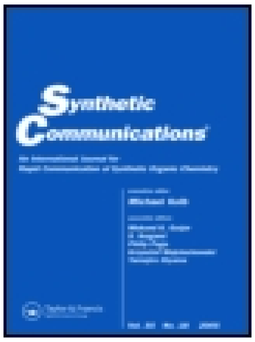

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Feasible selective synthesis of 3-Acetylindoles and 3-Acetoacetylindoles from *β*-ethylthio-*β*-indolyl *α*, *β*-unsaturated ketones

Wen-Ju Wang and Hai-Feng Yu

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ABSTRACT
An efficient and selective synthesis of 3-acetyl free(N-H)/N-substituded indoles and 3-acetoacetyl free(N-H)/N-substituded indoles has been developed via the hydrolysis reaction of *β*-ethylthio-*β*-indoly *α*, *β*-unsaturated ketones in the presence of 3 equivalent of NaOH and 5 mol% of H_2SO_4, respectively. The procedure features easy operation, excellent yields, and high selectivity, compatibility and practicability.

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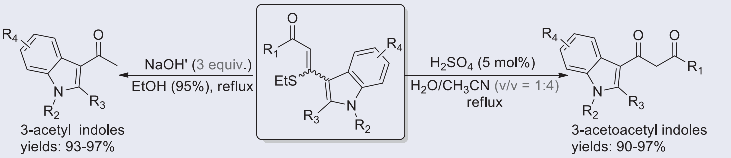
KEYWORDS
3-acetylindole; 3-acetoacetylindole; *β*-ethylthio- *β* -indoly *α*; *β*-unsaturated ketone; selectivity; acetylation

GRAPHICAL ABSTRACT



Introduction

Indole derivatives are frequently found in many natural bioactive products and in important pharmaceuticals.[1] 3-acylindoles are an important subset of indole derivatives due to their versatile synthetic values and their privileged core structures in many biologically active indole derivatives.[2] Consequently, much effort has focused on the synthesis of 3-acylindoles.[3–12] In the past decades, the direct 3-acylation of indoles had been well-documented, and is well known synthetic procedures of 3-acylindoles. These acylation reactions include Friedel-Crafts acylations,[3] Vilsmeier-Haack reactions,[4] reactions of indole salts with acetyl chlorides,[5] reaction between indole and N-(2-haloacyl)pyridinium[6] and transition –metal catalyzed acylation of indoles with Nitriles[7] or anlines.[8] Recently, transition-metal catalyzed cyclization reactions of acyclic N-aryl enamines bearing acyl group to afford 3-acylindoles had been also developed.[9] For 3-acetoacetylindoles, besides Friedel-Crafts acylation of indoles,[10] they can also be efficiently synthesized from either the nucleophilic addition between indoles and diketene

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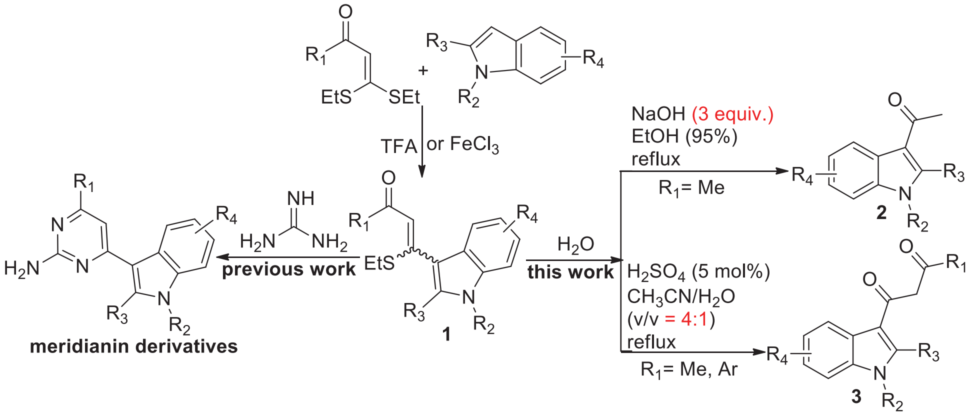


Scheme 1. Synthesis and application β-ethyltho-β-indolyl α, β-unsaturated ketones **1**.

[11] or the condensation reaction of 3-acetylindoles and carboxylate ester.[12] However, despite tremendous efforts to develop more efficient strategies in these areas, some marked drawbacks, such as harsh conditions, poor yields especially on free (N-H) indoles due to competing reactions at N1 and C3 as well as polymerization and dimerization under acidic conditions, the need of expensive catalyst, and poor generality, limit their practical applicability. Therefore, an efficient, simple, practical and general methodology for the synthesis of both 3-acylindoles and 3-acetoacetylindoles are highly desirable.

Our group recently initiated the investigation of the functionalization of indoles based on versatile synthetic intermediate α-ketene dithioacetals,[13] and β-ethyltho- β-indolyl α, β- unsaturated ketones **1** had successfully been prepared in good yields via trifluoroacetic acid (TFA) or $FeCl_3$-mediated selective desulfitative carbon-carbon coupling reaction between indoles and α-oxo ketene dithioacetals.[13a,13b] Compounds **1** could be regarded as versatile intermediates in the synthesis of potentially useful indole derivatives due to their structural features of multi-reaction center and multi-functional group (Scheme 1). As a result, we are interested in their transformation, and their condensation reactions with guanidine affording indole alkaloids meridianin derivatives had recently been realized (Scheme 1).[13a] As part of our continuing research in the context, on the basis of the significance of 3-acetyl/acetoacetyl indoles, our group more recently studied the desulfitative hydrolysis reaction of compounds **1** to synthesize 3-acetyl/acetoacetylindoles. It was found that the hydrolysis reaction efficiently occurred in the presence of alkali or acid affording 3-acetylindoles and 3-acetoacetylindoles in excellent yields, respectively (Scheme 1). Herein, we would like to report our findings.

Results and discussion

The hydrolysis reaction of 4-(ethylthio)-4-(1H-indol-3-yl)but-3-en-2-one **1a** was selected as a model reaction to screen the experimental conditions. Initially, we examined the reaction in the presence of NaOH (1 equiv.) in EtOH (95%). The reaction did not occur at 25 °C, the starting material **1a** was recovered in 95% yield (Table 1, entry 1). To our delight, when the reaction was carried out in reflux for 24 h, two stable white solid

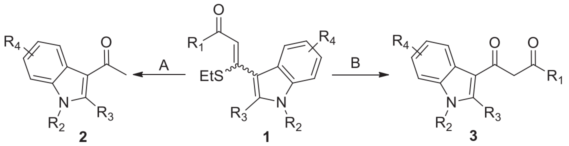
Table 1. Screening of conditionsa.

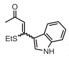
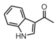
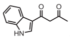
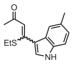
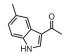
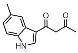
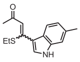
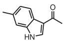
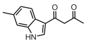
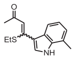
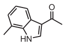
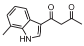
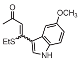
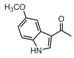
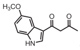
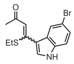
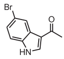
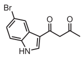
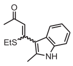
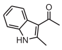
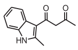
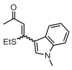
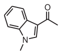
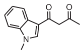
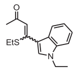
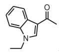
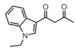
					Yield/%[b]	
Entry	catalyst	Solvent	Temp. (°C)	Time (h)	2[a]	3[a]
1	NaOH (1 equiv.)	EtOH (95%)	25	24	0 (95)[c]	0
2	NaOH (1 equiv.)	EtOH (95%)	reflux	24	39(34)[c]	18
3	NaOH (2 equiv.)	EtOH (95%)	reflux	24	84	10
4	NaOH (3 equiv.)	EtOH (95%)	reflux	18	94	0
5	$FeCl_3 \cdot 6H_2O$ (10 mol%)	$CH_3CN + H_2O$ (v/v = 4:1)	reflux	3	0	95
6	HAc (10 mol%)	$CH_3CN + H_2O$ (v/v = 4:1)	reflux	10	0	88(5)[c]
7	H_2SO_4 (10 mol%)	$CH_3CN + H_2O$ (v/v = 4:1)	reflux	2	0	95
8	H_3PO_4 (10 mol%)	$CH_3CN + H_2O$ (v/v = 4:1)	reflux	4	0	93
9	HCl (10 mol%)	$CH_3CN + H_2O$ (v/v = 4:1)	reflux	8	0	85(7)[c]
10	H_2SO_4 (5 mol%)	$CH_3CN + H_2O$ (v/v = 4:1)	reflux	3	0	96
11	H_2SO_4 (3 mol%)	$CH_3CN + H_2O$ (v/v = 4:1)	reflux	7	0	94
12	H_2SO_4 (5 mol%)	$CH_3CN + H_2O$ (v/v = 7:3)	reflux	5	0	93

[a] Reaction condition: **1a** (0.25 mmol), solvent 1 mL.
[b] Isolated yield.
[c] Percentage recovery of **1a**.

product were obtained in 39% and 18% yield, respectively, with 34% recovery of the starting material **1a**. From the spectral and analytical data, the products were characterized as 1-(1H-indol-3-yl)ethanone **2a** (39%) and 1-(1H-indol-3-yl) butane-1, 3-dione **3a** (13%), respectively (Table 1, entry 2). It was noteworthy that **3a** was an indissociable mixture of enol and keto isomers, reaching the keto/enol ratio of 10:9 determined by ^{1}H NMR. The result suggested that the reaction in the present of NaOH gave 3-acetylindole **2a** in preference to 3-acetoacetylindole **3a**, in which the deacetylation reaction of **3a** easily happened to yield **2a**. The yield of **2a** was markedly improved by further elevating the amount of NaOH (Table 1, Entries 3, 4), and the reaction exclusively afforded **2a** in 94% in the presence of 3 equivalent of NaOH (Table 1, Entry 4). We recently developed an efficient protocol for $FeCl_3 \bullet 6H_2O$ or protonic acids catalyzed desulfitative hydrolysis of chain α-ketene dithioacetals in CH_3CN/H_2O (volume ratio 4:1) to afford β-ketothioester.[14] Therefore, we next examined the desulfitative hydrolysis of **1a** in reflux in the present of 10 mol% of $FeCl_3 \bullet 6H_2O$ in CH_3CN/H_2O (volume ratio 4:1), and only the desired 1-(1H-indol-3-yl) butane-1,3-dione **3a** was yield in 96% yield, (Table 1, entry 5). Further screening revealed that readily available H_2SO_4 showed the best catalytic effect to the hydrolysis reaction (Table 1, entries 6–10), and the reaction could be performed very efficiently to produce **3a** in 96% yield in the present of 5% of H_2SO_4 (Table 1, entry 9). Additionally, it was found that further lessening either the ratio of CH_3CN to H_2O or the amount of H_2SO_4 markedly reduced the reaction efficiency (Table 1, Entries 11, 12). Accordingly, the reaction conditions are optimized as follow: conditions A for the synthesis of 3-acetylindoles **2**: EtOH (95%) as reaction medium, 3 equivalent of NaOH as catalyst and in reflux; conditions B for the synthesis of 3-acetoacetylindoles **3**: CH_3CN/H_2O (v/v = 4:1) as reaction medium, 5 mol% of H_2SO_4 as catalyst and in reflux.

Table 2. Selective synthesis of **2** and **3**[a].



Entry	1	Cond.	Product	Yield[%][b]	Enol:Keto[c]
1	 **1a**	A	 **2a**	94	
2		B	 **3a**	96	10:9
3	 **1b**	A	 **2b**	93	
4		B	 **3b**	95	5:4
5	 **1c**	A	 **2c**	97	
6		B	 **3c**	95	5:4
7	 **1d**	A	 **2d**	93	
8		B	 **3d**	97	5:4
9	 **1e**	A	 **2e**	96	
10		B	 **3e**	95	1:1
11	 **1f**	A	 **2f**	94	
12		B	 **3f**	95	1:1
13[d]	 **1g**	A	 **2g**	92	
14[e]		B	 **3g**	90	3:1
15	 **1h**	A	 **2h**	97	
16		B	 **3h**	96	5:4
17	 **1i**	A	 **2i**	94	
18		B	 **3i**	93	4:3

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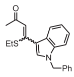
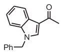
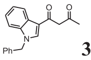
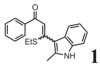
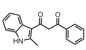
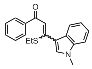
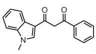
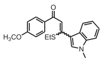
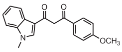
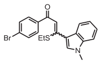
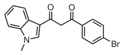
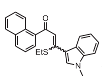
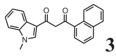
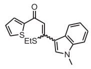
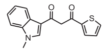
19	 **1j**	A	 **2j**	95	
20		B	 **3j**	94	5:3
21	 **1k**	B	 **3k**	95	9:1
22	 **1l**	B	 **3l**	97	4:1
23	 **1m**	B	 **3m**	95	2:1
24	 **1n**	B	 **3n**	96	6:1
25	 **1o**	B	 **3o**	94	9:1
26	 **1p**	B	 **3p**	95	5:4

[a]Reaction condition: condition A: **1** (0.25 mmol), NaOH (0.075 mmol), 95% EtOH (1 mL), reflux, 18 h; condition B: **1** (0.25 mmol), H_2SO_4 (5 mol%), H_2O/CH_3CN (1 mL, v/v = 1:4), reflux, 3 h.

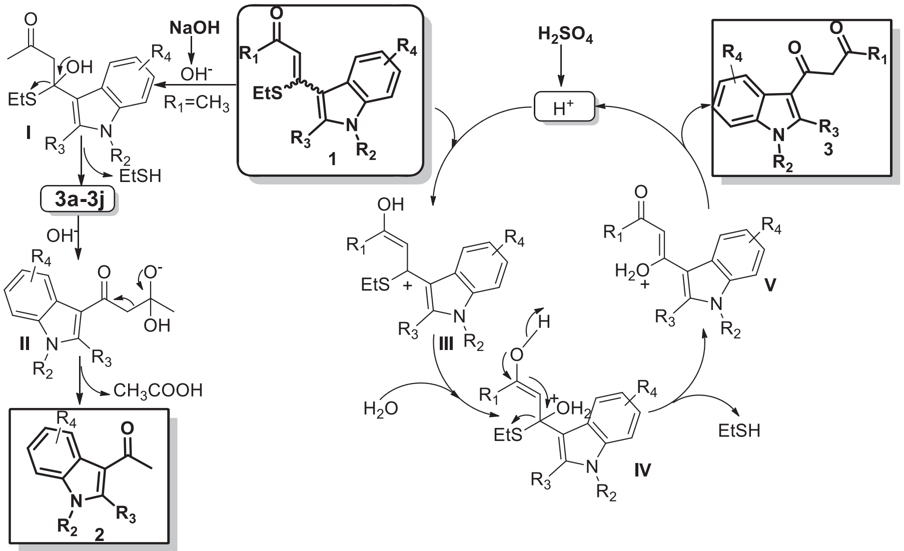
[b]Isolated yields.

[c]Keto/enol ratio of **3** determined by ^1H NMR.

[d]The reaction was carried out in the presence of 5 equiv. of NaOH for 30 h.

[e]The reaction was completed in the presence of 30 mol% of H_2SO_4 for 12 h.

With the optimized conditions in hand, we investigated the scope for the synthesis of both 3-acetylindoles **2** and 3-acetoacetylindoles **3**. The results were summarized in Table 2. The hydrolysis of 4-(ethylthio)-4-(indol-3-yl)but-3-en-2-one **1a**-**1f** proceeded smoothly to efficiently give corresponding 3-acetyl free (N-H) indoles **2** and 3-acetoacetyl free indoles **3** in excellent yields, respectively (Table 2, entries 1–12), and obviously the electronic effects of both electron-withdrawing and -donating substitutents at the 5-, 6- and 7-positions on the indole rings in **1** are insignicant to the hydrolysis reaction (Table 2, entries 2–12). However, the substitutents at the 2- positions on the indole rings in **1** showed a significant impact on the reaction due to the steric hindrance effect. The hydrolysis of 4-(ethylthio)-4- (2-methyl-1H-indol-3-yl)but-3-en-2-one **1 g** could efficiently performed to afford **2 g** or **3 g** in excellent yield by both prolonging reaction time and increasing the amount of catalysts (Table 2, entries 13–14). Similarly, 4-(1-alkyl-1H-indol-3-yl) -4-(ethylthio) but-3-en-2-ones **1h-1j** were also suitable for the hydrolysis, and corresponding 3-acytal N-substitued indoles **2h-2j** and 3-acetoacetyl N-substitued indoles **3h-3j** were obtained in excellent yields, respectively (Table 2, entries 15–20). Furthermore, we explored the reaction outcome of the hydrolysis reactions of 3-(ethylthio)-3- (indol-3-yl)-1–aryl prop-2-en-1-one **1k-1p** under condition B, and found that the reactions proceeded smoothly to offer corresponding 1-(indol-3-yl)-3-aryl propane- 1,3-dione **3k-3p** in excellent yields (Table 2, entries 21–26). It was worth noting that 3-acetoacetylindoles **3** were always obtained as the mixture of enol/keto isomers, and their molar ratios were determined by ^1H NMR. In general, the enol isomers of compounds **3** are in preference to their keto isomers, compound **3o** reaching the highest keto/enol ratio of 9:1(Table 2, Entry 25).



Scheme 2. Plausible Mechanism for the synthesis of compounds **2** and **3.**

On the basis of the reported work[14] and the obtained results, a possible reaction mechanism for the synthesis of both 3-acetylindoles **2** and 3-acetoacetylindoles **3** was proposed in Scheme 2.

In the presence of NaOH, Michael addition of **1** (R_1=CH_3) initially occured with the formation of adduct **I**, which is transformed into 3-acetoacetylindoles **3a-3j** by elimination of ethanethiol. Then, 3-acetylindoles **2** were obtained from the NaOH promoted the deacetylation of **3** by intermediate **II**. In the presence of H_2SO_4, **1** formed the carbocation **III** by the combination of **1** with H^+. Subsequently, nucleophilic attack at the cationic carbon atom of **III** by H_2O lead to the formation of intermediate **IV**, which converted into the intermediate **V** after the removal of thiol. Finally, 3-acetoacetylindoles **3** were yielded after the elimination of H^+ of intermediate **V**. The released H^+ further completes the catalytic cycle.

In summary, very first time we have developed a novel and efficient route to selectively generate 3-acetylindoles **2** and 3-acetoacetylindoles **3** from the NaOH-mediated and H_2SO_4 catalyzed hydrolysis reaction of readily available β-ethyltho-β-indolyl α, β-unsaturated ketones **1,** respectively. 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 13C{^{1}H} NMR spectra were recorded on a Bruker DRX-600 spectrometer and all chemical shift values refer to TMS = 0.00 ppm or $CDCl_3$ ((^{1}H), 7.26 ppm; (^{13}C), 77.16 ppm). The HRMS analysis was achieved on Bruck microTof by using ESI method. All the melting points were uncorrected. Analytical TLC plates, Sigma-Aldrich silica gel

60F200 were viewed by UV light (254 nm). Chromatogr-aphic purifications were performed on SDZF silica gel 160.

Typical procedure for the preparation of 3-acetyl-indoles 2: synthesis of 2a

The mixture of 4-(ethylthio)-4-(1H-indol-3-yl)but-3-en-2-one **1a** (61.3 mg, 0.25 mmol), NaOH (30 mg, 0.75 mmol) in 95% of EtOH (1 mL) was stirred in reflux for 18 h until **1a** was completely consumed by TLC monitoring. Water (20 mL) was then added to the reaction mixture, and 1-(1H-indol-3-yl)ethanone **2a** as a solid deposited from the reaction system. After filtered, the crude product **2a** was purified by flash silica gel chromatography (petroleum ether (60–90 °C)/acetic ether = 8:1, v/v) to give pure **2a** (37.4 mg, 94%) as a colorless crystal.«

Typical procedure for the preparation of 3-aceto-acetylindoles 3: synthesis of 3a

To a stirred solution of 4-(ethylthio)-4-(1H-indol-3-yl)but-3-en-2-one **1a** (61.3 mg, 0.25 mmol) and H_2O (0.2 mL) in acetonitrile (0.8 mL) was added H_2SO_4 (0.68 µL, 0.0125 mmol), and the resulting mixture was heated to reflux. When TLC monitoring on silica gel indicated complete consumption of **1a**, the mixture was cooled to ambient temperature, and solvent was evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography [eluent: petroleum ether (60—90 °C)/ AcOEt =10:1 v/v], affording 1-(1H-indol-3-yl) butane-1, 3-dione **3a** (48.2 mg, 96%) as a colorless crystal.

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