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Green Cyclocondensation of β-Ethylthio-β-indolyl-α, β-unsaturated Ketones with Semicarbazide Hydrochloride as Hydrazine Equivalent in Water: Aqueous Synthesis of 3-Pyrazolyl Indoles

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Abstract

A green and efficient cyclocondensation reaction of β-ethylthio-β-indolyl-α, β-unsaturated ketones with semicarbazide hydrochloride as hydrazine equivalent to prepare 3-pyrazolyl indoles had been developed in the presence of 3 equiv. of PEG-400 in reflux water. This procedure did not require toxic hydrazine and product purification, eliminating the use of toxic liquid chemicals.

Keywords

3-pyrazolyl indoles; semicarbazide hydrochloride; polyethylene glycols; aqueous synthesis; hydrazine equivalent.

Introduction

β-Ethyltho-β-indolyl-α, β-unsaturated ketones are emerging as versatile intermediates in the synthesis of potentially useful indole derivatives due to their structural features of multi-reaction center and multi-functional group[1,2]. 3-Pyrazolyl indoles as an important subset of

indole derivatives had exhibited their versatile synthetic values [3-7] and a broad spectrum of biological activities [8-10] such as antimicrobial [11], anti-inflammatory [12] and antioxidant [13, 14]. 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[15-22], the direct coupling of indole derivatives and pyrazole derivatives[23, 24], acid-catalyzed intramolecular cyclization reaction of *N*-propargylation of *N*-acetyl-*N*-tosyl-hydrazine [25], and other procedures[26-28]. However, all the reported reactions are performed in organic medium and extremely toxic hydrazines appear 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 great importance and necessity.

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[29]. 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.

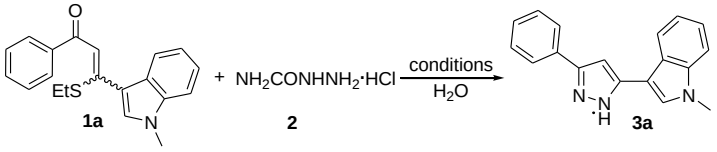
During the last two decades, organic reaction in water had received more and more attention in green chemistry because the use of water can remarkably reduce the discharge of harmful organic solvents[30-35]. Recently, in our research on the organic reaction in water[36-39], we reported the thioacetalization[36] and synthesis of dithiines[37] utilizing ketene dithioacetals as odorless thiol equivalent in water, DBSA-catalyzed Friedel-Crafts alkylation of ketene dithioacetals with alcohols[38] and hydrolysis of chain α-oxo ketene dithioacetals in water[39]. As part of our continuing research in the context, we more recently 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 hydro- chloride in water. Herein, we would like to report our findings.

Results and Discussion

β-Ethyltho-β-indolyl-α, β-unsaturated ketones **1** were easily prepared in good yields via acid mediated selective desulfitative carbon-carbon coupling reaction between indoles and α-oxo ketene dithio-acetals[1, 40]. Over the past decades, polyethylene glycols (PEGs) as nonionic surfactant and organic reaction media had received more and more attention due to their unique merits such as non-toxic, inexpensive, non-flammable, low volatility and good water solubility, which were consistent with the concept of green chemistry [41-44]. Initially, The 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 semi-carbazide hydrochloride **2** (0.25 mmol) was carried out in reflux water (1 mL) for 24 h, and a white solid product, which was characterized as 1-methyl-3-(3- phenyl-1*H*- pyrazol-5-yl)-1*H*-indole **3a** on the basis of its spectral and analytical data, was obtained in 45% yield, along with 50% recovery of **1a** (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 **3a**, **1a** and **2a** in hot water prevented the performance of further cyclization reaction of **1a** to yield **3a**. Subsequently, the reaction was carried out in the presence of nonionic surfactant PEG-400. It was found that on changing the amount of PEG-400 from 1equiv. to 3 equiv. the field of **3a** remarkably increased (Table 1, entries 6-8), while further elevating the amount slightly improved the yield of **3a**(Table 1, entry 9), which indicates that the perfect amount can be obtained when the reaction is proceeded in the presence of 3 equiv. of PEG-400. Finally, we tested the influence of the amount of **2**(Table 1, entries 10 and 11)**.** When 2 equiv. of **2** was used, the reaction was finished within 13 h to afford the only desired product **3a** in 93% yield. It is noteworthy that **3a** 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: 3 equiv. of PEG-400, 2 equiv. of semicarbazide hydrochloride **2** and a temperature of 100°C .

Table 1 Screening of the reaction conditions[a]



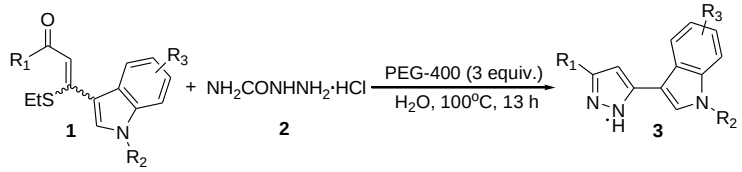
Entry	**2** (equiv.)	PEG-400 (equiv.)	Temp. (°C)	T (h)	Yield (%)[b]
1	1.0	0	100	24	45(50)[c]
2	1.5	0	100	24	47 (48)[c]
3	2.0	0	100	24	55 (39)[c]
4	2.0	0	100	36	56 (38)[c]
5	2.0	0	120	24	55 (41)[c]
6	1.0	1	100	24	60 (34)[c]
7	1.0	2	100	24	70 (24)[c]
8	1.0	3	100	24	81(12)[c]
9	1.0	4	100	24	82(13)[c]
10	1.5	3	100	24	87(7)[c]
11	2.0	3	100	13	93

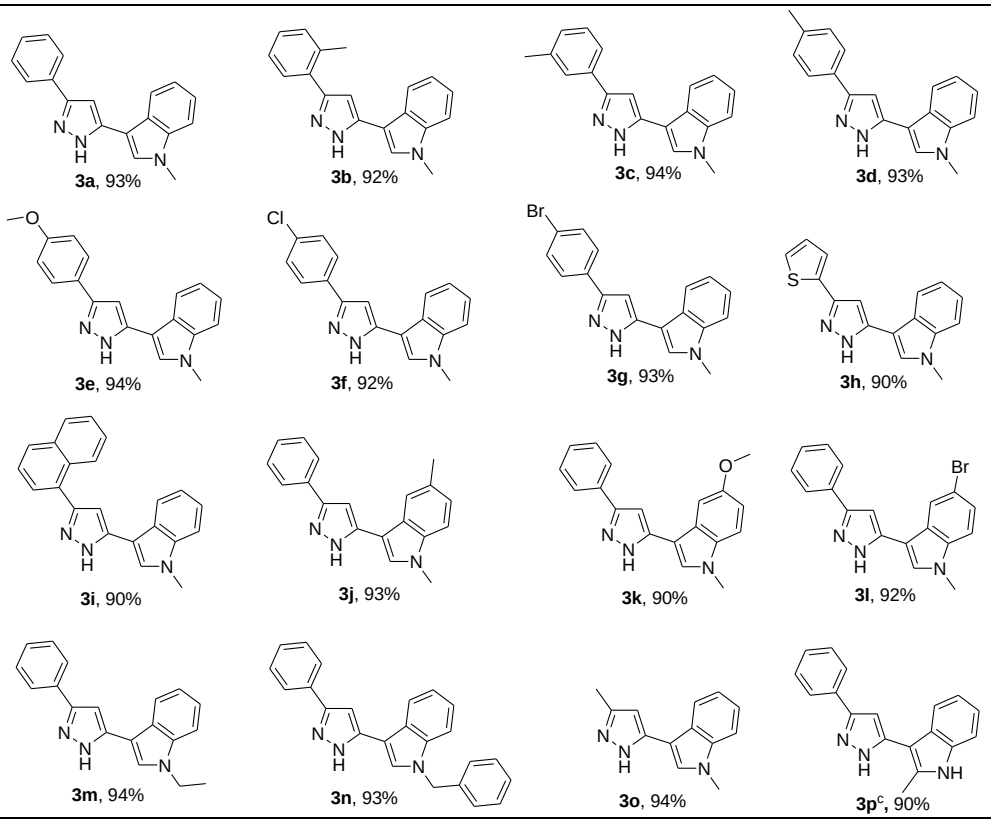
[a] Reaction conditions: **1a** (0.25 mmol), water (1 mL); [b] Isolated yields; [c] The recovery of **1a**.

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-ethylthio-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/ bromo-/meth -oxy-1-methyl-1*H*-indol-3-yl)-3-(ethylthio)-1-phenyl prop-2-en-1-one, (Z/E)-3-(1-ethyl/benzyl-1*H*-indol-3-yl)-3-(ethyl-thio)-1-phenylprop-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 desired 3-pyrazolyl indoles **3a-3o** in excellent yield. 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, **3p** was obtained in 90% yield by both prolonging reaction time and further elevating reaction temperature. It was

worth noting both the Z/E ratio of **1** and the substitutents with electron-withdrawing or electron-donating on phenyl or indolyl in **1** did not remarkably affect the formation of **3**. **3** are all white solid, 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.

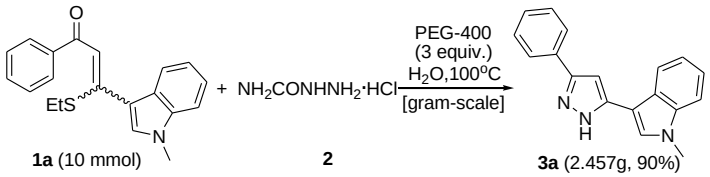
Table 2 synthesis of 3-pyrazolyl indoles **3**[a, b,]





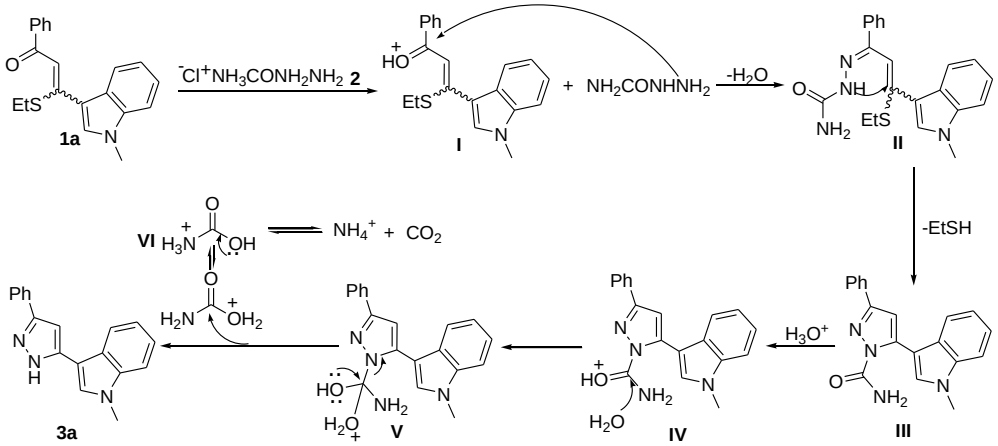
[a] Reaction conditions: **1** (0.25 mmol), **2** (56.2 mg, 0.5 mmol), PEG-400 (0.25 mL, 0.75 mmol), H_2O (1 mL), 100°C; [b]Isolated yields; [c] **3p** was synthetized when the reaction was performed at 120 °C for 48 h in sealed tube.

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



Scheme 1 the scalability of the process

Based on the obtained results and the reported work[29], the proposed mechanism for the formation of 3-pyrazolyl indoles **3** was presented in Scheme 2. It is clear that the pyrazole-1-carboxamide derivative **III** was firstly formed by an intramolecular dehydration cyclocondensation of imine intermediate **II** from nucleophilic addition of semicarbazide to protonated **I**. Then, **III** exists in a protonated form **IV** under acidic conditions and nucleophilic attack of water leads to its transformation into intermediate **V** which decomposed easily to provide 3-pyrazolyl indoles **3a** and protonated carbamic acid **VI**. Unsubstituted carbamic acid is an unstable compound and its proton-induced decomposition into ammonium ion and CO_2 proceeds via its cation form **VI** as an intermediate formed through the protonation of the nitrogen atom[45] .



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

Conclusion

In conclusion, a green, clean and efficient protocol for synthesis of 3-pyrazolyl indoles had been developed via the cyclocondensation reaction of β-ethylthio-β-indolyl-α, β-unsaturated ketones and semi -carbazide hydrochloride as efficient hydrazine equivalent in the presence of 3 equiv. of PEG-400 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.

Supporting Information

Supporting Information File 1:

Experimental procedures and characterization of all compounds, NMR spectra.

Acknowledgements

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