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Article

Green and Efficient Synthesis of 3-Pyrazolyl Indoles in Water

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Abstract A green and efficient synthesis of 3-pyrazolyl indoles was developed by the cyclocondensation reaction of *β*-ethylthio-*β*-indolyl-*α*,*β*-unsaturated ketones with semicarbazide hydrochloride as hydrazine equivalent in the presence of 3 equiv. of PEG-400(**1**a/PEG mole ratio of 1:3) in reflux water. This procedure did not require toxic hydrazine and product purification, eliminating the use of toxic liquid chemicals.

Keywords 3-Pyrazolyl indole; Green synthesis; Semicarbazide hydrochloride; Polyethylene glycol; Hydrazine equivalent

1 Introduction

3-Pyrazolyl indoles as an important subset of indole derivatives have exhibited their versatile synthetic values[1—4] and a broad spectrum of biological activities[5—7], such as antimicrobial[8], anti-inflammatory[9] and antioxidant[10,11]. As a result, much effort has focused on the synthesis of 3-pyrazolyl indoles, mainly including the cyclocondensation of 1,3-diketones and related derivatives with hydrazines[12—19], the direct coupling of indole derivatives and pyrazole derivatives[20,21], acid-catalyzed intramolecular cyclization reaction of *N*-propargylation of *N*-acetyl-*N*-tosylhydrazine[22], and other procedures[23—25]. However, all the reported reactions are performed in organic medium and extremely toxic hydrazines as a main nitrogen source for most of reactions, which can lead to serious environmental and safety problems. Therefore, from the green chemistry point of view, the development of environmentally compliance synthesis of 3-pyrazolyl indoles is of great importance and necessity. During the last two decades, organic reaction in water had received more and more attention in green chemistry because the use of water can remarkably reduce the discharge of harmful organic solvents[26—31]. Recently, in our research on the organic reaction in water[32—35], we reported the thioacetalization[32] and synthesis of dithiines[33] using ketene dithioacetals as odorless thiol equivalent in water, DBSA-catalyzed Friedel-Crafts alkylation of ketene dithioacetals with alcohols[34] and hydrolysis of chain *α*-oxo ketene dithioacetals in water[35]. As part of our continuing research in the context, we more recently have developed a green protocol for the synthesis of 3-pyrazolyl indoles by the cyclocondensation of *β*-ethylthio-*β*- indolyl-*α*,*β*-unsaturated ketones and semicarbazide hydrochloride as nitrogen source in water. *β*-Ethylthio-*β*-indolyl-*α*,*β*-unsaturated ketones, which are easily prepared in good yields *via* acid mediated selective desulfitative carbon-carbon coupling reaction between indoles and *α*-oxo ketene dithioacetals[36,37], are emerging as versatile intermediates in the synthesis of potentially useful indole derivatives due to their structural features of multireaction center and multi-functional group[36,38]. Commercially available and stable semicarbazide hydrochloride as odorless and efficient hydrazine equivalent had successfully been used in the synthesis of 1*H*-pyrazole-3-carboxylates[39]. Compared with hydrazine hydrates, the atom economy of the reaction was lower when semicarbazide hydrochloride was used. However, from the toxicity point of view, semicarbazide hydrochloride is a much better choice than the genotoxic and carcinogenic hydrazine. Herein, we would like to report our findings.

2 Experimental

2.1 General Considerations

^{1}H and ^{13}C{1H} NMR spectra were recorded on a Bruker DRX-600 spectrometer and the chemical shift values(*δ*) of TMS refer to 0. The HRMS analysis was achieved on a 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).

2.2 Typical Procedure for the Preparation of 3-Pyrazolyl Indoles(3)

The mixture of compounds **1**(0.25 mmol) and **2**(56.2 mg, 0.50 mmol) and PEG-400(0.25 mL, 0.75 mmol) in water(1 mL) in 20 mL reaction tube was stirred at reflux until compounds **1** was completely consumed by TLC monitoring. After the mixture was allowed to cool down to ambient temperature, some white solid deposited from the reaction system. The white solid was collected by filtration and washed with water(3×25 mL) to

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give compounds **3** in good yields.

1-Methyl-3-(3-phenyl-1*H*-pyrazol-5-yl)-1*H*-indole(**3**a): a white solid, m. p. 220—222 °C. ^{1}H NMR (DMSO-d_6, 600 MHz), *δ*: 13.1(br, 1H), 8.10(s, 1H), 7.91(s, 2H), 7.77(s, 1H), 7.50(d, *J*=7.7 Hz, 1H), 7.45(t, *J*=7.2 Hz, 2H), 7.33(t, *J*=7.0 Hz, 1H), 7.25(t, *J*=7.4 Hz,1H), 7.18(t, *J*=7.1 Hz, 1H), 7.06(s, 1H), 3.85(s, 3H). ^{13}C NMR(DMSO-d_6, 150 MHz), *δ*: 136.9(2C), 128.7(2C), 127.5, 127.3(3C), 125.1(5 C), 121.8, 119.8, 110.1, 98.8, 32.7. HRMS, *m/z*, cacld. for $C_{18}H_{16}N_3^+$([M+H]$^+$) 274.1339; found: 274.1349.

1-Methyl-3-[3-(*o*-tolyl)-1*H*-pyrazol-5-yl]-1*H*-indole(**3**b): a white solid, m. p. 163—165 °C. ^{1}H NMR ($CDCl_3$, 600 MHz), *δ*: 8.02(d, *J*=7.9 Hz, 1H), 7.52(d, *J*=7.5 Hz, 1H), 7.33(d, *J*=8.3 Hz, 1H), 7.32(s, 2H), 7.28(d, *J*=7.7 Hz, 1H), 7.26(d, *J*=7.4 Hz, 2H), 7.22—7.20(m, 1H), 7.18(t, *J*=7.1 Hz, 1H), 3.69(s, 3H), 2.49(s, 3H). ^{13}C NMR($CDCl_3$, 150 MHz), *δ*: 137.2, 136.2, 131.0(2C), 129.2, 128.2, 126.9(2C), 126.1, 126.0(2C), 122.3, 120.4, 120.3(2C), 109.6, 103.1, 32.9, 21.1. HRMS, *m/z*, cacld. for $C_{19}H_{18}N_3^+$([M+H]$^+$) 288.1495; found: 288.1488.

1-Methyl-3-[3-(m-tolyl)-1*H*-pyrazol-5-yl]-1*H*-indole(**3**c): a white solid, m. p. 190—192 °C. ^{1}H NMR(acetone-d_6, 600 MHz), *δ*: 12.22(s, 1H), 8.13(d, *J*=7.9 Hz, 1H), 7.77(s, 1H), 7.72(d, *J*=7.7 Hz, 1H), 7.68(s, 1H), 7.45(d, *J*=8.2 Hz, 1H), 7.31(t, *J*=7.6 Hz, 1H), 7.25(t, *J*=7.9 Hz, 1H), 7.18—7.14(m, 2H), 7.01(s, 1H), 3.89(s, 3H), 2.39(s, 3H). ^{13}C NMR(acetone-d_6, 150 MHz), *δ*: 138.9, 138.3, 129.4(2C), 129.0, 127.8(2C), 126.9(2C), 123.4(2C), 122.8(2C), 120.7(2C), 110.6, 99.9, 33.1, 21.5. HRMS, *m/z*, cacld. for $C_{19}H_{18}N_3^+$([M+H]$^+$) 288.1495; found: 288.1490.

1-Methyl-3-[3-(p-tolyl)-1*H*-pyrazol-5-yl]-1*H*-indole(**3**d): a white solid, m. p. 214—216 °C. ^{1}H NMR($CDCl_3$, 600 MHz), *δ*: 7.98(d, *J*=7.7 Hz, 1H), 7.65(d, *J*=7.6 Hz, 2H), 7.33—7.29(m, 3H), 7.22(t, *J*=7.2 Hz, 1H), 7.16(d, *J*=7.8 Hz, 2H), 6.78(s, 1H), 3.62(s, 3H), 2.37(s, 3H). ^{13}C NMR($CDCl_3$, 150 MHz), *δ*: 137.7, 137.2, 129.5(3C), 127.0(2C), 125.9, 125.7(4C), 122.3, 120.3, 120.2, 109.6, 99.8, 32.8, 21.4. HRMS, *m/z*, cacld. for $C_{19}H_{18}N_3^+$([M+H]$^+$) 288.1495; found: 288.1498.

3-[3-(4-Methoxyphenyl)-1*H*-pyrazol-5-yl]-1-methyl-1*H*-indole(**3**e): a white solid, m. p. 186—188 °C. ^{1}H NMR($CDCl_3$, 600 MHz), *δ*: 7.96(d, *J*=7.2 Hz, 1H), 7.66(d, *J*=7.6 Hz, 2H), 7.30(s, 3H), 7.29(s, 1H), 7.25(s,1H), 7.22—7.20(m, 1H), 6.83(d, *J*=8.6 Hz, 2H), 6.72(s, 1H), 3.79(s, 3H), 3.54(s, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz), *δ*: 159.4, 137.1, 127.0(6 C), 125.9, 122.2, 120.2, 120.1, 114.1(3C), 109.6, 99.4, 55.4, 32.8. HRMS, *m/z*, cacld. for $C_{19}H_{18}N_3O^+$([M+H]$^+$) 304.1444; found: 304.1448.

3-[3-(4-Chlorophenyl)-1*H*-pyrazol-5-yl]-1-methyl-1*H*-indole(**3**f): a white solid, m. p. 247—249 °C. ^{1}H NMR(DMSO-d_6, 600 MHz), *δ*: 13.1(s, 1H), 8.02—7.85(m, 3H), 7.80(s, 1H), 7.51(s, 1H), 7.49(s, 2H), 7.26—7.11(m, 3H), 3.85(s, 3H). ^{13}CNMR(DMSO-d_6, 150 MHz), *δ*: 150.3, 139.1, 137.3, 133.4, 132.1, 129.0, 127.8(2C), 127.3(2C), 125.2, 122.4, 120.5, 120.2, 110.7, 104.8, 99.2, 33.2. HRMS, *m/z*, cacld. for $C_{18}H_{15}ClN_3^+$ ([M+H]$^+$) 308.0949; found: 308.0955.

3-[3-(4-Bromophenyl)-1*H*-pyrazol-5-yl]-1-methyl-1*H*-indole(**3**g): a white solid, m. p. 167—169 °C. ^{1}H NMR(DMSO-d_6, 600 MHz), *δ*: 13.1(s, 1H), 8.0(d, *J*=7.3 Hz, 1H), 7.90(d, *J*=7.4 Hz, 2H), 7.77(s, 1H), 7.61(d, *J*=7.4 Hz, 2H), 7.52(d, *J*=7.6 Hz,1H), 7.26—7.19(m, 2H), 7.12(s, 1H), 3.86(s, 3H). ^{13}C NMR(DMSO-d_6, 150 MHz), *δ*: 149.9, 138.7, 136.8, 133.3, 131.9, 131.5(2C), 127.2(2C), 124.7, 122.0, 120.2, 120.0, 119.7, 110.2, 104.3, 98.8, 32.8. HRMS, *m/z*, cacld. for $C_{18}H_{15}BrN_3^+$ ([M+H]$^+$) 352.0444; found: 352.0440.

1-Methyl-3-[3-(thiophen-2-yl)-1*H*-pyrazol-5-yl]-1*H*-indole (**3**h): a white solid, m. p. 248—250 °C. ^{1}H NMR(DMSO-d_6, 600 MHz), *δ*: 13.0(s, 1H), 7.96(d, *J*=7.6 Hz, 1H), 7.77(s, 1H), 7.52(d, *J*=8.0 Hz, 1H), 7.51(d, *J*=3.4 Hz,1H), 7.44(s, 1H), 7.27(t, *J*=6.9 Hz,1H), 7.20(t, *J*=6.7 Hz, 1H), 7.11(s, 1H), 6.97(s, 1H), 3.86(s, 3H). ^{13}C NMR(DMSO-d_6, 150 MHz), *δ*: 146.7, 138.5, 137.4, 136.8, 127.6, 127.4, 124.7, 124.4, 123.6, 122.0, 120.0, 119.6, 110.3, 104.1, 98.4, 32.8. HRMS, *m/z*, cacld. for $C_{16}H_{14}N_3S^+$([M+H]$^+$) 280.0903; found: 280.0910.

1-Methyl-3-[3-(naphthalen-1-yl)-1*H*-pyrazol-5-yl]-1*H*-indole(**3**i): a white solid, m. p. 164—166 °C. ^{1}H NMR($CDCl_3$, 600 MHz), *δ*:12.5(s, 1H), 8.43(s, 1H), 7.98(s, 1H), 7.81(d, *J*=7.7 Hz, 1H), 7.72(d, *J*=8.0Hz, 1H), 7.58(s, 1H), 7.44—7.41 (m, 2H), 7.25—7.23(m, 3H), 7.14(t, *J*=6.8 Hz, 2H), 6.84(s, 1H), 3.38(s, 3H). ^{13}C NMR($CDCl_3$, 150 MHz), *δ*: 137.0, 133.7, 131.3, 128.4, 128.2(2C), 127.0(2C), 126.9(2C), 126.3, 125.8(3C), 125.2(2C), 122.0, 120.1(2C), 109.4, 103.7, 32.4. HRMS, *m/z*, cacld. for $C_{22}H_{18}N_3^+$([M+H]$^+$) 324.1495; found: 324.1490.

1,5-Dimethyl-3-(3-phenyl-1*H*-pyrazol-5-yl)-1*H*-indole(**3**j): a white solid, m. p. 227—229 °C. ^{1}H NMR(acetone-d_6, 600 MHz), *δ*: 12.25(br, 1H), 7.94(d, *J*=7.7 Hz, 3H), 7.63(s, 1H), 7.43(t, *J*=7.6 Hz, 2H), 7.33(d, *J*=8.3 Hz, 1H), 7.31(d, *J*=7.4 Hz, 1H), 7.08(d, *J*=8.3 Hz, 1H), 7.02(s, 1H), 3.84(s, 3H), 2.47(s, 3H). ^{13}C NMR(acetone-d_6, 150 MHz), *δ*: 136.8, 129.7, 129.5(3C), 128.3, 127.8(2C), 126.9, 126.2(4C), 124.4, 110.3, 99.7, 99.7, 33.1, 21.6. HRMS, *m/z*, cacld. for $C_{19}H_{18}N_3^+$ ([M+H]$^+$) 288.1495; found: 288.1500.

5-Methoxy-1-methyl-3-(3-phenyl-1*H*-pyrazol-5-yl)-1*H*-indole(**3**k): a white solid, m. p. 225 —227 °C. ^{1}H NMR(acetone-d_6, 600 MHz), *δ*: 12.25(br, 1H), 7.93(d, *J*=7.5 Hz, 2H), 7.64(s, 1H), 7.44(t, *J*=7.6 Hz, 2H), 7.35(d, *J*=8.9 Hz, 1H), 7.33(t, *J*=7.4 Hz, 1H), 6.99(s, 1H), 6.90(dd, J_1=8.8 Hz, J_2=2.3 Hz, 1H), 3.87(s, 3H), 3.86(s, 3H). ^{13}C NMR(acetone-d_6, 150 MHz), *δ*: 155.8, 133.6, 129.6(3C), 128.4(4C), 127.1, 126.3(4C), 113.1, 111.4, 99.7, 56.0, 33.3. HRMS, *m/z*, cacld. for $C_{19}H_{18}N_3O^+$ ([M+H]$^+$) 304.1444; found: 304.1441.

5-Bromo-1-methyl-3-(3-phenyl-1*H*-pyrazol-5-yl)-1*H*-indole (**3**l): a white solid, m. p. 245—247 °C. ^{1}H NMR(acetone-d_6, 600 MHz), *δ*: 8.36(s, 1H), 7.91(d, *J*=7.6 Hz, 2H), 7.74(s, 1H), 7.47—7.43(m, 3H), 7.36—7.34(m, 2H), 7.04(s, 1H), 3.91(s, 3H). ^{13}C NMR(acetone-d_6, 150 MHz), *δ*: 137.1, 129.7(3C), 129.4(2C), 128.6, 128.3, 126.3(4C), 125.4, 124.1, 113.8, 112.6, 100.1, 33.4. HRMS, *m/z*, cacld. for $C_{18}H_{15}BrN_3^+$([M+H]$^+$) 352.0444; found: 352.0447.

1-Ethyl-3-(3-phenyl-1*H*-pyrazol-5-yl)-1*H*-indole(**3**m): a white solid, m. p. 176—177 °C. ^{1}H NMR(acetone-d_6, 400 MHz), *δ*: 8.13(d, *J*=7.8 Hz, 1H), 7.95(d, *J*=8.4 Hz, 2H), 7.75(s, 1H), 7.48—8.41(m, 3H), 7.31(t, *J*=7.4 Hz, 1H), 7.23(t, *J*=7.1 Hz, 1 H), 7.21—7.15(m, 1H), 7.04(s, 1H), 4.28—4.23(m, 2H), 1.44(t, *J*=7.2 Hz, 3H). ^{13}C NMR(acetone-d_6, 100 MHz), *δ*: 137.3, 129.5(4C), 128.3, 126.8, 126.2(4C), 126.1, 122.7, 121.4,

120.7, 110.6, 99.9, 41.6, 15.7. HRMS, *m/z*, cacld. for $C_{19}H_{18}N_3^+$([M+H]$^+$) 288.1495; found: 288.1502.

1-Benzyl-3-(3-phenyl-1*H*-pyrazol-5-yl)-1*H*-indole(**3**n): a white solid, m. p. 193—195 °C. ^{1}H NMR($CDCl_3$, 600 MHz), δ 11.7(s, 1H), 7.97(d, *J*=7.3 Hz, 1H), 7.74(d, *J*=7.2 Hz, 2H), 7.36(s, 1H), 7.32(t, *J*=7.1 Hz, 2H), 7.28(d, *J*=7.3 Hz, 1H), 7.26(t, *J*=8.2 Hz, 1H), 7.23(d, *J*=7.2 Hz, 1H), 7.20—7.17(m, 4H), 7.03(dd, J_1=7.4 Hz, J_2=2.9 Hz, 2H), 6.79(s, 1H), 5.05(s, 2H). ^{13}C NMR($CDCl_3$, 150 MHz), δ: 136.8, 136.7, 128.8(4C), 128.7, 128.6, 127.8, 127.7, 126.8(4C), 126.3, 126.0, 125.6(2C), 122.4, 120.5, 120.2, 110.2, 100.0, 50.0. HRMS, *m/z*, cacld. for $C_{24}H_{20}N_3^+$([M+H]$^+$) 350.1652; found: 350.1660.

1-Methyl-3-(3-methyl-1*H*-pyrazol-5-yl)-1*H*-indole(**3**o): a white solid, m. p. 174—176 °C. ^{1}H NMR(DMSO-d_6, 400 MHz), δ: 8.01(d, *J*=7.8 Hz, 1H), 7.63(s, 1H), 7.44(d, *J*=8.1 Hz, 1H), 7.19(t, *J*=7.7 Hz, 1H), 7.10(t, *J*=7.8 Hz, 1H), 6.30(s, 1H), 3.80(s, 3H), 2.26(s, 3H). ^{13}C NMR(DMSO-d_6, 100 MHz), δ: 138.0(2C), 128.2(2C), 126.4, 122.7(2C), 121.8, 120.6(2C), 111.0, 102.0, 33.7. HRMS, *m/z*, cacld. for $C_{13}H_{14}N_3^+$([M+H]$^+$) 212.1182; found: 212.1179.

2-Methyl-3-(3-phenyl-1*H*-pyrazol-5-yl)-1*H*-indole(**3**p): a white solid, m. p. 184—186 °C. ^{1}H NMR($CDCl_3$, 600 MHz), δ: 8.05(s, 1H), 7.80(d, *J*=7.6 Hz, 2H), 7.75(d, *J*=7.7 Hz, 1H), 7.33(t, *J*=7.6 Hz, 2H), 7.28(t, *J*=7.2 Hz 1H), 7.24(t, *J*=8.0 Hz 1H), 7.16(t, *J*=7.2 Hz 1H), 7.11(t, *J*=7.5 Hz 1H), 6.71(s, 1H), 2.41(s, 3H). ^{13}C NMR($CDCl_3$, 150 MHz), δ: 135.1, 133.4, 128.7(4C), 127.7, 127.1, 125.7(4C), 121.8, 120.5, 118.6, 110.5, 101.5, 12.7. HRMS, *m/z*, cacld. for $C_{18}H_{16}N_3^+$([M+H]$^+$) 274.1339; found: 274.1330.

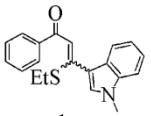
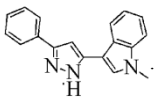
3 Results and Discussion

Initially, the reaction of (*Z/E*)-3-(ethylthio)-3-(1-methyl-1*H*-indol-3-yl)-1-phenylprop-2-en-1-one **1**a(0.25 mmol) with semicarbazide hydrochloride **2**(0.25 mmol) was carried out in reflux water(1 mL) for 24 h, and a white solid, which was characterized as 1-methyl-3-(3-phenyl-1*H*-pyrazol-5-yl)-1*H*-indole(**3**a) on the basis of its spectral and analytical data, was obtained in a 45% yield, along with 50% recovery of compound **1**a(Table 1, entry 1). Next, systematic investigations were performed to identify the optimal conditions, and the results were summarized in Table 1. We found that this reaction proceeded less efficiently even further elevating reaction temperature and prolonging reaction time in the absence of surfactants(Table 1, entries 2—5), in which the formed thick solid mixture including compounds **3**a, **1**a and **2**a in hot water prevented the performance of further cyclization reaction of compound **1**a to yielding compound **3**a. Subsequently, the reaction was carried out in the presence of nonionic surfactant PEG-400 with unique merits, such as non-toxic, inexpensive, non-flammable, low volatility and good water solubility, which were consistent with the concept of green chemistry[40—43]. It was found that on changing the mole ratio of compound **1**a and PEG-400 from 1:1 to 1:3, the field of compound **3**a remarkably increased(Table 1, entries 6—8), while further elevating the mole ratio slightly improved the yield of compound **3**a(Table 1, entry 9), which indicates that the perfect mole ratio can be obtained when the reaction is proceeded in the presence of compound **1**a/PEG-400 mole ratio of 1:3. Finally, we tested the influence of the amount of compound **2**(Table 1, entries 10 and 11). When the mole ratio of compounds **1**a and **2** is 1:2 was used, the reaction was finished within 13 h to afford the only desired product **3**a in a 93% yield. It is noteworthy that compound **3**a is easily obtained after being filtered since it is a white solid and deposits from the reaction system once formed. Accordingly, the reaction conditions were optimized as follows: compound **1**a/PEG-400 mole ratio of 1:3, compound **1**a/compound **2** mole ratio of 1:2 and the temperature of 100 °C .

Next, we used the optimized reaction conditions to define the scope of this cyclocondensation for the synthesis of 3-pyrazolyl indoles, and the results are summarized in Table 2. We found that a variety of *β*-ethyl-thio-*β*-indolyl-*α*,*β*-unsaturated ketones **1**, such as (*Z/E*)-3-(ethylthio)-3-(1-methyl-1*H*-indol-3-yl)-1-arylprop-2-en-1-ones, (*Z/E*)-3-(5-methyl/brmo-/methoxy-1-methyl-1*H*-indol-3-yl)-3-(ethylthio)-1-phenylprop-2-en-1-one, (*Z/E*)-3-(1-ethyl/benzyl-1*H*-indol-3-yl)-3-(ethylthio)-1-phenyl prop-2-en-1-one and (*Z/E*)-4-(ethylthio)-4-(1-methyl-1*H*-indol-3-yl)but-3-en-2-one, smoothly reacted with semicarbazide hydrochloride(**2**) to afford

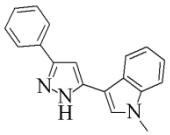
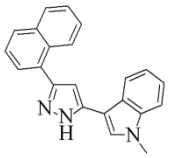
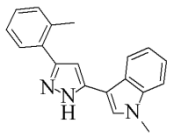
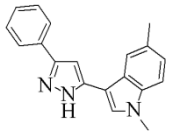
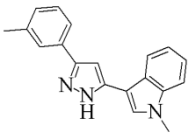
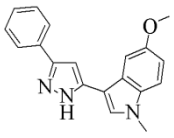
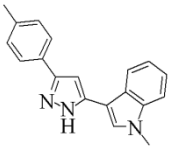
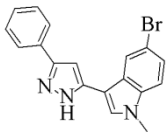
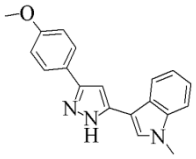
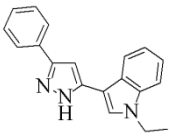
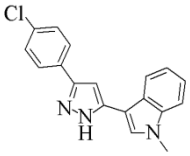
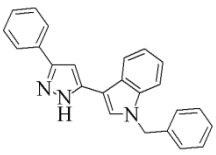
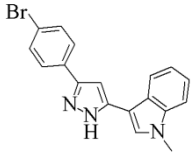
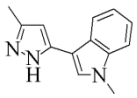
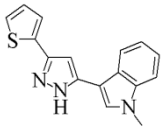
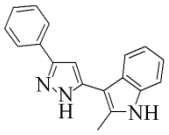
Table 1 Screening of the reaction conditions[a]

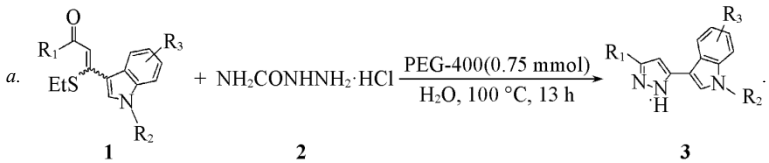
Entry	Compound **1**a:compound **2**(mole ratio)	Compound **1**a: PEG-400(mole ratio)	Temp./°C	*T*/h	Yield[b](%)
1	1:1	0	100	24	45(50)[c]
2	2:3	0	100	24	47(48)[c]
3	1:2	0	100	24	55(39)[c]
4	1:2	0	100	36	56(38)[c]
5	1:2	0	120	24	55(41)[c]
6	1:1	1:1	100	24	60(34)[c]
7	1:1	1:2	100	24	70(24)[c]
8	1:1	1:3	100	24	81(12)[c]
9	1:1	1:4	100	24	82(13)[c]
10	2:3	1:3	100	24	87(7)[c]
11	1:2	1:3	100	13	93

a.  + $NH_2CONHNH_2\cdot HCl$ $\xrightarrow[H_2O]{\text{Conditions}}$  . Reaction conditions: compound **1**a(0.25 mmol), H_2O(1 mL); *b*. isolated yields; *c*. the recovery of compound **1**a(data in brackets).

1a **2** **3**a

Table 2 Synthesis of 3-pyrazolyl indoles(3)[a,b]

Compound	Structure	Yield(%)	Compound	Structure	Yield(%)
3a		93	**3**i		90
3b		92	**3**j		93
3c		94	**3**k		90
3d		93	**3**l		92
3e		94	**3**m		94
3f		92	**3**n		93
3g		93	**3**o		94
3h		90	**3**p[c]		90



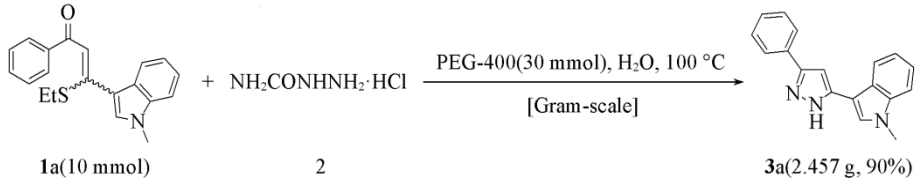
1 **2** **3**

a. Reaction conditions: **1**(0.25 mmol), **2**(56.2 mg, 0.5 mmol), PEG-400(0.25 mL, 0.75 mmol), H_2O(1 mL), 100 °C; *b.* isolated yields; *c.* compound **3**p was synthetized when the reaction was performed at 120 °C for 48 h in a sealed tube.

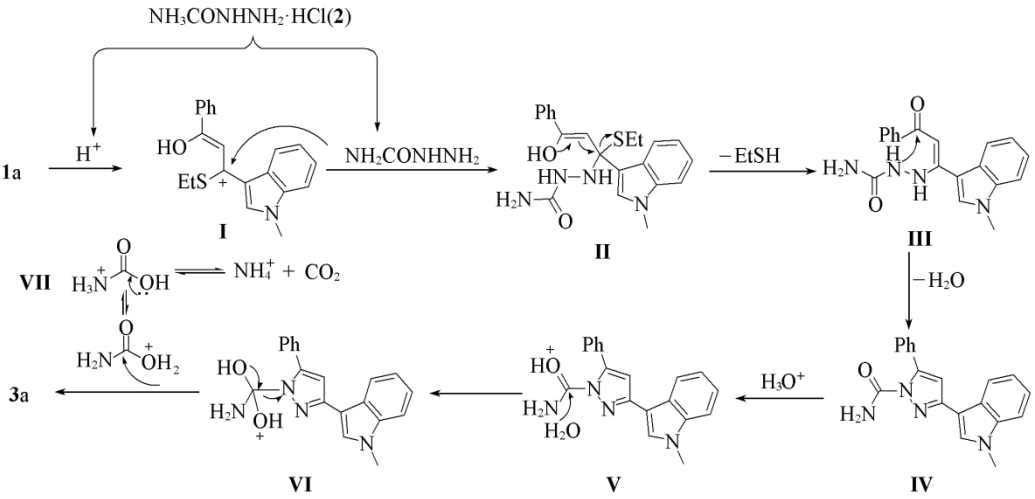
desired 3-pyrazolyl indoles(**3**a—**3**o) in excellent yields. In the case of (*Z*/*E*)-3-(ethylthio)-3-(2-methyl-1*H*-indol-3-yl)-1-phenylprop-2-en-1-one, although the steric bulk of the C2 of substituent in indolyl could hinder this cyclocondensation, compound **3**p was obtained in a 90% yield by both prolonging reaction time and further elevating reaction temperature. It was worth noting both the *Z*/*E* ratio of compound **1** and the substitutents with electron-withdrawing or electron-donating on phenyl or indolyl in compound **1** did not remarkably affect the formation of compound **3**. Compound **3** are all white solids, and are easily obtained after being filtered from the reaction system. In addition, the evaporated aqueous phase can be used many times in the same reaction.

Furthermore, we also checked the scalability of the process(Scheme 1). It was found that the cyclocondensation reaction of compound **1**a(10 mmol) and compound **2** successfully afforded gram-quantities of the desired product compound **3**a in a 90% yield.

Based on the obtained results and the reported work[39], the proposed mechanism for the formation of 3-pyrazolyl indoles(**3**) is presented in Scheme 2. It is clear that semicarbazide hydrochloride(**2**) firstly releases both H^+ and semicarbazide.



Scheme 1 Scalability of the process



Scheme 2 Plausible mechanism for the synthesis of 3-pyrazolyl indoles in water

Then, the reaction is presumably initiated by the protonation of the polarized C═C bond of compound **1**a to form carbocation **I**, which is additionally stabilized by adjacent electron-donating both ethylthio and 1-methyl-1*H*-indol-3-yl groups. Nucleophilic attack at the cationic carbon atom of intermediate **I** by semicarbazide forms the intermediate **III** *via* elimination of an EtSH of the intermediate **II**. The pyrazole-1-carboxamide derivative(**IV**) is formed by an intramolecular dehydration cyclocondensation of imine intermediate **III**. Subsequently, intermediate **IV** exists in a protonated form(**V**) under acidic conditions and nucleophilic attack of water leads to its transformation into intermediate **VI**, which decomposed easily to provide 3-pyrazolyl indole(**3**a) and protonated carbamic acid (**VII**). Unsubstituted carbamic acid is an unstable compound and its proton-induced decomposition into ammonium ion and CO_2 proceeds *via* its cation form(**VII**) as an intermediate formed through the protonation of the nitrogen atom[44] .

4 Conclusions

In conclusion, a green, clean and efficient protocol for the synthesis of 3-pyrazolyl indoles was developed *via* the cyclocondensation reaction of *β*-ethylthio-*β*-indolyl-*α*,*β*-unsaturated ketones and semicarbazide hydrochloride as efficient hydrazine equivalent in the presence of compound **1**a/PEG-400, mole ratio of 1:3, in reflux water. The protocol was characterized by avoiding the use of toxic hydrazine, catalyst free, excellent yields and easy work-up forming no harmful by-product and requiring no chromategraphic purification.

Electronic Supplementary Material

Supplementary material is available in the online version of this article at http://dx.doi.org/10.1007/s40242-019-0011-8.

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