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Tetrahedron Letters 48 (2007) 4297–4300

Tetrahedron Letters

Sulfamic acid-catalyzed Michael addition of indoles and pyrrole to electron-deficient nitroolefins under solvent-free condition

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Received 4 January 2007; revised 3 April 2007; accepted 4 April 2007
Available online 11 April 2007

Abstract—Sulfamic acid (SA) effectively catalyze the Michael addition of indoles and pyrrole to nitroolefins under solvent-free condition to afford the corresponding Michael adducts in good to excellent yields.

Michael reaction is one of the most important carbon–carbon bond-forming reactions.[1] Among the Michael acceptors, nitroolefins are very attractive, since the nitro moiety is a strong electron-withdrawing group that can be readily transformed into a range of different functionalities,[2] which lead to important building blocks and products.[3] Till date, a great deal of catalysts were used to catalyze the Michael addition of indoles to nitroalkenes, however, most of them were Lewis acids.[4,5] In recent years, small organic molecules such as thiourea were found to catalyze the above-mentioned reaction.[6] Although many catalysts catalyzed for the alkylations of indoles have been already described in the literature, they were mainly focused on the (Michael) addition reactions of indoles to carbonyls. With the corresponding solid-base[7] and solid-acid[8] catalyzed 1,4-addition to α,β-unsaturated compounds were remarkably less explored. Herein, we report sulfamic acid (SA)[9] which effectively catalyze Michael addition of indoles and pyrrole to nitroolefins under solvent-free condition to afford the corresponding Michael adducts in good to excellent yields.

Table 1. The solvent effect on Michael addition of indole to β-nitrostyrene[a]

Entry	Solvent	Temperature (°C)	Reaction time (h)	Yield[b] (%)
1	MeOH	20	12	85
2	MeOH	65	4	92
3	CH_2Cl_2	40	12	78
4	C_2H_5OH	78	7	90
5	Solvent-free	60	0.5	96

[a] Reaction condition: indole 1 mmol, β-nitrostyrene 1.1 mmol, SA 0.01 g (10 mol %).
[b] Isolated yield.

In our initial study, indole was first reacted with β-nitrostyrene in methanol at 20 °C for 12 h, the expected product was obtained in 85% yield (Table 1, entry 1). To improve the yield, the same reaction was performed in refluxing methanol, which increased the yield to 92% (Scheme 1, Table 1, entry 2). Furthermore, to know the effect of solvent, CH_2Cl_2 and ethanol were used, the reaction resulted in less yields than that of methanol (Table 1, entries 3 and 4). Finally the reaction was carried out under solvent-free condition; interestingly, it was completed in 0.5 h and afforded the product in excellent yield (96%) (Table 1, entry 5).[10] The acceleration effect was probably attributed to the concentration effect.[11]

The optimized procedure for Michael addition of indole to nitroolefin was found to be as follows: the mixture of indole (1 mmol), nitroolefin (1.1 mmol) and SA (sulfamic acid, 0.1 mmol) was heated at 60 °C. The optimized procedure was used for the reaction of different indoles with β-nitrostyrenes, and the exclusive 3-substituted indole derivatives **3a**–**k** were obtained in good to excellent yields (Scheme 2, Table 2, entries 1–11). Their structures were confirmed by NMR, MS spectral data and X-ray analysis of **3j** (Fig. 1).[12,13]As seen in Table 2, the indole bearing Br group resulted in a lower yield, and needed a

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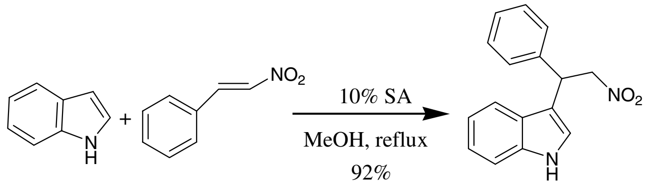
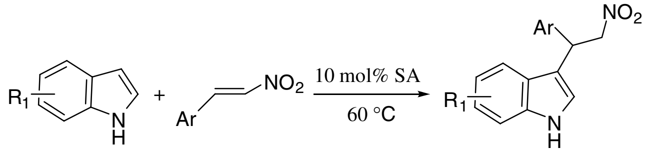
doi:10.1016/j.tetlet.2007.04.011



Scheme 1.



Scheme 2.

longer reaction time (Table 2, entry 2). In contrast, the indole bearing methyl group at the 2- and 4-position, afforded the corresponding products in excellent yield (Table 2, entries 3 and 4). In the case of 4-(benzyloxy)-1*H*-indole, the yield was slightly lower (Table 2, entry 5), which was probably attributed to the steric effect of the benzyloxy group. This reaction also tolerated different substituents such as dimethyl-amino, methoxy group at the phenyl ring in β-nitrostyrenes (Table 2, entries 6, 10, 11). Using 2-nitrovinyl furan derived from 2-furaldehyde instead of β-nitrostyrene, the similar product **3g** was obtained (Table 2, entry 7). On the basis of the results obtained, the reaction was extended to pyrrole, and found that SA can also efficiently catalyze the reaction of pyrrole with different β-nitrostyrenes, affording 2-substituted pyrrole derivatives in good to excellent yields (Scheme 3, Table 2, entries 12–14).

Table 2. Michael addition of indoles and pyrrole to nitroolefins catalyzed by SA under solvent-free condition

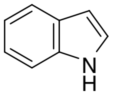
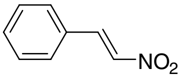
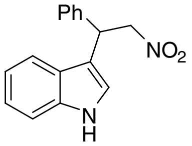
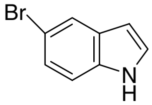
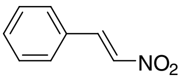
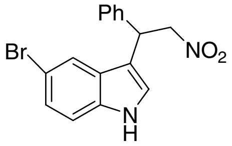
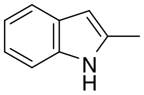
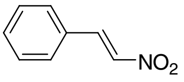
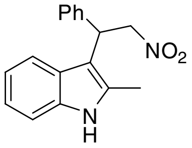
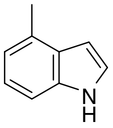
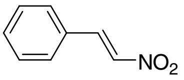
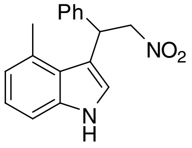
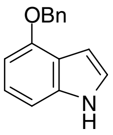
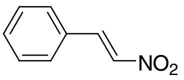
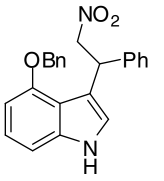
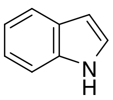
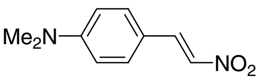
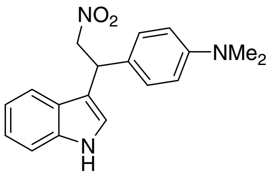
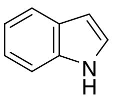
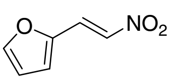
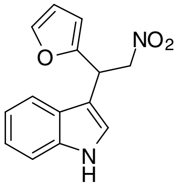
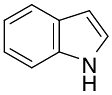
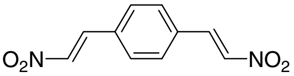
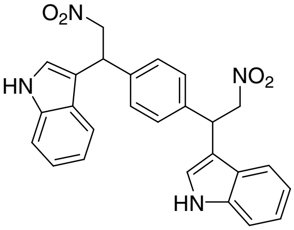
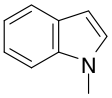
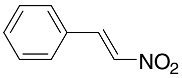
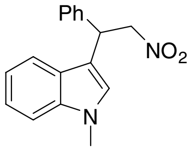
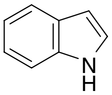
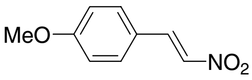
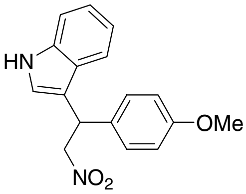
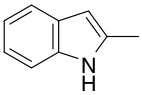
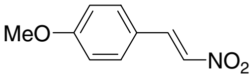
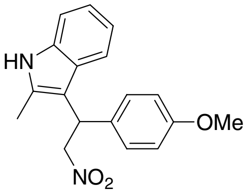
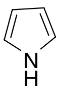
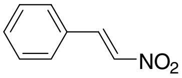
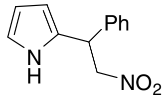
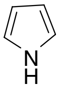
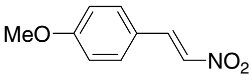
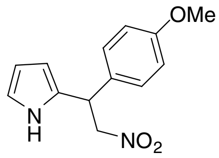
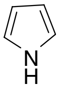
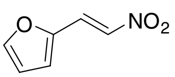
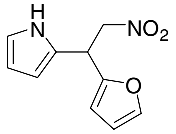
Entry	Indole (or pyrrole)	Nitroolefin	Product	Product no.	Time (h)	Yield[a] (%)
1				**3a**	0.5	96
2				**3b**	3	81
3				**3c**	0.5	99
4				**3d**	0.5	92
5				**3e**	1	87
6				**3f**	4	85
7				**3g**	0.5	90

Table 2 (*continued*)

Entry	Indole (or pyrrole)	Nitroolefin	Product	Product no.	Time (h)	Yield[a] (%)
8				**3h**	2	80
9				**3i**	4	87
10				**3j**	0.5	95
11				**3k**	0.5	90
12				**3l**	6	83
13				**3m**	4	91
14				**3n**	4	95

[a] Isolated yield.

It is known that the 3-position of the indole is the preferred site for electrophilic attack. In the presence of SA, the electrophilic attack uniquely occurred at the 3-position of the indole ring (Table 2, entries 1–11), showing that the SA catalyzed Michael addition had a good regioselectivity. As anticipated if the 3-position was occupied, the reaction could not proceed. In our experiments, 3-carbaldehyde indole, 3-cyanoindole and 3-hydroxymethylindole were used for the reaction; they all remained intact with β-nitrostyrene under given condition even after 12 h. In addition, substituents at the 1-position could affect the reaction, 1-methylindole could react with β-nitrostyrene to afford the expected product (Table 2, entry 9); however, *N*-Boc and *N*-Ts indole could not work at all under the same condition. This could be attributed to the electron-withdrawing of Boc and Ts groups, which deactivated the indole ring. The Michael addition of pyrrole to nitroolefins catalyzed by SA exclusively resulted in 2-substituted pyrrole derivatives (Table 2, entries 12–14), which also showed good regioselectivity of pyrrole at the 2-position.[6d]

In conclusion, we have developed a novel efficient and cost-effective method for Michael addition of indoles and pyrrole to nitroolefins catalyzed by SA. This method has advantages such as mild condition, high yields, short reaction time, and is a green method for the synthesis of important 3-substituted indole derivatives and 2-substituted pyrrole derivatives.

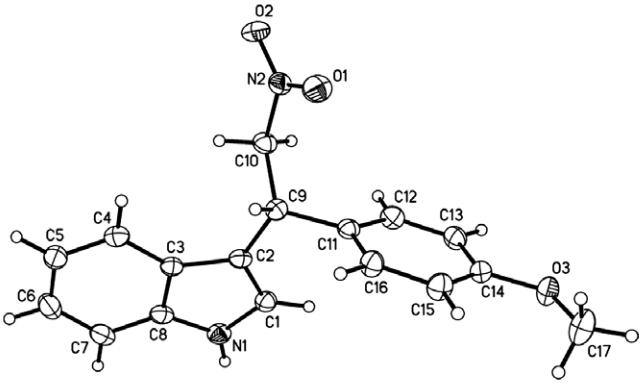
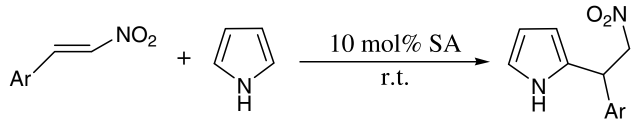


Figure 1. X-ray analysis of compound **3j**.



Scheme 3.

Acknowledgements

We thank the Key Laboratory of Organic Synthesis of Jiangsu Province and Suzhou Scientific Committee for financial supports (JSK016 and SG 0219).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.04.011.

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10. General procedure for synthesis of compound **3a**: Indole 0.12 g (1 mmol), β-nitrostyrene (1.1 mmol) and SA (Sulfamic acid) 0.01 g (0.1 mmol) were mixed, followed by heating at 60 °C. After the completion of the reaction monitored by TLC (about 30 min), the mixture was subjected to short column chromatography (acetone–petroleum ether 1:8 as eluent) to give pure **3a**. Brown solid, mp 97–99 °C, ^1H NMR ($CDCl_3$, 300 MHz): δ 4.88–5.20 (m, 3H, $CHCH_2NO_2$), 6.97 (s, 1H, C=CH), 7.04–7.44 (m, 9H, ArH), 8.06 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 42.0, 80.0, 111.9, 114.8, 119.4, 120.4, 122.1, 123.1, 126.5, 128.0, 128.2, 129.4, 136.9, 139.6. HRMS: calcd for $C_{16}H_{14}N_2O_2$ 266.1055, found 266.1055.
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12. X-ray data for **3j** have been deposited at the Cambridge Crystallographic Data Centre, deposition number CCDC 630885. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk). Crystal data for **3j**: $C_{17}H_{16}N_2O_3$; $Mr = 296.32$, colourless block crystals, 0.50 × 0.30 × 0.10 mm, monoclinic, space group $P2_1/n$, $a = 8.4935(15)$ Å, $b = 9.5430(16)$ Å, $c = 18.326(3)$ Å, $\beta = 100.636(4)°$, $Z = 4$, $V = 1459.8(4)$ Å^3, $D_c = 1.348$ g/cm^3, $F(000) = 624$, $\mu(\mathrm{MoK}\alpha) = 0.094$ mm^{-1}. Intensity data were collected on a Rigaku MERCURY CCD with graphite monochromated MoKα radiation ($\lambda = 0.71070$ Å) by using ω–2θ scan mode in the range of $3.11 < \theta < 25.34°$. Out of 2675 unique reflections measured 2146 reflections with $I > 2\sigma(I)$ were used in the refinement. The structure was solved by direct methods and refined by full-matrix least-squares on F^2 using SHELXL-97.[13] Non-hydrogen atoms were refined with anisotropic displacement parameters. The final refinement was converged to $R = 0.0633$ and $\omega R = 0.1261$.
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