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# Sulfamic acid as a cost-effective and recyclable solid acid catalyst for Friedel–Crafts alkylation of indole with $\alpha,\beta$-unsaturated carbonyl compound and benzyl alcohol

Jing Yang [a], Juan Zhang [a], Tian Tian Chen [b], De Mei Sun [a], Ji Li [c], Xue Fen Wu [a,*]

[a] *Henan University of Traditional Chinese Medicine, Zhengzhou 450008, China*
[b] *Henan Chemical Industry Research Institute Co., Ltd., Zhengzhou 450052, China*
[c] *Institute of Chemistry, Henan Academy of Science, Zhengzhou 450002, China*

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## Abstract

Sulfamic acid was proved to be a cost-effective and recyclable catalyst for Friedel–Crafts type reaction of indole with $\alpha,\beta$-unsaturated carbonyl compound and benzyl alcohol. Various indoles, $\alpha,\beta$-unsaturated carbonyl compounds and a benzyl alcohol were successfully used in this type of reaction, and the corresponding products were obtained in good to excellent yields.

*Keywords:* Sulfamic acid; Michael reaction of indole; Acid catalysis; Alkylation of indole with benzyl alcohol

Recently, the development of new and efficient transformations of heterocyclic compounds into several derivatives has attracted much attention in organic synthesis [1]. The Michael reaction of indoles with $\alpha,\beta$-unsaturated carbonyl compounds provides easy access to 3-substituted indoles, which are important building blocks for the synthesis of biologically important compounds and natural products. Several Lewis acids were found to catalyze the conjugate addition of heterocyclic compounds to electron deficient olefins, such as Bi [2], In [3], Yb [4], Sc [5], Cu [6] and Au salts [7]. In view of the fact that 3-substituted indoles are generally used in pharmaceutical synthesis, therefore potential contaminations of metal species to the products have to be considered when the reactions were applied in a practical synthesis. For this purpose, many organocatalysts were used as alternative catalysts, such as triflic acid [8], $I_2$ [9], cyanuric chloride [10], ionic liquid [11], and tetrabutylammonium hydrogen sulfate (TBAHS) [12]. However, recovery of these homogeneous catalysts is generally not easy. In order to overcome this problem, some solid acids, such as clay [13] and sulfonated amorphous carbon [14], were also examined. Although promising results were obtained in these cases, in order to further improve the synthetic efficiency and facilitate the recovery of the catalyst, an eco-friendly and a cost-effective catalyst system that enables selective formation of the desired product and easy recovery of the catalyst is still appealingly needed.

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[*] Corresponding author.
*E-mail address:* xfwwxf@163.com (X.F. Wu).

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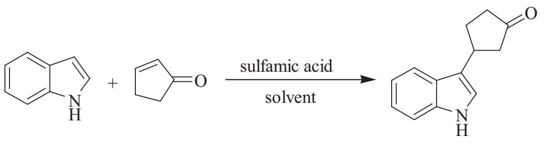
Sulfamic acid ($H_2NSO_3H$) is a common inorganic acid with mild acidity that is nonvolatile, noncorrosive, and utilized as a stable, low cost, highly efficient green catalyst in organic synthesis [15]. Sulfamic acid has also been used in Michael addition of indoles to electron-deficient nitroolefins [16]. However, there are no reports of using sulfamic acid as a catalyst for Friedel–Crafts alkylation of indole with $\alpha,\beta$-unsaturated carbonyl compound. Herein, we report a sulfamic acid-catalyzed Friedel–Crafts alkylation of indoles with two kinds of electrophiles including $\alpha,\beta$-unsaturated carbonyl compound and benzyl alcohol. Particularly, Friedel–Crafts alkylation reaction of indole with benzyl alcohol catalyzed by sulfamic acid has not been reported yet.

Initially, sulfamic acid was used as a catalyst in a Michael reaction of indole **1a** with cyclopent-2-enone **2a** [17]. As shown in Table 1, 15 mmol% of sulfamic acid is sufficient enough for catalyzing the model reaction toward completion (entries 1 and 2). Among all the solvents examined, acetonitrile was found to be the best, and after 8 h of reaction in this solvent, a maximum yield of **3a**, 89%, was obtained (entries 3–7). With a shortened reaction time, 4 h, the yield of **3a** decreased to 68% (entry 8). At lower temperature, 50 °C, the yield obtained is rather poor. It should be noted that a solid could be observed after cooling the reaction system from 80 °C to room temperature (15 °C). After filtration and washing, the solid could be recovered. Following measurement of melting point revealed that the obtained solid is sulfamic acid. We thus examined the performance of the recovered sulfamic acid in the model reaction. In order to facilitate recycling of sulfamic acid, in this case, the reaction was performed in a large scale (10 mmol). As we expected, the yield of **3a** remains unchanged, and therefore, the catalyst here is, indeed, recyclable. With this experiment, the applicability of this method for practical synthesis was also well elucidated.

The substrate scope with respect to both indole and $\alpha,\beta$-unsaturated carbonyl compound was then examined. As shown in Table 2, when **2a** was used as electrophile, various indoles could be used in the sulfamic acid system, and the corresponding adducts were obtained in generally high yields. Particularly, functional groups, such as methoxy and nitrile, which are generally unstable under strongly acidic condition, were also proved to be applicable in this reaction. The scope of the reaction with respect to $\alpha,\beta$-unsaturated compound was next investigated and also found to be excellent. As Table 3 illustrates, many $\alpha,\beta$-unsaturated ketones could be employed without significantly affecting the yield of the Michael adduct. Particularly, $\alpha,\beta$-unsaturated ketones containing sulfur- or oxygen-heterocycle functionalities were also applied in the reaction uneventfully (entries 4 and 5). However, a limitation was found when using $\alpha,\beta$-unsaturated ester as substrate (Table 3, entry 8).

Encouraged by the promising results obtained in Michael reaction of indole, we then tried to extend the catalytic system to the other Friedel–Crafts type reaction. Recently, alkylation reactions of indoles with benzyl alcohols have been extensively investigated [18]. Although various acid catalysts were proved to be effective for this type of reaction [19], alkylation reaction of indole with benzyl alcohol catalyzed by sulfamic acid has not been reported yet. We thus

Table 1
Sulfamic acid-catalyzed Michael reaction of indole with cyclopent-2-enone.[a]

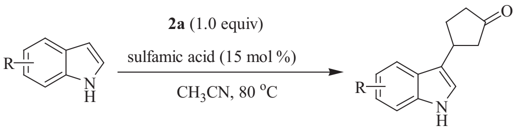


| Entry | Catalyst amount (mol%) | Solvent | Time (h) | Temperature (°C) | Yield (%) |
|---|---|---|---|---|---|
| 1 | 10 | $CH_3CN$ | 8 | 80 | 74 |
| 2 | 15 | $CH_3CN$ | 8 | 80 | 89 |
| 3 | 15 | 1,4-Dioxane | 8 | 80 | 63 |
| 4 | 15 | DCE | 8 | 80 | 48 |
| 5 | 15 | Toluene | 8 | 80 | 12 |
| 6 | 15 | DMF | 8 | 80 | 17 |
| 7 | 15 | DMSO | 8 | 80 | 35 |
| 8 | 15 | $CH_3CN$ | 4 | 80 | 68 |
| 9 | 15 | $CH_3CN$ | 8 | 50 | 41 |
| 10[b] | 15 | $CH_3CN$ | 8 | 80 | 89 |

[a] Solvent: 1.0 mL, **1a**: 1.0 mmol, **2a**: 1.0 mmol.

[b] The reaction scale: 10 mmol, and sulfamic acid was used in the second run.

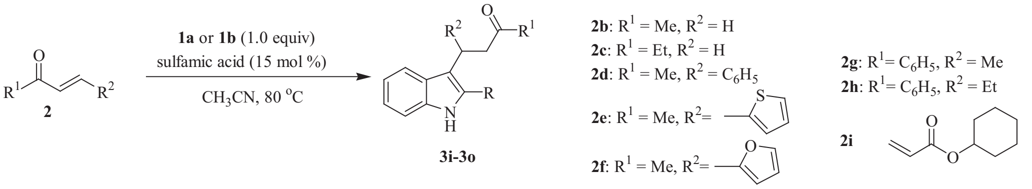
Table 2
Substrate scope for indoles.[a]



| Entry | Indole | | Product | Time (h) | Yield (%) |
|---|---|---|---|---|---|
| 1 | 2-Methylindole | **1b** | **3b** | 6 | 91 |
| 2 | 5-Bromoindole | **1c** | **3c** | 10 | 86 |
| 3 | 5-Methoxyindole | **1d** | **3d** | 10 | 92 |
| 4 | 1-Methylindole | **1e** | **3e** | 8 | 97 |
| 5 | 6-Fluoroindole | **1f** | **3f** | 8 | 83 |
| 6 | 2-Methyl-5-mothoxyindole | **1g** | **3g** | 8 | 95 |
| 7 | 5-Cyanoindole | **1h** | **3h** | 8 | 77 |

[a] Acetonitrile: 1.0 mL, indole: 1.0 mmol, **2a**: 1.0 mmol.

Table 3
Substrate scope for $\alpha,\beta$-unsaturated compound.[a]

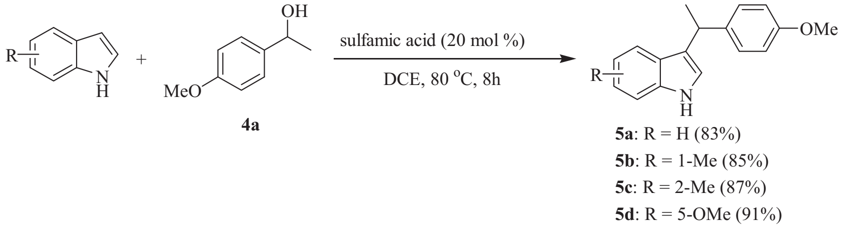


| Entry | $\alpha,\beta$-Unsaturated compound | Indole | Product | Time (h) | Yield (%) |
|---|---|---|---|---|---|
| 1 | **2b** | **1a** | **3i** | 6 | 94 |
| 2 | **2c** | **1a** | **3j** | 6 | 96 |
| 3 | **2d** | **1b** | **3k** | 8 | 92 |
| 4 | **2e** | **1b** | **3l** | 8 | 81 |
| 5 | **2f** | **1b** | **3m** | 8 | 76 |
| 6 | **2g** | **1a** | **3n** | 8 | 90 |
| 7 | **2h** | **1a** | **3o** | 10 | 82 |
| 8 | **2i** | **1a** | – | 20 | 0 |

[a] Acetonitrile: 1.0 mL, indole: 1.0 mmol, $\alpha,\beta$-unsaturated compound: 1.0 mmol.

investigated the feasibility of using sulfamic acid as a catalyst for this reaction. As shown in Scheme 1, the reactions of indoles with a benzyl alcohol, 1-(4-methoxyphenyl)-1-ethanol **4a**, proceeded very well, and the corresponding alkylation products were obtained in good to excellent yields. These results indicated again that sulfamic acid is an effective catalyst for promoting Friedel–Crafts type reactions of indoles.

*Spectroscopic data of selected product (**5d**): 3-[1-(4-methoxyphenyl)ethyl]-5-methoxy-1H-indole:* Red oil, $^1H$ NMR (acetone-$d_6$): 1.62 (d, 3H, $J = 7.2$ Hz), 3.67 (s, 3H), 3.74 (s, 3H), 4.25 (q, 1H, $J = 7.2$ Hz), 6.71 (dd, 1H,



Scheme 1. Friedel–Crafts alkylation of indoles with **4a** catalyzed by sulfamic acid.

$J_a = 2.8$ Hz, $J_b = 8.8$ Hz), 6.76–6.82 (m, 3H), 7.12 (d, 1H, $J = 1.6$ Hz), 7.21–7.29 (m, 3H), 9.82 (bs, 1H); $^{13}$C NMR (acetone-$d_6$): 22.0, 36.1, 54.7, 55.0, 101.5, 111.3, 111.8, 113.6, 120.4, 122.3, 127.6, 128.3, 132.5, 139.7, 153.5, 157.9; IR (cm$^{-1}$): 3028, 2961, 2930, 2831, 1714, 1609, 1582, 1512, 1457, 1247, 1178, 922, 836, 799; HRMS *m/z* (ESI) calcd. for $C_{18}H_{19}NNaO_2$ [M+Na]$^+$ 304.1313, found 304.1306.

In conclusion, sulfamic acid was proved to be a cost-effective and recyclable catalyst for Friedel–Crafts type reaction of indole with $\alpha,\beta$-unsaturated ketone and benzyl alcohol. Many substrates could be used in these reactions, and the corresponding products were obtained in good to excellent yields.

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