Carbohydrate-Based Tolylsulfonyl Hydrazines: Effective Catalysts for Michael Addition of Indoles to Electron-Deficient Olefins in Water

Peng Wu,[a,b] Yiqian Wan,[b] Jiwen Cai*[a,b]

[a] School of Pharmaceutical Sciences, Sun Yat-Sen University, Guangzhou 510080, P. R. of China

[b] School of Chemistry and Chemical Engineering, Sun Yat-Sen University, Guangzhou 510275, P. R. of China
Fax +86(20)87334718; E-mail: puscjw@mail.sysu.edu.cn

Received 20 December 2007

Abstract: Carbohydrate-based tolylsulfonyl hydrazines were used for the first time to catalyze the Michael reaction of indoles to electron-deficient olefins in aqueous media to afford 3-substituted indole derivatives in good to excellent yields at room temperature.

Key words: carbohydrate-based tolylsulfonyl hydrazines, catalyst, Michael addition of indole, water

The question of how to carry out catalytic organic reactions in aqueous media is of current interest, because water is cheap, safe and environmentally benign.[1] However, using water as the sole medium for organic reactions is not always practical because of the poor solubility of organic molecules in water, as well as the fact that water could inhibit the catalyst's activity.[1] Consequently, catalysts suitable for the activation of organic reactions in water require special design.

Amine-based organocatalysis is an effective platform for carrying out organic transformations, and many powerful amine-based catalysts have been developed in recent years.[2] Although a few aminocatalysts could be used in water,[3] most of the reactions were typically performed in organic solvents. On the other hand, organic reactions in nature could readily occur in water. Enzymes exploit hydrogen bonding interaction together with other nonbonded dipole-dipole, electrostatic, and steric interactions, to orient the substrate and stabilize the transition state, and therefore promote the reaction effectively.[4] This observation indicated that hydrogen bonding plays a key role in organocatalysis in water and made us wonder whether carbohydrate-based compounds could be used as catalysts to activate organic reaction in water.

Indole derivatives are known to possess various biological properties, and 3-substituted indole compounds are important building blocks for the synthesis of different therapeutic agents and natural products.[5] Most of the reported synthetic protocols to attain 3-alkylated indoles involved conjugate addition to electron-deficient olefin in the presence of proton[6] or other Lewis acids.[7] Kobayashi and Firouzabadi reported two procedures to prepare 3-alkylated indoles using scandium dodecyl sulfate and aluminum dodecyl sulfate as catalysts in aqueous media, respectively.[8] These acid-catalyzed reactions of indoles required precise control of acidity to avoid side reactions such as dimerization or polymerization. Moreover, the metal salt employed as Lewis acid catalyst is often expensive and toxic to the environment. As part of our effort to develop green catalytic systems,[9] we report herein the catalytic results of carbohydrate-based tolylsulfonyl hydrazines (Figure 1) for the conjugate addition of indoles to electron-deficient olefins in aqueous media.

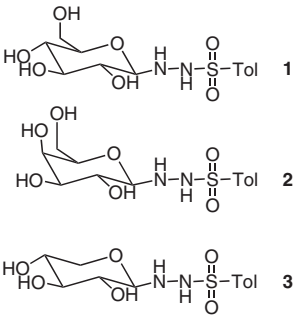


Figure 1 Carbohydrate-based tolylsulfonyl hydrazines[10]

We chose the addition of indole to β-nitrostyrene in aqueous media as the model reaction, and the catalytic efficiency of the three glycosyl derivatives **1**–**3** in aqueous media was evaluated. As summarized in Table 1, good yields were achieved for all the three catalysts, with the glucose derivative (compound **1**) being the most efficient (Table 1, entries 1–3). Furthermore, the effect of the catalyst loading was investigated. It was found that 10 mol% of catalyst gave the best result. Increasing the catalyst loading to 20 mol% did not improve the yield of the desired product (Table 1, entry 8). Interestingly, the reaction occurred sluggishly in organic solvents such as $CHCl_3$ and THF (Table 1, entries 5 and 6). Finally, it was found that the target Michael adduct was obtained only in a trace amount in the absence of catalyst even with prolonged reaction time (Table 1, entry 7).

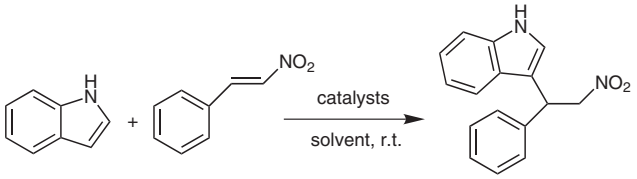
Based upon the results obtained above, the scope of the substrates was investigated and the results are summarized in Table 2. In general, good-to-excellent yields of Michael adducts were obtained. The reaction uniquely occurred at the 3-position of the indole ring, indicating that the addition reaction was regioselective. The catalyst was effective for indole and substituted indoles, affording 3-substituted target compounds in 81–96% yields. The cat-

SYNLETT 2008, No. 8, pp 1193–1198
Advanced online publication: 16.04.2008
DOI: 10.1055/s-2008-1072735; Art ID: W21907ST

alytic efficiency toward substituted indoles was similar for catalysts **1**–**3** (Table 2, entry 10). Indole carrying Br group resulted in a lower yield, and needed a longer reaction time (Table 2, entry 16).

For the activated olefin, a different substituent such as methoxy at the phenyl ring in β-nitrostyrene was tolerated (Table 2, entry 5). When 2-(2-nitrovinyl)furan was employed, the target product was obtained under the same reaction conditions (Table 2, entry 9). In the case of an acyclic α,β-unsaturated carbonyl compound, the Michael adduct was obtained, with slightly lower yield (Table 2, entry 15). For cyclic α,β-unsaturated carbonyl substrates, the target products were obtained in 91% and 89% yields (Table 2, entries 17 and 18). In addition, even though the carbohydrate-based amine could effectively catalyze the reaction of 1-methylindole with electron-deficient olefins (Table 2, entries 10–14), *N*-Boc-indole was not reactive under the same reaction conditions. The electron-withdrawing Boc group might deactivate the indole ring and result in failure of the reaction.

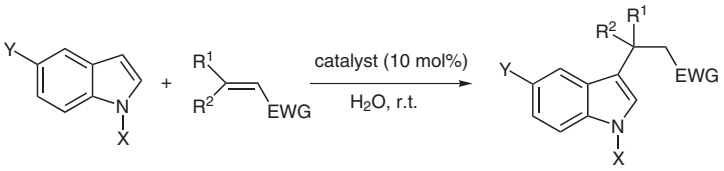
Table 1 Catalytic Efficiency of Carbohydrate-Based Tolylsulfonyl Hydrazines on the Michael Reaction in Various Media



Entry	Catalyst (mol%)	Solvent	Time (h)	Yield (%)[b]
1	**1** (10)	H_2O	14	92
2	**2** (10)	H_2O	16	85
3	**3** (10)	H_2O	16	82
4	**1** (10)	toluene	24	20
5	**1** (10)	$CHCl_3$	24	23
6	**1** (10)	THF	24	32
7	–	H_2O	48	trace
8	**1** (20)	H_2O	14	93

[a] All reactions were performed at r.t.[11]
[b] Yield of isolated product.

Table 2 Michael Addition of Indoles to Electron-Deficient Olefins Catalyzed by Carbohydrate-Based Tolylsulfonyl Hydrazine[a]



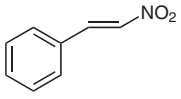
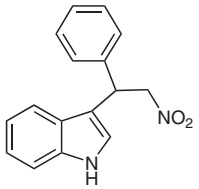
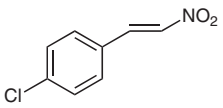
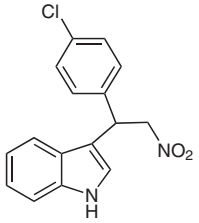
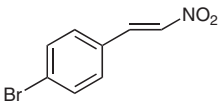
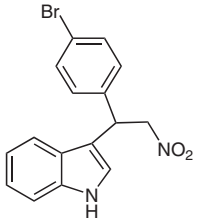
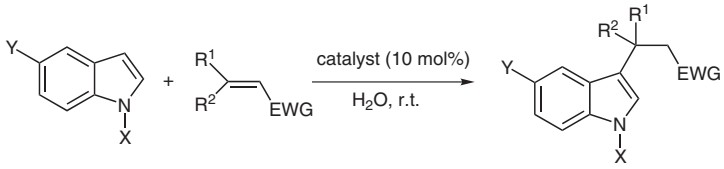
Entry	Indole X	Indole Y	Olefin	Product	Time (h)	Yield (%)[b]
1	H	H			14	93
2	H	H			15	90
3	H	H			18	85

Table 2 Michael Addition of Indoles to Electron-Deficient Olefins Catalyzed by Carbohydrate-Based Tolylsulfonyl Hydrazine[a] (continued)



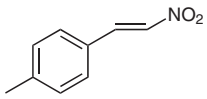
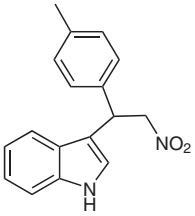
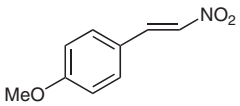
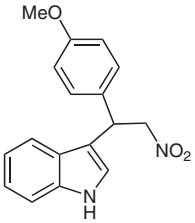
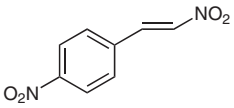
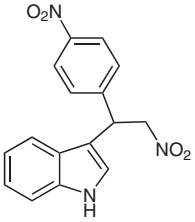
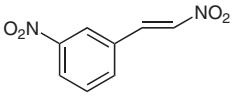
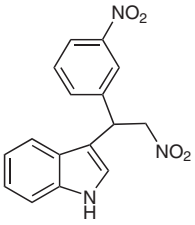
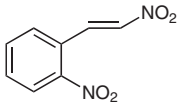
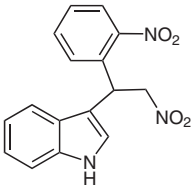
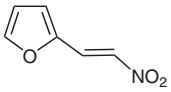
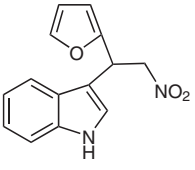
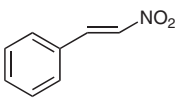
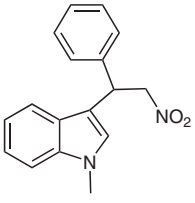
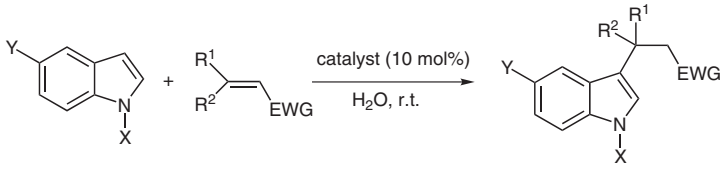
Entry	Indole X	Indole Y	Olefin	Product	Time (h)	Yield (%)[b]
4	H	H			12	90
5	H	H			14	86
6	H	H			19	87
7	H	H			20	85
8	H	H			22	82
9	H	H			15	96
10	Me	H			14	94 83[c] 81[d]

Table 2 Michael Addition of Indoles to Electron-Deficient Olefins Catalyzed by Carbohydrate-Based Tolylsulfonyl Hydrazine[a] (continued)



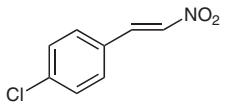
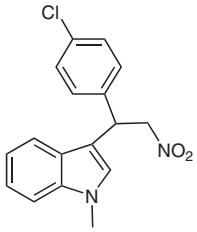
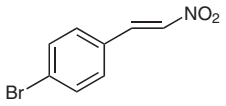
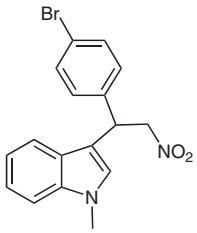
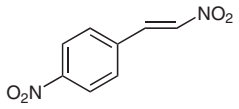
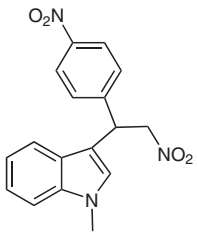
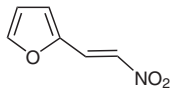
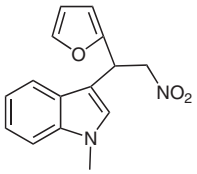
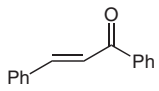
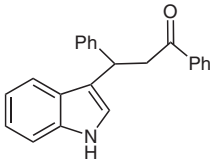
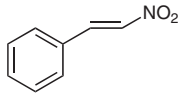
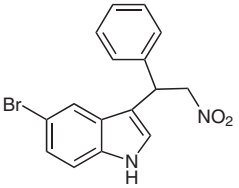
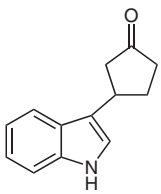
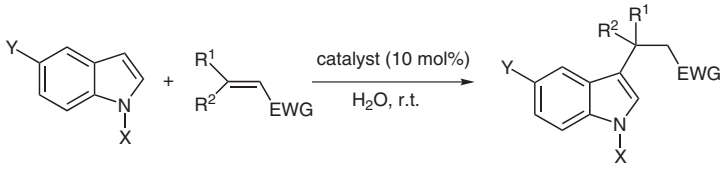
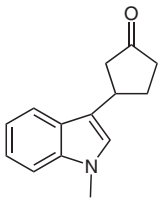
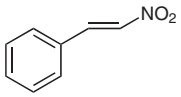
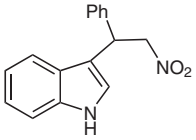
Entry	Indole X	Indole Y	Olefin	Product	Time (h)	Yield (%)[b]
11	Me	H			19	90
12	Me	H			15	93
13	Me	H			22	86
14	Me	H			15	95
15	H	H			24	82
16	H	Br			24	81
17	H	H			12	91

Table 2 Michael Addition of Indoles to Electron-Deficient Olefins Catalyzed by Carbohydrate-Based Tolylsulfonyl Hydrazine[a] (continued)



Entry	Indole X	Indole Y	Olefin	Product	Time (h)	Yield (%)[b]
18	Me	H			12	89
19	H	H			24	27[e]

[a] All reactions were performed at r.t.
[b] Yield of isolated product.
[c] Catalyzed by catalyst **2**.
[d] Catalyzed by catalyst **3**.
[e] Catalyzed by $PhNHNHSO_2PhMe$ + SDS.

It was noteworthy that the reaction did not proceed when it was catalyzed by $PhNHNHSO_2Tol$, in which the carbohydrate group of the effective catalysts **1**–**3** was substituted by a phenyl group. However, when assisted by sodium dodecyl sulfonate (SDS), the target product could be obtained in 27% yield (Table 2, entry 19). This observation indicated that the tolylsulfonyl hydrazine group was the effective catalytic functional group in the catalyst molecule, and the carbohydrate part functioned as a surfactant to promote better interaction between the organic substrates and the catalyst in aqueous media.

In conclusion, we have reported the first carbohydrate-based tolylsulfonyl hydrazines for Michael addition of indoles to electron-deficient olefins in water. It is a green process for the synthesis of 3-substituted indole derivatives. The reaction conditions are mild and could produce product in high yield and with good substrate scope.

Acknowledgment

We are thankful for the financial support from the 985 project, Sun Yat-Sen University.

References and Notes

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(11) **Typical Experimental Procedure**: A mixture of the olefin (1 mmol) and catalyst **1** (0.1 mmol) in H_2O (1 mL) was treated with indole (2 mmol). The resulting suspension was stirred at r.t. and the reaction was monitored by TLC until the starting material was consumed. The mixture was quenched with a sat. aq NaCl solution and then extracted with EtOAc (3×20 mL). The organic layers were combined and washed with brine, and dried over anhyd $MgSO_4$. The solvent was removed in vacuo to yield the crude product. Purification by silica gel chromatography using 100–200 mesh ZCX II eluted with hexane–EtOAc (5:1) afforded the Michael product.