102.9 (pyrazole –**C**$HCNH_2$), 38.1 (**C**(Indole)(Ph)), 12.5 ($CH_3$). The characterization data of all compounds could be found in the supporting information provided with this article.

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