Base-Catalyzed Conjugate Addition of Thiols to Indolyl Acrylic Acids and in situ Decarboxylation: An Expedient Synthesis of Functionalized 3-(1-Thio)ethyl-1*H*-indoles

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Abstract: A one-pot, two-step method for the synthesis of 3-(1-thio)ethyl-1*H*-indoles is described herein. This simple procedure involves the Michael addition of thiols to 3-indoleacrylic acids followed by in situ decarboxylation of the Michael adduct in the presence of a catalytic amount of K_2CO_3 in DMF at 100 °C. The method was found to be fairly general with various thiols and different 3-indoleacrylic acids.

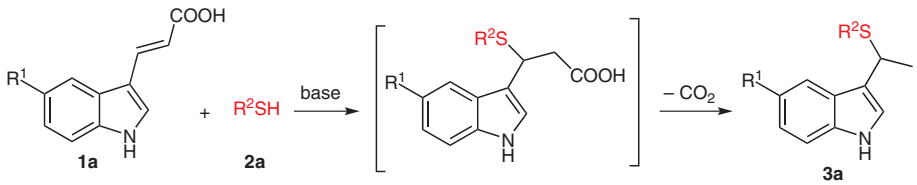
Key words: indole, thiol, conjugate addition, decarboxylation, 3-[1-(thio)ethyl]-1*H*-indole

Indole and many of its derivatives are most important structural units in many naturally occurring compounds as they possess a variety of pharmacological and biological properties.[1] The importance of indole is due to their use as key intermediates in the synthesis of numerous natural compounds, including uleine,[2] aspidospermidine,[3] ibophyllidine alkaloids,[4] and hapalindole alkaloids,[5] which exhibit significant antibacterial and antimycotic activity. In particular, 3-substituted indoles are versatile intermediates for the synthesis of a wide variety of indole scaffolds.[6] Owing to the synthetic importance, various methods were developed to introduce functionalized groups at the 3-position of indole. The most frequently employed procedure for the synthesis of 3-substituted indole derivatives include the Friedel–Crafts/Michael-type reaction of indoles with α,β-unsaturated systems employing an array of catalysts or reagents.[7]

Organosulfur compounds play an important role in organic synthesis due to the ease of incorporation of the element into complex structures and the ability to modify the oxidation state of the atom.[8] Therefore, the interconversion of one oxidation state to another is the crucial aspect of the successful use of sulfur in synthetic applications.[9] The fused heterocyclic system containing both thiol and indole moieties are found to exhibit biological activity.[10] Moreover, indolyl aryl sulfones act as resistant against HIV-1 carrying NNRTI resistance mutations.[11]

In general, the elimination of CO_2 (decarboxylation) from the carboxylic acids is difficult and often requires harsh and forcing conditions, such as high pressures or temperatures,[12] except for some activated acids such as β-carbonyl acetic acids. However, the decarboxylation of α-amino acids is a well-known reaction, and this strategy is employed for the decarboxylation of tryptophan towards the synthesis of tryptamine which is the potential compound for the synthesis of indole alkaloids.[13] In continuation of our research work on indoles[14] and thiols[15] we were interested to study the Michael addition of thiols to 3-indoleacrylic acids and interestingly found that Michael addition was followed by in situ decarboxylation. Hence, we have developed a one-pot, two-step reaction for the synthesis of 3-[1-(thio)ethyl]-1*H*-indoles from thiols and 3-indoleacrylic acids catalyzed by base in good to excellent yields (Scheme 1).

Preliminary investigation was mainly focused on the evaluation of various inorganic bases including NaOH, KOH, Na_2CO_3, and K_2CO_3. All of these bases were found to be effective for alkylation of thiols (entries 2–5, Table 1). Among them, K_2CO_3 was found to be the best choice of base for the alkylation of thiol with 3-indoleacrylic acid (entry 5, Table 1). Similarly, the effect of various solvents was examined in conjunction with K_2CO_3. Trace amount of the desired product was obtained in toluene (entry 6), and no detectable product was observed with EtOH, CH_2Cl_2, THF, and Et_2O (entries 7–10, Table 1). With DMF as the solvent, product yields were high which may be due to the high solvating property of DMF. According



Scheme 1 Synthesis of 3-[1-(thio)ethyl]-1*H*-indoles via conjugate addition and in situ decarboxylation; for R^1 and R^2, see Tables 2 and 3

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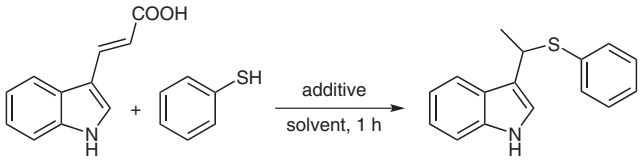
to Table 1, the best yield of the 3-[1-(thio)ethyl]-1*H*-indole was obtained with K_2CO_3 (20 mol%) in DMF at 100 °C (entry 5, Table 1).

To further explore the scope and limitations of this methodology, we tested the alkylation reaction of various thiols with 3-indoleacrylic acid (Table 2). As can be seen from Table 2, alkylation of various aryl and alkyl thiols proceeded well with 3-indoleacrylic acid to afford the corresponding 3-[1-(thio)ethyl]-1*H*-indoles in moderate to excellent yields. Excellent yield was obtained with thiophenol (entry 1, Table 2). Other than thiophenol, various substituted aromatic thiols containing electron-donating or -withdrawing groups proceeded well to give the corresponding alkylated products in good yields. Moreover, the Michael addition of 3-indoleacrylic acid with thiols containing electron-withdrawing groups required shorter reaction times compared to the reaction of thiols with electron-donating groups.

Table 1 Reaction of 3-Indoleacrylic Acid with Thiolphenol under Different Reaction Conditions[a]

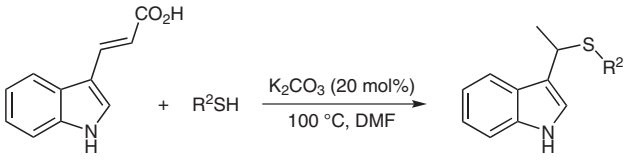


Entry	Additive	Solvent	Temp (°C)	Yield of **3a** (%)[b]
1	none	DMF	100	4
2	NaOH	DMF	100	77
3	KOH	DMF	100	79
4	Na_2CO_3	DMF	100	83
5	K_2CO_3	DMF	100	93
6	K_2CO_3	toluene	100	trace
7	K_2CO_3	EtOH	reflux	0[c]
8	K_2CO_3	CH_2Cl_2	reflux	0[c]
9	K_2CO_3	THF	reflux	0[c]
10	K_2CO_3	Et_2O	reflux	0[c]

[a] Conditions: **1a** (1 mmol), **2a** (1.5 mmol), additive (20 mol%), solvent (1 mL).
[b] NMR yield.
[c] No reaction.

This can be attributed to differences in acidity between the various thiols (entries 2 and 9, 13 and 14, Table 2). Michael addition of 3-indoleacrylic acid with thiols was controlled by the steric factors of the reactant thiol partner. For example, addition of 3-indoleacrylic acid with *para*-substituted thiophenols occurred with high efficiency in short reaction times (entries 2, 8, 9, and 11), whereas *ortho*-substituted thiophenols required longer reaction times for the respective alkylation (entries 3 and 5). Sterically hindered reactants such as naphthalene thiols (entries 6 and 7) also reacted well under these reaction conditions. In general, aromatic thiols are less reactive than aliphatic thiols, because the aromatic thiolate ion is more resonance-stabilized than the aliphatic thiolate ion. In contrast, we observed that aliphatic thiols undergo Michael addition in longer reaction times (entries 13 and 14, Table 2).

Table 2 Michael Addition of 3-Indoleacrylic Acid with Various Thiols Catalyzed by K_2CO_3[a]



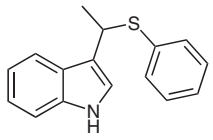
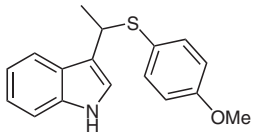
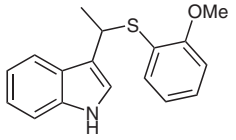
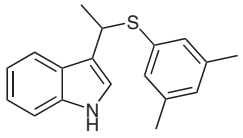
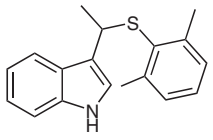
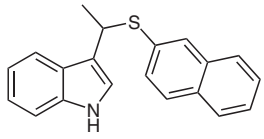
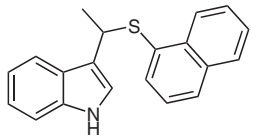
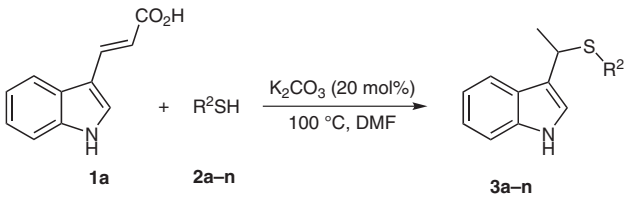
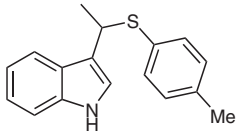
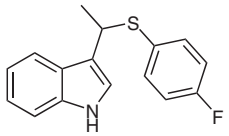
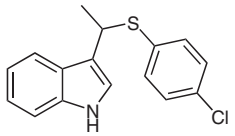
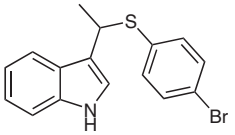
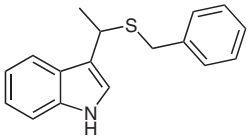
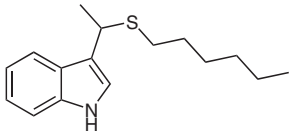
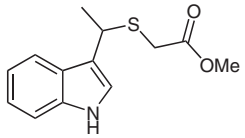
Entry	Product **3**[16]	Time (h)	Yield (%)[b]
1	 **3a**	1	93
2	 **3b**	1.5	91
3	 **3c**	3	88
4	 **3d**	1	90
5	 **3e**	3	86
6	 **3f**	1.5	91
7	 **3g**	3.5	94

Table 2 Michael Addition of 3-Indoleacrylic Acid with Various Thiols Catalyzed by K_2CO_3[a] (continued)



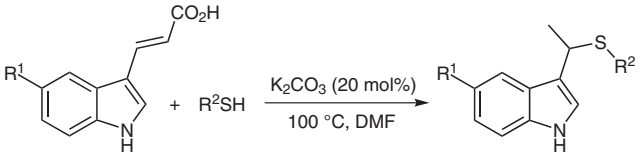
1a **2a–n** **3a–n**

Entry	Product **3**[16]	Time (h)	Yield (%)[b]
8	 **3h**	1.5	90
9	 **3i**	1	92
10	 **3j**	0.6	90
11	 **3k**	0.6	91
12	 **3l**	2	63
13	 **3m**	10	54
14	 **3n**	8	71

[a] Conditions: **1** (1 mmol), **2** (1.5 mmol), K_2CO_3 (20 mol%), DMF (1 mL), 100 °C.
[b] Isolated yield.

Similarly, the alkylation of various thiols was examined with structurally divergent 3-indoleacrylic acid derivatives, and the results are shown in Table 3. The results demonstrated that 3-indoleacrylic acid containing electron-withdrawing groups (Cl and Br, entries 1–9, Table 3) reacted faster with higher yields, whereas alkylation of 3-indoleacrylic acid containing electron-donating groups was sluggish and showed a marginal decline in the yield (entry 10, Table 3).

Table 3 Reaction of Different 3-Indoleacrylic Acids with Various Thiols Catalyzed by K_2CO_3[a]



1b R^1 = Br
1c R^1 = Cl
1d R^1 = Me

2a,**b**,**f**,**j**–**l** **4a–j**

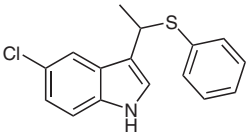
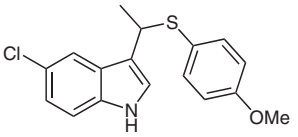
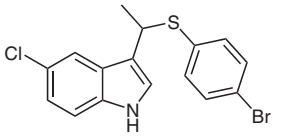
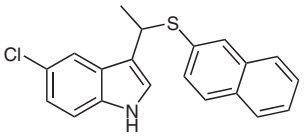
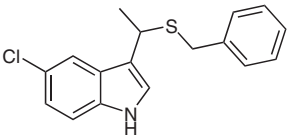
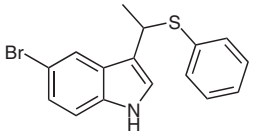
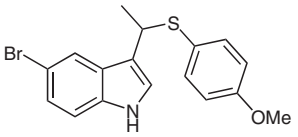
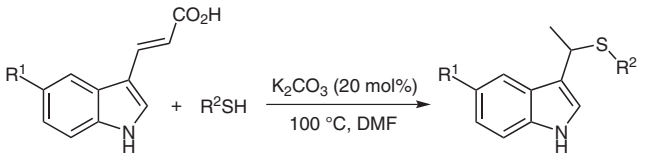
Entry	Product **4**[16]	Time (h)	Yield (%)[b]
1	 **4a**	1.5	94
2	 **4b**	1	87
3	 **4c**	1	95
4	 **4d**	0.3	90
5	 **4e**	0.5	34
6	 **4f**	2.5	82
7	 **4g**	13	91

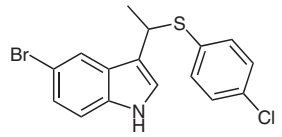
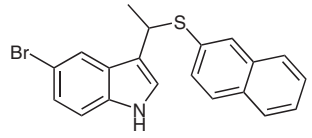
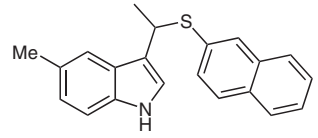
Table 3 Reaction of Different 3-Indoleacrylic Acids with Various Thiols Catalyzed by K_2CO_3[a] (continued)



1b R^1 = Br
1c R^1 = Cl
1d R^1 = Me

2a,**b**,**f**,**j**–**l**

4a–**j**

Entry	Product **4**[16]	Time (h)	Yield (%)[b]
8	 **4h**	3.5	94
9	 **4i**	0.5	89
10	 **4j**	0.6	71

[a] Conditions: **1** (1 mmol), **2** (1.5 mmol), K_2CO_3 (20 mol%), DMF (1 mL), 100 °C.
[b] Isolated yield.

The study was also extended to probe the alkylation of thiophenol with 3-indole-2-phenylacrylic acids (Scheme 2). Michael addition of 3-indolylacrylic acid containing α-substituted anisole (**5a**) with thiophenol required longer reaction times to afford the Michael adduct in moderate yields. On the other hand, 4-chlorophenyl-3-(1*H*-indol-3-yl)acrylic acid (**5b**) proceeded relatively in shorter reaction time with high yields of Michael addition product (**6b**). This may be due to the presence of electron-withdrawing 4-ClC_6H_4 in the α-position of 3-indolylacrylic acid that makes it more electrophilic (**5b**), which favors the nucleophilic attack of the incoming thiolate ion.

In summary, we have developed a tandem Michael addition–decarboxylation reaction for the synthesis of 3-[1-(thio)ethyl]-1*H*-indoles catalyzed by K_2CO_3. Notably, we have demonstrated that the present protocol is equally facile with various substituted thiols and structurally divergent 3-indoleacrylic acids. The cheap and commercially available catalyst, the simple procedure, and the mild conditions make this method potentially useful in organic synthesis.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

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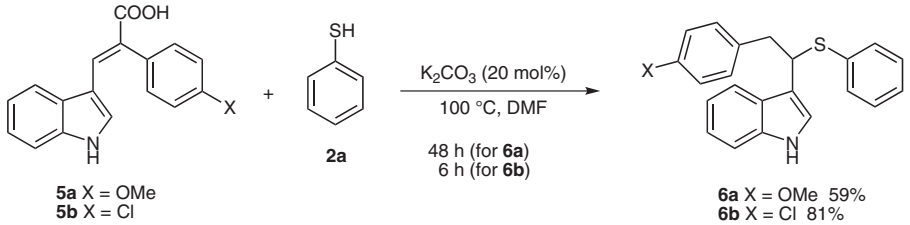

5a X = OMe
5b X = Cl

6a X = OMe 59%
6b X = Cl 81%

Scheme 2 The reaction of α-substituted 3-(1*H*-indol-3-yl)-2-phenylacrylic acids with thiophenols

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(16) **Typical Procedure for the Synthesis of 3-[1-(Phenylthio)ethyl]-1*H*-indole (3a)**

A mixture containing 3-indoleacrylic acid (187 mg, 1 mmol), thiophenol (165 mg, 1.5 mmol), and K_2CO_3 (27 mg, 0.2 mmol) in DMF (1 mL) was stirred at 100 °C for 1 h (monitored by TLC). After completion of the reaction, the mixture was poured into an ice-cold dilute HCl (aq) solution and the solution then extracted with CH_2Cl_2 (3 × 25 mL). The CH_2Cl_2 layers were washed with brine and dried over anhyd $MgSO_4$. After evaporation of the organic solvent, the crude product was purified by flash column chromatography, to afford 3-[1-(phenylthio)ethyl]-1*H*-indole (**3a**, 258 mg, 98% isolated yield). Colorless solid; mp 86–88 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (s, 1 H), 7.82 (d, *J* = 7.8 Hz, 1 H), 7.36–7.33 (m, 3 H), 7.25–7.14 (m, 5 H), 7.03 (d, *J* = 2.4 Hz, 1 H), 4.71 (q, *J* = 7.0 Hz, 1 H), 1.75 (d, *J* = 7 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.7, 135.9, 132.6, 128.8, 127.0, 126.3, 122.5, 122.0, 119.9, 119.7, 118.2, 111.4, 40.3, 22.1. HRMS: *m/z* calcd for $C_{16}H_{15}NS$ [M$^+$]: 253.0925; found: 253.0919.

3-[1-(4-Methoxyphenylthio)ethyl]-1*H*-indole (3b)

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (s, 1 H), 7.83 (d, *J* = 7.8 Hz, 1 H), 7.33 (d, *J* = 8.0 Hz, 1 H), 7.25 (d, *J* = 8.3 Hz, 2 H), 7.21 (t, *J* = 7.5 Hz, 1 H), 7.15 (t, *J* = 7.4 Hz, 1 H), 6.91 (d, *J* = 2.1 Hz, 1 H), 6.76 (d, *J* = 8.6 Hz, 2 H), 4.53 (q, *J* = 7.0 Hz, 1 H), 3.77 (s, 3 H) 1.69 (d, *J* = 7.0 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.7, 136.7, 136.3, 126.3, 125.8, 122.4, 121.9, 120.1, 119.7, 118.3, 114.3, 111.4, 55.5, 41.4, 21.8. HRMS: *m/z* calcd for $C_{17}H_{17}NOS$ [M$^+$]: 283.1031; found: 283.1035.

5-Chloro-3-[1-(phenylthio)ethyl]-1*H*-indole (4a)

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (s, 1 H), 7.76 (d, *J* = 1.8 Hz, 1 H), 7.34–7.31 (m, 2 H), 7.28–7.21 (m, 4 H), 7.16 (dd, *J* = 8.6, 1.9 Hz, 1 H), 7.04 (d, *J* = 2.4 Hz, 1 H), 4.63 (q, *J* = 7.0 Hz, 1 H), 1.73 (d, *J* = 7.0 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.5, 135.0, 132.9, 128.9, 127.4, 127.3, 125.6, 123.3, 122.9, 119.5, 118.2, 112.4, 40.1, 21.9. HRMS: *m/z* calcd for $C_{16}H_{14}ClNS$ [M$^+$]: 287.0535; found: 287.0533.