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Catalyst free cyclocondensation of β-ethylthio-β-indolyl-α, β-unsaturated ketones with hydrazines: Efficient synthesis of 3-pyrazolyl indoles

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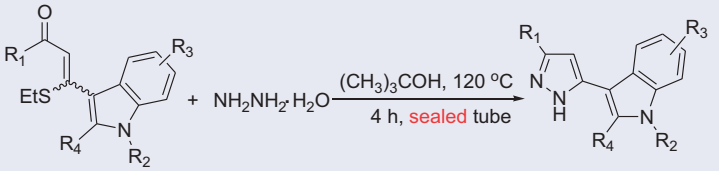
ABSTRACT

Catalyst free cyclocondensation of β-ethylthio-β-indolyl-α,β-unsaturated ketones with hydrazines has been developed, and 3-pyrazolyl indoles were efficiently synthesized in excellent yields. The catalyst free protocol avoids the use of a large excess of catalysts such as acids and bases, eliminating the discharge of harmful chemicals.

GRAPHICAL ABSTRACT



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Cyclocondensation; β-ethylthio-β-indolyl-α; β-unsaturated ketones; hydrazines; indole derivatives; 3-pyrazolyl indoles

Introduction

The synthesis of 3-pyrazolyl indoles had received more and more attention because of their versatile synthetic values[1] and exhibiting a broad spectrum of biological activities[2] such as antimicrobial[3], anti-inflammatory[4] and antioxidant.[5] As a result, versatile synthetic routes have been developed for the synthesis of 3-pyrazolyl indoles,[6–9] including the cyclocondensation of 1,3-diketones and related derivatives with hydrazines,[6] the direct coupling of indole derivatives and pyrazole derivatives,[7] acid-catalyzed intramolecular cyclization reaction of *N*-propargylation of *N*-acetyl-*N*-tosylhydrazine,[8] and other procedures.[9] However, despite tremendous efforts to develop more efficient strategies in these areas, the remarkable disadvantage of these reactions was frequent use of a large number of catalysts such as acids and bases, which can create serious environmental and safety problems. Thus, the development of catalyst free approaches to 3-pyrazolyl indoles avoiding the use and release of the toxic and hazardous materials which pollute the environment are highly desirable.

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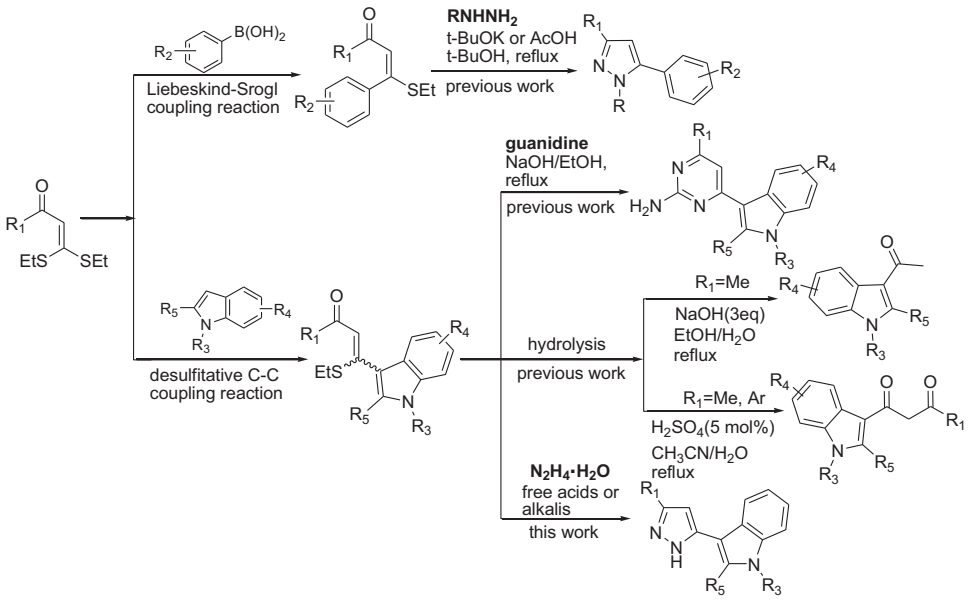


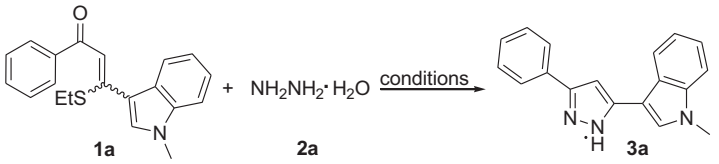
Scheme 1. Synthesis and application β-ethyltho-β-aryl-α,β-unsaturated ketones.

β-Ethyltho-β-aryl-α,β-unsaturated ketones could be regarded as versatile organic synthesis intermediates due to their structural features of multi-reaction center and multi-functional group (Scheme 1).[10,11] The condensation reactions of β-ethyltho-β-indolyl-α,β-unsaturated ketones with guanidine affording alkaloids meridianin derivatives 3-pyrimidyl indoles[10a] and hydrolysis reaction selective yielding 3-acetyl indoles and 3-acetoacetyl indoles[10b] had recently been realized (Scheme 1). In addition, we also realized that potassium *tert*-butoxide or acetic acid mediated regioselective cyclocondensation of β-ethyltho-β-phenyl-α,β-unsaturated ketones with hydrazines, affording only 1,3,5-trisubstituted pyrazoles in excellent yields.[11] As part of our continuing research in the context, keeping in mind environmental requirements and the significance of 3-pyrazolyl indoles, herein, we would like to report the catalyst free cyclocondensation of β-ethyltho-β-indolyl-α,β-unsaturated ketones with hydrazine hydrate to efficiently afford 3-pyrazolyl indoles. Unlike our previous work,[11] this work concentrates on the study of green catalyst free synthesis of 3-pyrazolyl indoles.

Results and discussion

β-Ethyltho-β-indolyl-α,β-unsaturated ketones **1**[10,12] 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.[13,14] The reactions of (Z/E)-3-(ethylthio)-3-(1-methyl-1*H*-indol-3-yl)-1-phenylprop-2-en-1-one **1a** with hydrazine hydrate **2a** was selected as a model reaction to screen the experimental conditions. We initially examined the cyclocondensation reaction of **1a** and **2a** in refluxing EtOH (95%) when their molar ratio was 1:1, and found the reactions gave a white solid product in 60% yield, which was characterized as 1-methyl-3-(3-phenyl-1H-pyrazol-5-yl)-1H-indole **3a** on the basis of its spectral and

Table 1. Screening of reaction conditions[a].



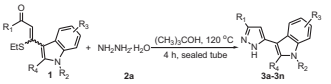
Entry	**1a**/**2a**(mol ratio)	Solvent	Temperature (°C)	Time (h)	Yield (%)[b]
1	1:1	CH_3CH_2OH (95%)	reflux	20	60
2	2:3	CH_3CH_2OH (95%)	reflux	18	63
3	1:2	CH_3CH_2OH (95%)	reflux	15	74
4	1:3	CH_3CH_2OH (95%)	reflux	14	77
5	1:2	CH_3CH_2OH	reflux	15	79
6	1:2	$CH_3CHOHCH_3$	reflux	13	81
7	1:2	$(CH_3)_3COH$	reflux	8	82
8[c]	1:2	$(CH_3)_3COH$	100	7	90
9[c]	**1:2**	**$(CH_3)_3COH$**	**120**	**4**	**94**
10[c]	1:2	$(CH_3)_3COH$	130	3	93

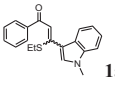
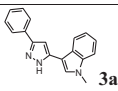
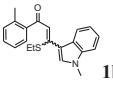
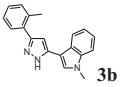
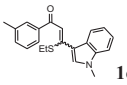
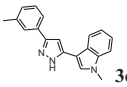
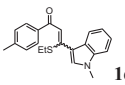
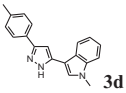
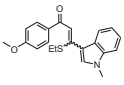
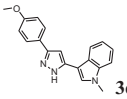
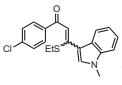
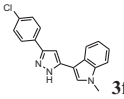
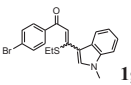
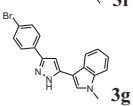
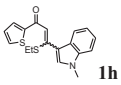
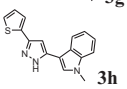
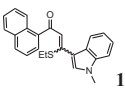
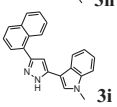
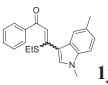
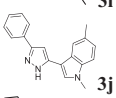
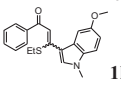
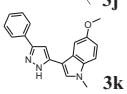
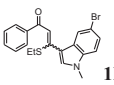
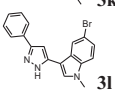
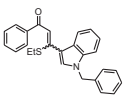
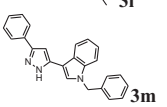
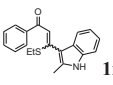
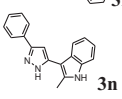
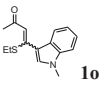
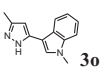
[a]Reaction conditions: **1a** (0.5 mmol), solvent (1 mL); [b]Yield of isolated products; [c]the reaction performed in sealed tube.

analytical data (Table 1, Entry1). The result showed that the cyclocondensation reaction of **1a** and **2a** could effectively carry out without acids or bases catalysis to yield **3a**. Next, we studied the nonacid or alkali mediated reactions in detail under various conditions to identify the optimal conditions. It was found that on changing the molar ratio of **1a** and **2a** from 1:1 to 1:2, the yield of **3a** was markedly increased, while further reducing the ratio slightly improved the yield of **3a**, which indicates that the prefect ratio can be obtained when the reaction is proceeded with 1:2 molar ratio of **1a** and **2a** (Table 1, Entries1–4). Subsequently, we tested the influence of reaction medium, and found that the reaction proceeded more efficiently in tertbutyl alcohol ($(CH_3)_3COH$) than in ethanol (CH_3CH_2OH) and isopropyl alcohol ($CH_3CHOHCH_3$). (Table 1, Entries 5–7). The reaction efficiency was markedly improved by elevating the reaction temperature, and the reaction could be completed in 4 h at 120 °C to produce **3a** in 94% yield (Table 1, Entries8–10). Accordingly, the optimal reaction conditions are a **1a**/**2a** ratio of 1:2, *tert*-butyl alcohol ($(CH_3)_3COH$) as the solvent, and run the reaction at 120 °C (Table 1, Entry 9).

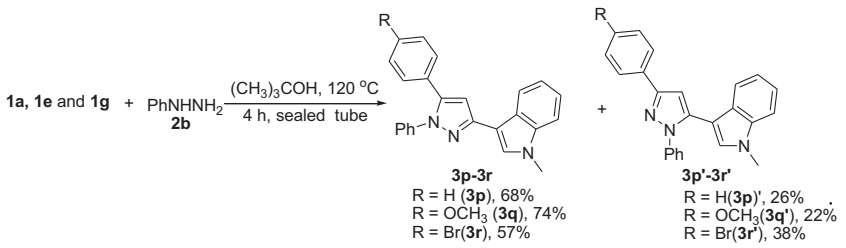
With the optimized conditions in hand, we examined the reaction of various β-ethylthio-β-indolyl-α,β-unsaturated ketones **1 b-o** with hydrazines **2** to define the scope of the reaction, and the results are summarized in Table 2 and Scheme 2. The compounds **1**, such as (*Z*/*E*)-3-(ethylthio)-3-(1-methyl-1*H*-indol-3-yl)-1-arylprop-2-en-1-ones **1a-1i** (Table 2, Entry1-9), (*Z*/*E*)-3-(5-methyl/bromo/methoxy-1-methyl-1*H*-indol-3-yl)-3-(ethylthio)-1-phenylprop-2-en-1-one **1j**, **1k** and **1 l** (Table 2, Entry 10-12), (*Z*/*E*)-3-(1-benzyl-1*H*-indol-3-yl)-3-(ethylthio)-1-phenylprop-2-en-1-one **1 m** (Table 2, Entry 13), (Z/E)-3-(ethylthio)-3-(2-methyl-1*H*-indol-3-yl)-1-phenylprop-2-en-1-one **1n** and (*Z*/*E*)-4-(ethylthio)-4-(1-methyl-1*H*-indol-3-yl)but-3-en-2-one **1o** (Table 2, Entries14 and 15), reacted smoothly with hydrazine hydrate **2a** to efficiently give corresponding 3-pyrazolyl indoles **3a-3o** in excellent yields, respectively. Obviously, the electronic effects of both electron-withdrawing and-donating substitutents on phenyl or indolyl in **1** are insignicant to the cyclocondensation reaction. However, the substituents

Table 2. synthesis of 3-pyrazolyl indoles **3a–3o**[a].



Entry	1	3	Yield(%)[b]
1	 **1a**	 **3a**	94
2	 **1b**	 **3b**	92
3	 **1c**	 **3c**	94
4	 **1d**	 **3d**	92
5	 **1e**	 **3e**	92
6	 **1f**	 **3f**	91
7	 **1g**	 **3g**	95
8	 **1h**	 **3h**	91
9	 **1i**	 **3i**	90
10	 **1j**	 **3j**	93
11	 **1k**	 **3k**	94
12	 **1l**	 **3l**	95
13	 **1m**	 **3m**	94
14[c]	 **1n**	 **3n**	90
15	 **1o**	 **3o**	93

[a]Condition: **1** (0.5 mmol), **2a** (1 mmol), $(CH_3)_3COH$ (1 mL), 120 °C, 4 h; [b]Isolated yields; [c]The reaction takes 8 h to complete.



Scheme 2. The cyclocondensation reaction of **1a, 1e** and **1 g** and phenylhydrazine **2b**.

at the 2-positions on the indole rings in **1** showed a significant impact on the reaction due to the steric hindrance effect. For example, it took a longer time for the cyclocondensation reaction of **1n** and **2a** to afford **3n** to complete (Table 2, Entry 14). It was worth noting that the (*E*)/(*Z*)-configurations of **1** did not affect the cyclocondensation of β- ethyltho-β-indolyl-α,β-unsaturated ketones **1** with hydrazines **2** to efficiently afford 3-pyrazolyl indoles **3**.

Furthermore, we explored the cyclocondensation reaction outcome of the substituted hydrazine phenylhydrazine **2 b** and **1a** under the optimized conditions, and found that the reactions proceeded smoothly to offer 3-(1,5-diphenyl-1H-pyrazol-3-yl)-1-methyl-1H-indole **3p** in 65% yield and its tautomer 3-(1,3-diphenyl-1H-pyrazol-5-yl)-1-methyl-1H-indole **3p′** in 30% yield. The result suggested that the reaction gave **3p** in preference to 3**p′**. The isomeric **3p** and **3p′** can be separated effectively because they have different R_f values (petroleum ether/ethyl acetate10:1, v/v), in which the R_f value of **3p′** is slightly smaller than that of **3p**. The structure of **3p′** was confirmed with the help of spectral and analytical data as well as alternative synthesis by reported method[11], while structural determination of **3q** on the basis of spectral and analytical data and by comparison of **3p′**. Both **1e** and **1 g** efficiently underwent the same reaction with **2 b** to preferentially produce corresponding **3q** and **3r** in moderate yield (Scheme 1).

In summary, the catalyst free cyclocondensation reaction of β-ethyltho-β-indolyl-α,β-unsaturated carbonyl ketones and hydrazines could efficiently carried out in $(CH_3)_3COH$ at 120 °C to afford 3-pyrazolyl indoles in excellent yields. The procedure is characterized by reducing the discharge of chemical waste, which is of great significance to the protection of the environment. Further investigation of the application of β-ethyltho-β-indolyl-α,β-unsaturated ketones is ongoing in our group.

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 δ 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-pyrazolyl indoles 3

A mixture of β-ethyltho-β-indolyl-α,β-unsaturated ketones **1** (0.5 mmol), hydrazines **2** (1 mmol), and $(CH_3)_3COH$ (1 mL) were stirred for 4 h in 120 °C in sealed tube in which the conversion of **1** was completed as evidenced by TLC. After cooling to room temperature, the reaction mixture was purified by silica gel column chromatography (petroleum ether (60–90 °C)/ethyl acetate10:1, v/v) to give pure **3** as white crystal in excellent yields.

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