

A Highly Efficient Michael Addition of Indoles to α,β -Unsaturated Electron-Deficient Compounds in Acidic SDS Micellar Media

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The Michael addition of indoles to α,β -unsaturated electron deficient compounds was catalyzed efficiently at room temperature in acidic micellar solution of sodium dodecyl sulfate (SDS). The substitution on the indole nucleus occurred exclusively at the 3-position in good to excellent yields, and no N-alkylation products were observed.

Keywords: Michael addition, Indole, α,β -Unsaturated electron-deficient compounds, Micellar media

INTRODUCTION

Organic reactions in water without the use of any harmful organic solvents are of great current interest because water is an easily available, economical, safe, and environmentally benign solvent [1]. In addition, unique reactivity and selectivity that are not achieved in organic solvents are often observed in water [2]. However, organic solvents are still used, instead of water, for mainly two reasons. First, most organic substrates are not soluble in water, and as a result, water cannot function as a reaction medium. Second, many reactive substrates, reagents, and catalysts are sensitive towards water and maybe decomposed or deactivated in aqueous media. A possible new way to improve the solubility of substrates is the use of surface-active compounds that can form micelles [3] or vesicular structures. The use of micellar and vesicle-forming surfactants as catalysts has been investigated in detail for different reactions in aqueous solutions [4].

Michael reactions promoted by Lewis acids have attracted much attention as one of the important carbon-carbon bond-

forming reactions in organic synthesis [5]. Michael reaction of indoles with α,β -unsaturated carbonyl compounds provides easy access to 3-substituted indoles, which are important building blocks for the synthesis of important biologically active compounds and natural products. However, Michael reaction can be promoted by either protic [6] or Lewis acids [7]. In many cases, the acid-catalyzed conjugate addition of indoles requires careful control of acidity to prevent side reactions including dimerization or polymerization. Furthermore, many of these procedures have some drawbacks such as strong acidic conditions, expensive reagents, low yield of products, complex handling, and long reaction times. Thus, a fast and efficient method using a greener media is desirable for conjugate addition of indoles to electron-deficient olefins.

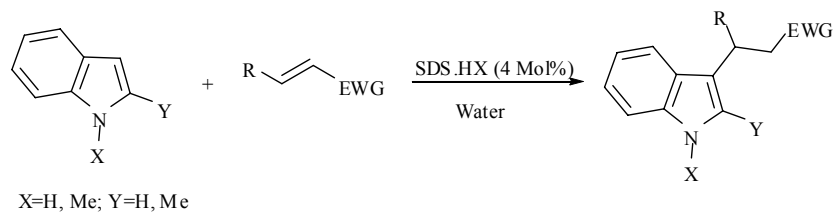
In this article, we report a highly efficient Michael addition of indoles to α,β -unsaturated electron-deficient compounds in acidic micellar solution of Sodium dodecyl sulfate [8] (Scheme 1).

EXPERIMENTAL

General Remarks

Chemicals were purchased from Merck and Fluka

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Scheme 1. Michael addition of indole α,β -unsaturated electron-deficient compounds

Chemical Companies. All the products are known and were characterized by comparison of their physical data with those reported in the literature. IR spectra were run on a Shimadzu model 8300 FT-IR spectrophotometer. NMR spectra were recorded on a Bruker Avance DPX-250. The purity of the products and the progress of the reactions were measured by TLC on silica-gel polygram SILG/UV₂₅₄ plates, or by a Shimadzu Gas Chromatograph GC-14A instrument with a flame ionization detector.

General Procedure for the Michael Addition of Indole to α,β -Unsaturated Electron-Deficient Compound

To an aqueous solution of SDS.HCl (4 ml; 0.08 mmol) was added indole (2 mmol.) and α,β -unsaturated electron-deficient compound (2.2 mmol). The mixture was stirred vigorously (800 rpm) at room temperature and monitored by TLC until the starting material was consumed. Then, an aqueous NaHCO₃ (5%) solution (5 ml) and brine (5 ml) were added to reaction mixture. The mixture was extracted with ethyl acetate (5 ml), dried over Na₂SO₄, and concentrated. Purification by a short silica gel chromatography afforded the desired products in 45-98% yields. Five mmol scale reactions were also carried out without any difficulties. For example, the reaction of indole (5 mmol, 0.585 g) and methyl vinyl ketone (6.0 mmol, 0.420 g) in the presence of 4 mol% of SDS.HCl afforded the product in 98% yield during 12 min.

The selected spectral data for 4-(1H-3-indolyl)butan-2-one (compound **a**): ¹H NMR (250 MHz, CDCl₃) δ (ppm): 8.38 (s, 1H, NH), 7.69 (d, $J = 7.7$ Hz, 1 H), 7.38-7.23 (m, 3H), 6.94 (s, 1H), 3.13 (t, $J = 7.4$ Hz, 2H), 2.88 (t, $J = 7.4$ Hz, 2H), 2.21 (s, 3H); ¹³C (63 MHz, CDCl₃) δ (ppm) = 209.6, 136.5, 127.2, 122.0, 121.8, 119.2, 118.7, 114.8, 111.5, 44.1, 30.1, 19.5; IR (KBr): 3321, 2923, 1701, 1355, 1162, 745 cm⁻¹; 4-(2-methyl-1H-3-indolyl)-4-phenylbutan-2-one (compound **g**): ¹H NMR

(250 MHz, CDCl₃) δ (ppm): 7.77 (s, 1H, NH), 7.74 (d, $J = 7.6$ Hz, 1 H), 7.21-6.86 (m, 8H), 4.74 (dd, $J_1 = 8.3$ Hz, $J_2 = 6.5$ Hz, 1H), 3.32 (dd, $J_1 = 16.2$ Hz, $J_2 = 8.3$ Hz, 1H), 3.20 (dd, $J_1 = 16.2$ Hz, $J_2 = 6.5$ Hz, 1H), 2.2 (s, 3H), 1.9 (s, 3H); ¹³C (63 MHz, CDCl₃) δ (ppm) = 208.3, 144.2, 135.5, 131.9, 128.4, 127.6, 126.0, 120.8, 119.2, 113.0, 110.6, 48.4, 36.9, 30.8, 12.1; IR (KBr): 3311, 3080, 2925, 1706, 1460, 1167, 729 cm⁻¹.

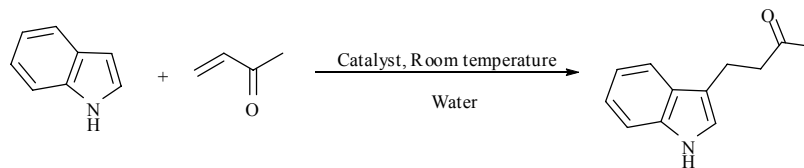
RESULTS AND DISCUSSION

First, the reaction of indole with methyl vinyl ketone was studied as a model reaction in the presence of sodium dodecyl sulphate (SDS) in water. It is notable that according to the literature [7d,7h] such a reaction was not satisfied; corresponding Michael adduct was produced under 20% after 24 h [7d] (Table 1, entry 1). Therefore, we decided to run the reaction in acidic media. For this purpose, Brønsted acids with different acidic strengths such as acetic acid, trichloroacetic acid, sulfuric acid, hydrochloric and perchloric acid were employed in the presence of SDS. Acetic acid, as a weak acid, in the presence of SDS was not able to conduct this reaction completely which proceeded in only 60% after 24 h (Table 1, entry 7). However, in the presence of strong acids, the rate of reaction was enhanced and completed in 12 min (Table 1, entries 3-6). In addition, hydrochloric acid in the absence of SDS was not effective and after a long reaction time most of the starting material remained intact (Table 1, entry 2).

According to the obtained results, the catalytic effect of acidic micellar solution of SDS in this reaction may be explained as follows. The SDS micellar solution conducts the hydrophobic indole and enone molecules into the micellar core. Here, indole and enone molecules are brought closely together and the enone molecule is activated by the protons accumulated on the surface of the micellar core and the reaction occurs smoothly. These characteristics are

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Table 1. Optimization of Michael Addition of Indole (2 mmol) to Methyl Vinyl Ketone (2.1 mmol) in Water (4 ml) at Room Temperature



Entry	Catalyst	Mol%	Time (min)	Yield (%) ^a
1	SDS	7.5	300	9[7h] (20)[7d]
2	HCl	4	60	5
3	SDS.HCl	4	12	98
4	SDS.HClO ₄	4	12	98
5	SDS.H ₂ SO ₄	4	12	94
6	SDS.CCl ₃ CO ₂ H	4	20	92
7	SDS.CH ₃ CO ₂ H	4	50	80
8	SDS.HCl	2	60	85

^aYield refer to isolated product.

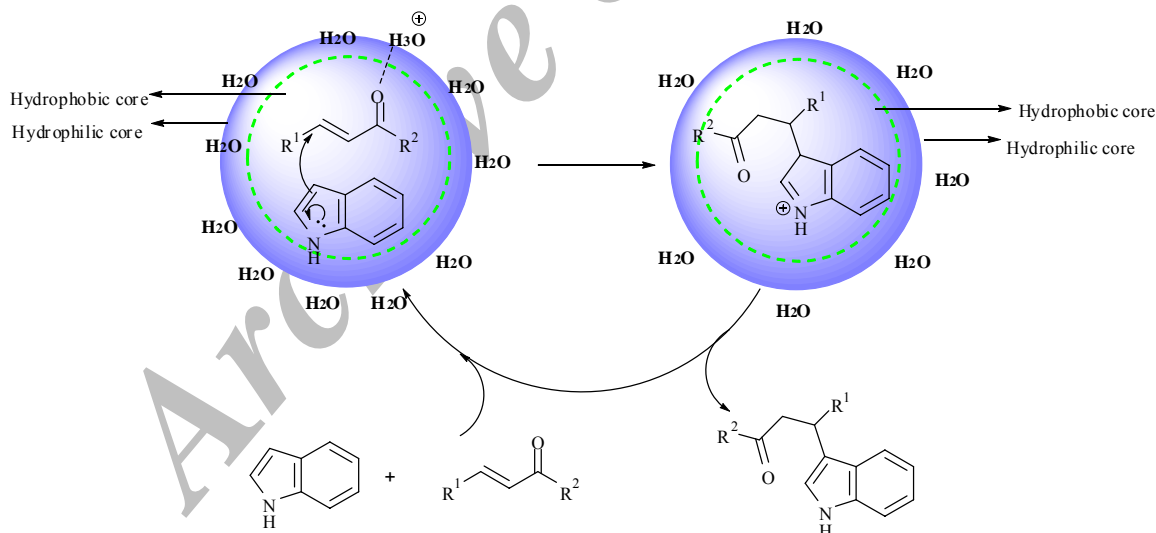




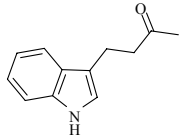

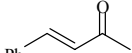
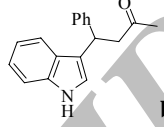

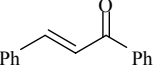
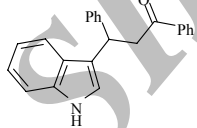

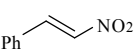
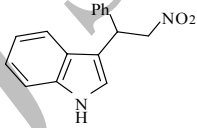
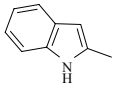

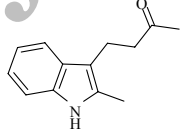
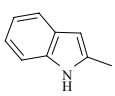
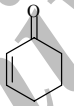
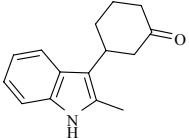
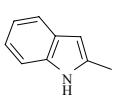
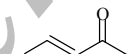
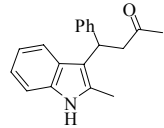
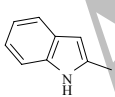
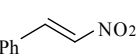
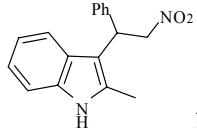
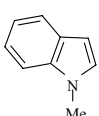

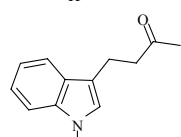
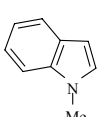

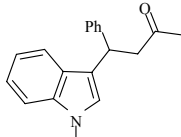
Fig. 1. Catalytic role of acidic micellar solution of SDS for the Michael addition of indole to α,β -unsaturated electron-deficient compound.

schematically presented in Fig. 1.

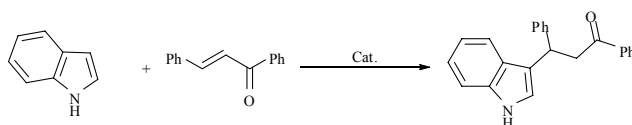
In order to examine the generality and scope of the reaction various α,β -unsaturated compounds reacted with indole, 2-methylindole and N-methylindole to yield the corresponding 3-alkylated products (Table 2). Therefore,

electron-deficient olefins such as methyl vinyl ketone, cyclohexenone, benzalacetone, chalcone and β -nitrostyrene afforded the desired products in good to excellent yields. With the methyl vinyl ketone, the Michael reactions were completed in 12 min to provide the products in 95-98% yields (Table 2,

Table 2. Michael Addition of Indoles to Electron-deficient Olefins Catalyzed by SDS.HCl in Water at Room Temperature

Entry	Indole	Olefin	Product ^a	Time (h)	Yield (%) ^b
1			 a	0.2	98
2			 b	3.5	78
3			 c	2.5	80
4			 d	2.0	85
5			 e	0.2	95
6			 f	0.5	94
7			 g	1.5	87
8			 h	1.5	88
9			 i	1.0	93
10			 j	7.0	45

^aAll products were characterized using standard spectroscopic methods (IR, ¹H and ¹³C NMR). ^bYield refer to pure isolated products from short silica gel column chromatography.

Table 3. Comparison between the Reaction of Indole with Chalcone Catalyzed by SDS.HCl and that Catalyzed by other Catalysts

Entry	Cat.	Mol%	Solvent	Time (h)	Yield (%)	Ref.
1	Sc(DS) ₃	2.5	Water	36	55	[7h]
2	InBr ₃	10	CH ₂ Cl ₂	24	52	[5b]
3	RuCl ₃	2.5	CH ₃ OH	3	80	[7b]
4	ZnBr ₂ /HAP	10	CH ₃ CN	24	70	[7c]
5	SDS.HCl	4	Water	2.5	80	-

entries 1, 5). The treatment of β -nitrostyrene with indole produced the corresponding 3-alkylated indole in 85-88% yields (Table 2, entries 4, 8). In the cases of more hindered α,β -enones, the reaction was very slow and prolonged to 3.5 h. This catalyst is exceptionally effective for Micheal addition of indole to chalcone to produce the desired product in 80% yield at room temperature in 2.5 h (Table 2, entry3). The efficiency of this catalyst is shown by being compared with the obtained results of other catalysts for a similar reaction (Table 3).

By comparison, Michael addition of indole to chalcone catalysed by SDS.HCl proceeded far more rapidly (2.5 h), which implied that Brønsted acid surfactant in water had a more efficient promoting effect.

The reactions were clean and the products were obtained in high yields without the formation of any side products such as N-alkylation. Furthermore, the indole nitrogen did not require prior protection and the avoidance of strong bases for deprotection permitted compatibility with a wide range of functional groups.

CONCLUSIONS

In conclusion, we have developed a new, fast, and efficient procedure for the synthesis of 3-substituted indoles in acidic micellar solution of SDS. Short reaction times, high yields, operational simplicity and environmentally friendly conditions are some of the related qualities that make this procedure a more desirable alternative to the conventional chemical synthesis.

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