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# Green and complementary regioselective synthesis of 3-(1–substituted pyrazol-3(or 5)-yl)indoles from β-ethyltho-β-indolyl-α,β-unsaturated ketones in water

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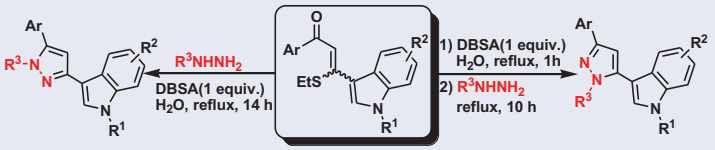
**ABSTRACT**

Eco-friendly and practical methods for the complementary regioselective synthesis of 3-(1-substituted pyrazol-3-yl) indoles and 3-(1-substituted pyrazol-5-yl) indoles, from DBSA-mediated regioselective cyclocondensation reaction of β-ethyltho-β-indolyl-α, β-unsaturated ketones and monosubstituted hydrazines in water through simply varying the appropriate reaction way, had been developed. The methods not only efficiently avoided the use of organic solvent but also exhibited attractive characteristics such as operational simplicity, broad substrate scope, easy separation of products and ease of scale-up.

**GRAPHICAL ABSTRACT**

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**KEYWORDS**
β-ethylthio-β-indolyl-α; β-unsaturated ketones; 3-pyrazolindoles; hydrazines; aqueous synthesis; regioselectivity

## Introduction

Over recent decades, the synthesis of 3-pyrazol indoles had attracted considerable attention due to many of them exhibiting a great diversity of good biological activities[1] such as antimicrobial,[2] anti-inflammatory[3] and antioxidant.[4] Although their synthesis had been well-documented, it remained a challenge to reach sufficient regio-selectivity for 3-(1-substituted pyrazol-3(or 5)-yl)indoles in the synthesis process. Recently, with a view to the goal, some effort had been devoted toward some researches[5]. Ila and coworkers investigated the cyclocondensation of arylhydrazines with 3-(1-methyl-1*H*-indol-3-yl)-1-aryl-3-thioxopropan-1-one or 3-(1-methyl-1*H*-indol-3-yl)-3-(methylthio)-1-arylprop-2-en-1-one, and isomeric 3-(pyrazol-5(or 3)-yl) −1-methyl-1*H*-indoles were obtained with complete regioselectivity, respectively[5a]. Gupton and coworkers regioselectively prepared isomeric 1-methyl-3-(1-aryl-1*H*-pyrazol-3(or 5)-yl)-1*H*-indoles by cyclocondensation of arylhydrazines with indole chloroenals or indole

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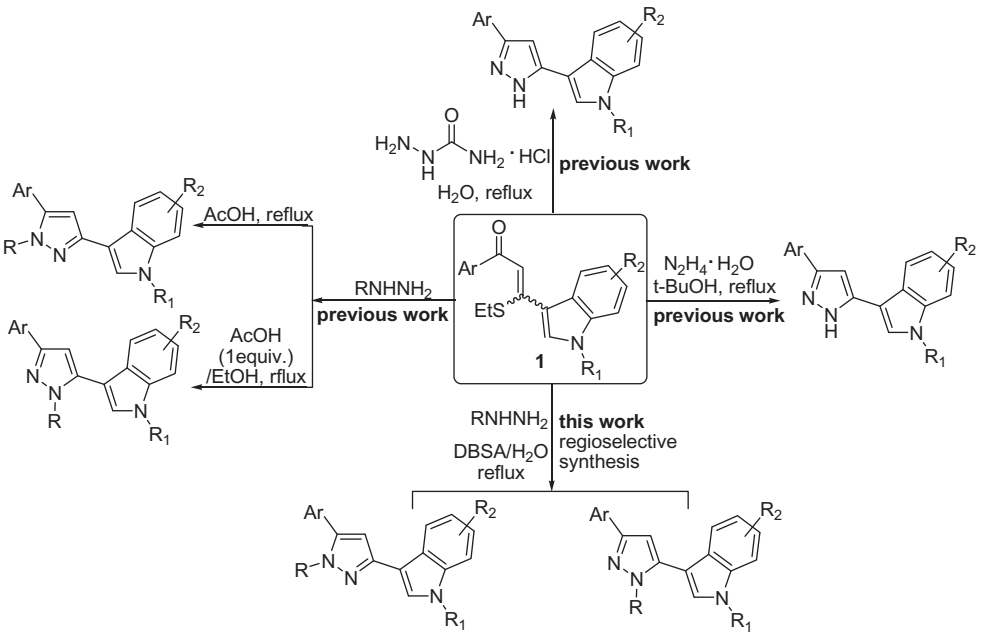
vinylogousamide[5b]. Usachev and coworkers achieved regio-controlled synthesis of 3-(1-phenyl-1*H*-pyrazol-3(or 5)-yl)-2-(trifluoro-methyl)-1*H*-indoles by the Fischer reactions of isomeric 1-phenyl-2-(1,1,1-trifluoro-3-(1-phenyl-1*H*-pyrazol-3(or 5)-yl)propan-2-ylidene)-hydrazines, respectively.[5c] However, all the reported reactions are performed in organic medium such as acetonitrile and dichloromethane, which can lead to serious environmental and safety problems. Therefore, the development of eco-friendly regioselective synthesis of 3-(1-substituted pyrazol-3(or 5)-yl)indoles is highly desirable.

With concerning of environmental problems, green organic synthesis was getting a full development in the past decades. As an important research topic in green synthesis, the organic reaction in water without the use of organic solvents had received more and more attention because water was noncorrosive, nonflammable, nontoxic, cheap and the most abundant solvent in nature, and its usage could remarkably reduce the discharge of a large amount of harmful organic solvents.[6] Therefore, we were interested in the organic reaction in water, and a range of aqueous organic reactions, including thioacetalization using ketene dithioacetals as odorless thiol equivalent,[7] Friedel-Crafts alkylation of cyclic ketene dithioacetals with alcohols[8] and hydrolysis of chain α-oxo ketene dithioacetals,[9] had been realized in our group.

*β*-Ethyltho-*β*-indolyl-α, *β*-unsaturated ketones **1** had been emerging as versatile intermediate in the synthesis of indole derivatives.[10] In view of the diverse good bio-activities of 3-pyrazol indole, we recently started to study its synthesis on the basis of **1**, and the catalyst free cyclocondensation reaction of **1** with hydrazine hydrate or semicarbazide hydrochloride as hydrazine equivalent efficiently giving 3-unsubstituted pyrazol indoles[11,12] and the regioselective cyclocondensation of **1** with mono-substituted hydrazines yielding the isomeric 3-(pyrazol-5-yl) indoles and 3-(pyrazol-3-yl)indoles by simply varying the appropriate reaction conditions[13] had been realized (Scheme 1).




**Scheme 1.** The synthesis of 3-pyrazolyl indoles from *β*-ethyltho-*β*-indolyl-α, *β*-unsaturated ketones **1**.

Most recently, with a view to developing an eco-friendly and highly regioselective synthesis of 3-pyrazol indoles, we studied in detail the cyclocondensation reaction of **1** and monosubstituted hydrazines in the presence of 4-dodecylbenzene sulfonic acid (DBSA) in water (Scheme 1), and found that the cyclocondensation reaction could regioselectively produce the isomeric 3-(pyrazol-3-yl)indoles and 3-(pyrazol-5-yl) indoles by simply varying the appropriate reaction procedure. Herein, it is our pleasure to report these results.

## Results and discussion

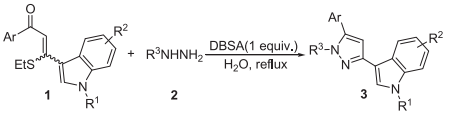
*β*-Ethyltho-*β*-indolyl-α, *β*-unsaturated ketones **1**[10a,14] were easily prepared in good yields *via* acid mediated selective desulfitative carbon-carbon coupling reaction between indoles and α-oxo ketene dithioacetals which are readily available and stable synthetic intermediate.[15] On the Basis of our previous work,[7–9] commercially available *p*-dodecylbenzenesulfonic acid (DBSA) was chosen as surfactant-combined catalyst in the current study.

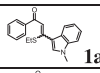
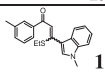
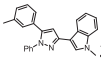
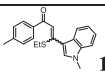
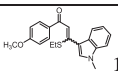
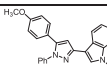
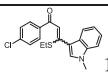
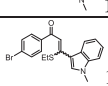
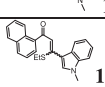
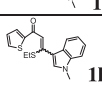
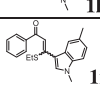
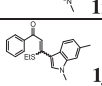
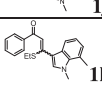
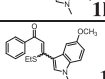
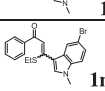
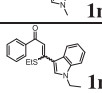
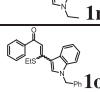
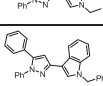
Initially, the model reaction of (Z/E)-3-(ethylthio)-3-(1-methyl-1*H*-indol-3-yl)-1-phenylprop-2-en-1-one **1a** (0.25 mmol) with phenylhydrazine **2a** (0.3 mmol) was performed in the presence of DBSA (0.25 mmol) in boiling water (2 mL). It was found that a white solid were precipitated from the reaction system when the reaction was refluxed for 14 h, and the pure white crystal, as 3-(1, 3-diphenyl-1*H*-pyrazol-3-yl)-1-methyl-1*H*-indole **3a** on the basis of the comparison of melting point and $R_f$ with that reported[13], was obtained in 78% yield by filtration and subsequent recrystallization with ethanol. Further increasing the amount of DBSA, the yield of **3a** was not improved markedly. The results indicated that the cyclocondensation reactions favored the formation of **3a** when the reaction of **1a** and **2a** was performed in the presence of DBSA in boiling water. Under the optimized conditions described above, the cyclocondensation reaction of **1b-1o** and phenylhydrazine **2a** smoothly carried out to furnish 3-(1-substituted pyrazol-3-yl)indoles **3b-3o** in medium to good yields (Table 1, entries 1–15). Similarly, the reaction of **1a** and mono-substituted hydrazines **2b–2e** also gave satisfactory results, and 3-(1-substituted pyrazol-3-yl) indoles **3p–3s** were produced in good yields (Table 1, entries 16-19).

Next, we turned our attention to the aqueous synthesis of 3-(1-substituted pyrazol-5-yl)indoles **4.** We previously reported that **1** could occur the DBSA-mediated hydrolysis reaction in water to produce **1′**,[10b] in which the electrophilicity of the carbon adjacent to aryl group and the carbon adjacent to indole group was altered. Therefore, when we examined the model reaction of **1a** and **2a, 2a** was added to reaction system after the mixture of **1a**, DBSA and $H_2O$ was refluxed for 1 h to yield **1a′**, and the reaction mixture was then further refluxed for 10 hour. To our delight, the reaction, which was a one-pot, two-step procedure, was very clean and only furnished 3-(1,3-diphenyl-1*H*-pyrazol-5-yl)-1-methyl-1*H*-indole **4a** in 92% yield by filtration and recrystallization with ethanol. As shown in Table 2, this methodology was also successfully applied to the reactions of **1b–1o** and **2a**, **1a** and **2b–2e**, producing the desired products **4 b–4s** in excellent yields, respectively.

Except for **4n** and **4r**, the products **3** and **4** were all white crystals, and were easily obtained by filtration and recrystallization with ethanol. In these reactions, electron-

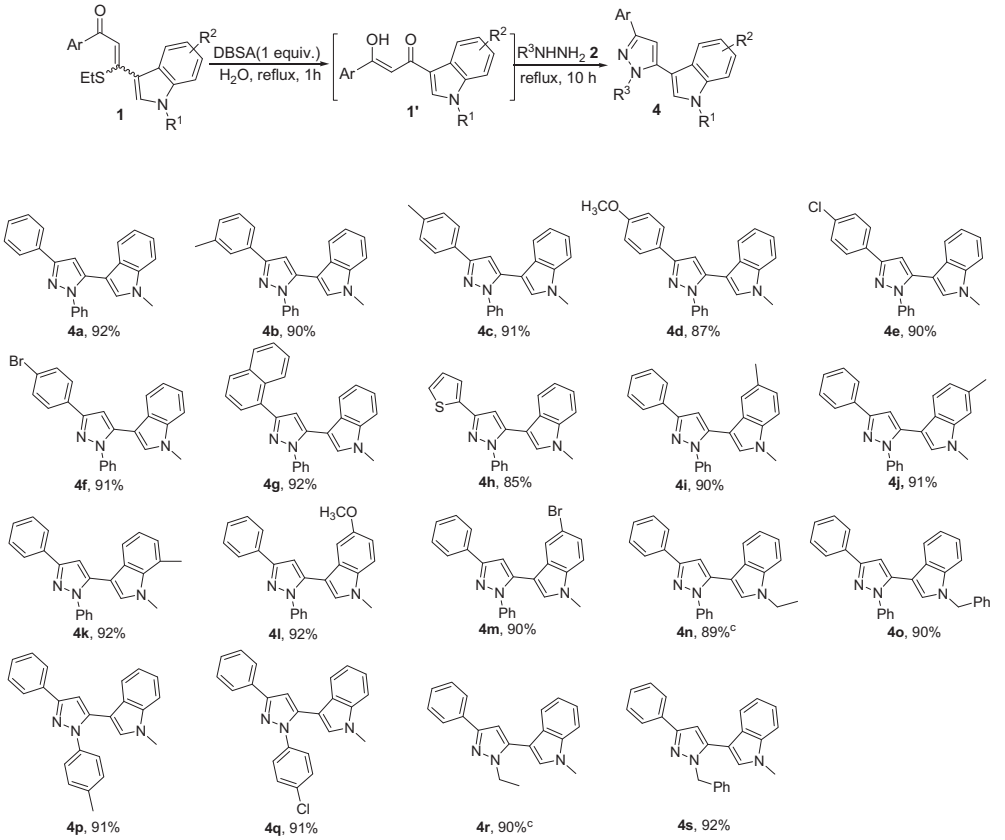
**Table 1.** The aqueous synthesis of 3-(1-substituted pyrazol-3-yl)indoles **3**[a].




| Entry | 1 | 2 | 3 | Yield **3** (%)[b] |
|---|---|---|---|---|
| 1 |  **1a** | PhNHNH$_2$ **2a** |  **3a** | 78 |
| 2 |  **1b** | |  **3b** | 75 |
| 3 |  **1c** | |  **3c** | 76 |
| 4 |  **1d** | |  **3d** | 75 |
| 5 |  **1e** | |  **3e** | 77 |
| 6 |  **1f** | |  **3f** | 78 |
| 7 |  **1g** | |  **3g** | 74 |
| 8 |  **1h** | |  **3h** | 65 |
| 9 |  **1i** | |  **3i** | 75 |
| 10 |  **1j** | |  **3j** | 76 |
| 11 |  **1k** | |  **3k** | 77 |
| 12 |  **1l** | |  **3l** | 79 |
| 13 |  **1m** | |  **3m** | 74 |
| 14 |  **1n** | |  **3n** | 72 |
| 15 |  **1o** | |  **3o** | 76 |
| 16 | **1a** | 4-OCH$_3$C$_6$H$_4$NHNH$_2$ **2b** |  **3p** | 73 |
| 17 | | 4-ClC$_6$H$_4$NHNH$_2$ **2c** |  **3q** | 74 |
| 18 | | CH$_3$CH$_2$NHNH$_2$ **2d** |  **3r** | 75 |
| 19 | | PhCH$_2$NHNH$_2$ **2e** |  **3s** | 73 |

[a]Reagents and conditions: **1** (0.25 mmol), **2** (0.3 mmol), DBSA (0.25 mmol), $H_2O$ (2 mL), reflux, 14 h; [b]Isolated yield.

**Table 2.** The aqueous synthesis of 3-(1-substituted pyrazol-5-yl) indoles **4**[a,b]

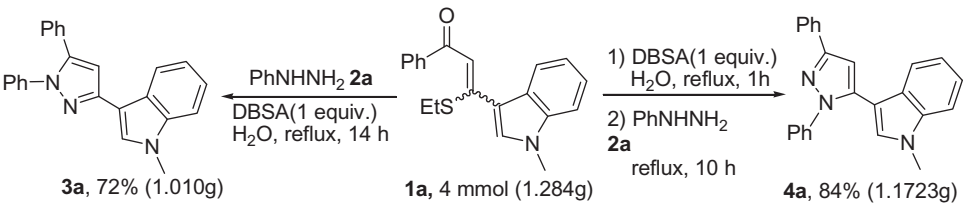



[a]Reagents and conditions: **1** (0.25 mmol), **2** (0.3 mmol), DBSA (0.25 mmol), $H_2O$ (2 mL), reflux; [b]Isolated yield; [c]the isolated yield by silica gel column chromatography (petroleum ether (60–90 °C)/ethyl ether 4:1, v/v).

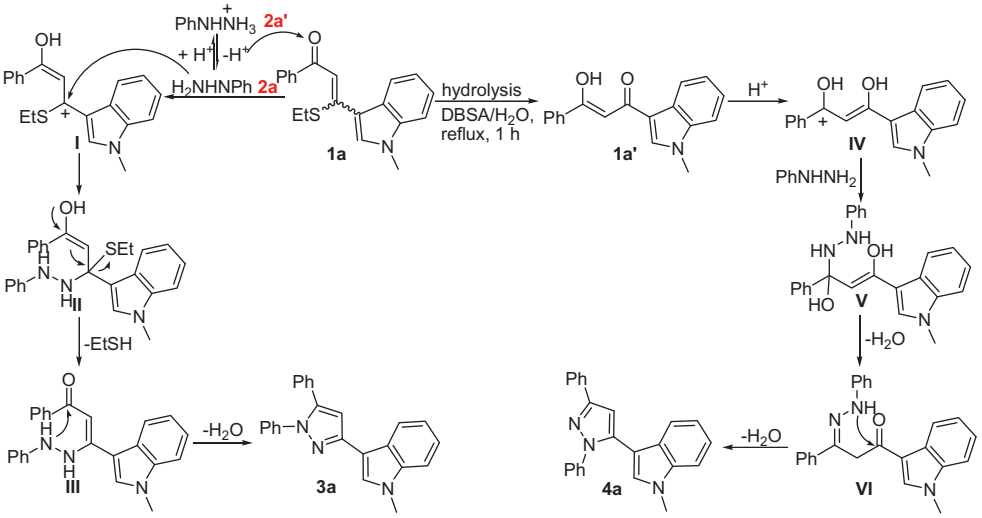
donating as well as electron-withdrawing substituents such as methyl, methoxy, chloro and bromo on either phenyl or indolyl were well tolerated. In addition, the Z/E configuration of **1** did not affect formation of the desired product **3** and **4**.

Furthermore, we used the model reaction of **1a** (4 mmol) and **2a** to assess the scalability of the above two processes (Scheme 2). The result showed that the cyclocondensation reaction based on the above two processes described could efficiently furnish gram-quantities of the desired product **3a** in 72% yield and **4a** in 88% yield, respectively.

On the basis of the above results and our previous works,[11–13] a possible mechanism for the synthesis of both **3** and **4** was proposed, asdepicted in Scheme 3. When **1a** and $PhNHNH_2$ **2a** was added to reaction system together, the protonation of $NH_2$ of **2a** firstly led to the formation of the cation **2a′** because of its higher basicity than that of NH in the presence of DBSA, and an equilibrium was present between **2a** and **2a′**. Then, **1a** was protonated by $H^+$ released by **2a′** to form carbocation **I**, which was attacked by $NH_2$ of **2a** to give intermediate **II.** Subsequently, the elimination of EtSH in **II** resulted in the formation of intermediate **III,** which occurs intramolecular cyclization




**Scheme 2.** The scalability of the process.




**Scheme 3.** Proposed mechanisms for the formation of **3** and **4**.

reaction to give **3a**. In the absence of **2a, 1a** occurred hydrolysis in the presence of DBSA in refluxing water to generate hydrolysate **1a′,** in which the carbonyl group further was protonated to afford carbocation **IV.** At this time **2a** was added to reaction mixture, and intermediate **V** was obtained through the attack of $NH_2$ of **2a** tocarbocation **IV.** Next, **V** occurred readily sequential dehydration and intramolecular cyclization reaction, furnishing **4a**.

In summary, for the first time, we had successfully developed the green and complementary regioselective synthesis of the isomeric 3-(1-substituted pyrazol-3-yl) indoles **3** and 3-(1-substituted pyrazol-5-yl)indoles **4** from DBSA-mediated cyclocon-densation of *β*-ethyltho-*β*-indolyl-*α*, *β*-unsaturated ketones **1** with monosubstituted hydrazines **2** in water by simply varying the appropriate reaction way. In sharp contrast to the reported methods,[5,11,13] the method not only revealed good flexibility and high synthesis efficiency because isomeric **3** and **4** could be obtained in good yield at will from the same reactant but also opened up a new avenue for cheap, convenient, green synthesis of isomeric **3** and **4**. In addition, except for **4n** and **4r**, **3** and **4** were all were easily obtained by filtration and recrystallization with ethanol.

## Experimental

### General considerations

A $^{1}H$ and $^{13}C$ NMR spectra were recorded on a Bruker DRX-600 spectrometer and the chemical shift values refer to $\delta$ TMS = 0.00 ppm; The HRMS analysis was achieved on Bruck micro Tof using ESI method. All the melting points were uncorrected. Analytical TLC plates, Sigma-Aldrich silica gel 60F200 were viewed by UV light (254 nm). Chromatographic purifications were performed on SDZF silica gel 160.

### Typical procedure for the preparation of 3

$\beta$-ethyltho-$\beta$-indolyl-$\alpha$, $\beta$-unsaturated ketones **1** (0.25 mmol) and hydrazines **2** (0.3 mmol) was added to water (2 mL) including 0.25 mmol DBSA, respectively. Then, the mixture was refluxed for 14 h until the conversion of **1** was completed as evidenced by TLC, in which a white solid was precipitated from the reaction system. After filtration and recrystallization with ethanol, pure **3** as white crystal were obtained in good yields.

### Typical procedure for the preparation of 4

After a mixture of **1** (0.25 mmol) and DBSA (0.25 mmol) in water (2 mL) was refluxed for 1 h, hydrazines **2** was added to the reaction mixture. Then further refluxing 10 h until the cyclocondensation reaction was completed as determined by TLC monitoring, in which a white solid was precipitated from the reaction system except the formation of **4n** and **4r**. After filtration and recrystallization with ethanol, pure **4a–m, 4o–q** and **4s** as white crystal were obtained in excellent yields. In the case of **4n** and **4r,** they could be obtained in excellent yields after the reaction mixtures were extracted using $CH_2Cl_2$ ($3 \times 10$ mL) and subsequently purified by silica gel column chromatography (petroleum ether (60–90 °C)/ethyl ether 4:1, v/v).

The products **3** and **4** were the known compounds, and their spectra agreed well with those reported in the literature.[13] The characterization data and copies of $^{1}H$ and $^{13}C$ NMR spectra for compounds of **3** and **4** can be found via the "Supporting Information" section of this article's webpage.

## Disclosure statement

No potential conflict of interest was reported by the author(s).

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