Michael addition of indole to α,β-unsaturated ketones catalysed by silica sulfuric acid under ultrasonic irradiation

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Silica sulfuric acid catalyses the Michael addition of indole to α,β-unsaturated ketones under ultrasonic irradiation to afford the corresponding β-indolylketones in 50–85% yields at room temperature.

Keywords*:* silica sulfuric acid, Michael addition, β-indolylketones, synthesis, ultrasound.

The investigation of the chemistry of indoles is an active area of heterocyclic chemistry.[1] β-Indolylketones have received attention as important building blocks for the synthesis of many natural products and other biologically active compounds.[2] A simple method for the synthesis of 3-alkylated indoles involves the conjugate addition of indoles to α,β-unsaturated compounds in the presence of either protic or Lewis acids.[3] Over the past few years, many synthetic methods for preparation of these compounds have been reported.[2,4] However, many of these procedures involved expensive reagents, long reaction times and complex methodology. More recently, β-indolylketones were found to be formed in acetonitrile in the presence of catalyst Bi $(OTf)_3$.[5] A acetonitrile is not an environmentally-friendly solvent in the context of green chemistry. For this reason, superior catalytic systems, which are cheap, accessible, and environmentally-friendly, are desirable.

Silica sulfuric acid is a good proton source in terms of its convenience, cheapness, easy production and insolubility in all organic solvents. It has been extensively used as a catalyst for many organic reactions, such as production of thionitrites and disulfides,[6] preparation of 3, 4-dihydropyrimidin-2(1*h*)-ones,[7] synthesis of aryloxyacetic acid and arylthioacetic acid esters.[8]

Ultrasound has increasingly been used in organic synthesis in the last three decades. Compared with traditional methods, the procedure is more convenient and easily controlled. A large number of organic reactions can be carried out in higher yields, shorter reaction time or milder conditions under ultrasound irradiation.[9] In continuation of our work in the synthesis of indole derivatives,[10] we describe the catalytic activity of silica sulfuric acid as a cheap catalyst in the ultrasound-accelerated Michael addition of indole to α, β-unsaturated ketones (Scheme 1).

As shown in entries 4 and 6 of Table 1, the sequence of adding reagents had a little influence on the yield. When the sequence of adding reagents was indole, anhydrous ethanol, catalyst, α, β-unsaturated ketone, 3-(1H-indol-3-yl)-1,3-diphenylpropan-1-one was obtained in 78% yield after 120 min, whereas the reaction in which the sequence of adding the reagents was α,β-unsaturated ketone, anhydrous ethanol, catalyst, indole, afforded 3-(1H-indol-3-yl)-1,3-diphenylpropan-1-one in 85% yield within 120 min.

We studied the influence of the amount of the catalyst on the reaction time and yield. As shown in Table 1, increasing the quantity of the catalyst can improve the yields. For example, when the amount of the catalyst is 50% mol, 3-(1H-indol-3-yl)-1,3-diphenylpropan-1-one was obtained in 73% yield within 120 min, whereas using 100% mol silica sulfuric acid, the reaction required only 120 min to give the desired product in 85% yield.

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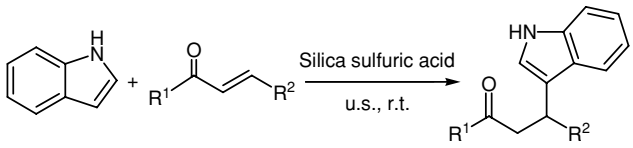


1 **2** **3**

Scheme 1

Table 1 The effects of reaction conditions on Michael addition of indole to benzalacetophenone catalysed by silica sulfuric acid under ultrasonic irradiation

Entry	Catalyst/%mol	Time/min	Isolated yield/%
1[a]	10	120	48
2[a]	20	120	71
3[b]	50	120	73
4[b]	100	120	85
5[b]	150	120	77
6[c]	100	120	78
7[b, d]	50	120	60

[a]The sequence of adding reagents was α,β-unsaturated ketone, anhydrous ethanol, indole, catalyst; [b]the sequence of adding reagents was α,β-unsaturated ketone, anhydrous ethanol, catalyst, indole; [c]the sequence of adding reagents was indole, anhydrous ethanol, catalyst, α,β-unsaturated ketone; [d]stirred without ultrasound

From the results in Table 1, the reaction conditions we chose were α, β-unsaturated ketone (1 mmol), silica sulfuric acid (100% mol), and indole (1 mmol). Under these reaction conditions, we carried out a series of experiment for reactions of indole with different α,β-unsaturated ketones under ultrasound irradiation.

As shown in Table 2, the addition of indole with some α, β-unsaturated ketones afforded β-indolylketones in good yield when catalysed by silica sulfuric acid in anhydrous ethanol under ultrasound irradiation. The dramatic improvement observed is with regard to reaction time. In the reaction catalysed by $InBr_3$,[4a] **3a** was obtained in 52% yield at room temperature using stirring for 16–24 h in CH_2Cl_2. whereas the present procedure results **3a** in 85% yield within 120 min.

We also carried out the reaction in the absence of ultrasound; the reaction of indole with **2a** gave **3a** in 60% yield using stirring for 120 min. It can easily be seen that the ultrasound technique represented a better procedure in terms of the higher yield, and shorter time.

Steric hindrance affects the yields. As shown in Table 2, when the amount of the catalyst was 100% mol, **3c** was obtained in 77% yield within 120 min, but the reaction of indole with **2h** gave **3h** in only 62% yield within 120 min.

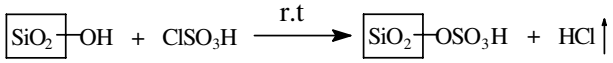
The reaction of indole with α,β-unsaturated ketones probably proceeds through the intermediate 3*H*-indolenine.[3]

In conclusion, we have found a practical procedure for the preparation of β-indolylketones catalysed by silica sulfuric acid from some α,β-unsaturated ketones and indole under

Table 2 The Michael reaction of indole to α,β-unsaturated ketones catalysed by silica sulfuric acid under ultrasonic irradiation

Entry	R^1	R^2	100%mol Catalyst[a]		M.p./°C
			Time/min	Yield/%	
a	C_6H_5	C_6H_5	120	85	125-126
b	C_6H_5	*p*-$CH_3C_6H_4$	110	69	127-128
c	C_6H_5	*p*-ClC_6H_4	120	77	118-120
d	C_6H_5	*p*-$CH_3OC_6H_4$	110	80	125-127
e	*p*-$CH_3OC_6H_4$	C_6H_5	120	55	182-183
f	*p*-ClC_6H_4	C_6H_5	140	56	159-161
g	*p*-$CH_3OC_6H_4$	*p*-$CH_3OC_6H_4$	140	50	163-164
h	C_6H_5	*m*-ClC_6H_4	120	62	38-40
i	C_6H_5	*m*-BrC_6H_4	120	71	40-42

[a]The sequence was α,β-unsaturated ketone, anhydrous ethanol, catalyst, indole.



Scheme 2

ultrasound irradiation. Our procedure is characterised by milder conditions, short reaction time, higher yield and an inexpensive catalyst.

Experimental

Melting points were uncorrected. ^{1}H NMR spectra were measured on a Bruker ADVANCE 400 (400 MHz) spectrometer using TMS as internal standard and $CDCl_3$ or CD_3COCD_3 as solvent. Elemental analyses were carried out using a HERAEUS analyser. Sonication was performed on a Shanghai Branson-BUG ultrasonic cleaner (with a frequency of 25 kHz and a nominal power of 250 W). The reaction flask was located in the maximum energy area in the cleaner, where the surface of reactants is slightly lower than the level of the water, and addition or removal of water was used to control the temperature of the water bath. All the products were confirmed by elemental analyses and their ^{1}H NMR data.

Preparation of silica sulfuric acid: A 500 ml round flask was used. It was equipped with a constant-pressure dropping funnel containing chlorosulfonic acid (30 g) and a gas inlet tube for conducting HCl gas over an absorbing solution i.e. water. Into it were charged 50 g of silica gel. Chlorosulfonic acid was added dropwise over a period of 30 min at room temperature. HCl gas evolved from the reaction vessel immediately (Scheme 2). After the addition was complete the mixture was shaken for 30 min. A white solid (silica sulfuric acid) (70.6 g) was obtained, then heated at 100–110 °C for 1 h, and finally stored in a desiccator until used.[6,8]

General procedure for preparation of β*-indolylketones*

α,β-Unsaturated ketones (**2**, 1 mmol), anhydrous ethanol (2 ml), silica sulfuric acid (270 mg), indole (**1**, 1 mmol), were mixed in a 50 ml Pyrex flask. The reaction mixture was irradiated in water bath of an ultrasonic cleaner at room temperature for a period as indicated in Table 2. The reaction mixture was dissolved in ethyl acetate, and the catalyst was removed by filtration and washed with ethyl acetate. The solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (200-300 mesh) eluted with petroleum ether or mixture of petroleum ether/ethyl acetate.

3a: ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 3.77 (dd, 1H, J_1=16.8 Hz, J_2=7.6 Hz, CH_2), 3.86(dd, 1H, J_1=16.8 Hz, J_2=6.8 Hz, CH_2), 5.11 (t, 1H, *J*=6.8 Hz, CH), 6.99–7.49 (m, 13H), 7.98 (d, 2H, *J*=7.2 Hz,), 8.04 (s, 1H, NH); Elemental analysis: found: C, 84.7; H, 5.95; N, 4.3 Calcd. for $C_{23}H_{19}NO$: C, 84.9; H, 5.9; N, 4.30%.

3b: ^{1}H NMR (CD_3COCD_3, 400 MHz) δ_H: 2.23 (s, 3H, CH_3), 3.84 (dd, 1H, J_1=7.6 Hz, J_2=16.8 Hz, CH_2), 3.92 (dd, 1H, J_1=6.8 Hz, J_2=16.8 Hz, CH_2), 5.01(t, 1H, *J*=7.2 Hz, CH), 6.90–7.63 (m, 12H), 8.06(d, 2H, *J*=8.0 Hz), 10.10 (s, 1H, NH); Elemental analysis: found: C, 85.05; H, 6.28; N, 4.2 Anal. Calcd for $C_{24}H_{21}NO$: C, 84.9; H, 6.24; N, 4.13%.

3c: ^{1}H NMR (CD_3COCD_3, 400 MHz) δ_H: 3.89 (dd, 1H, J_1=8.0 Hz, J_2=16 Hz, CH_2), 3.97 (dd, 1H, J_1=8.0 Hz, J_2=16 Hz, CH_2), 5.05 (t, 1H, *J*=8.0 Hz, CH), 6.92–7.62 (m, 12H), 8.07(d, 2H, *J*=4.0 Hz), 10.16 (s, 1H, NH); Elemental analysis: found: C, 76.92; H, 5.16; N, 3.7 Calcd. for $C_{23}H_{18}NOCl$: C, 76.77; H, 5.04; N, 3.89%.

3d: ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 3.69–3.85 (m, 5H), 5.04 (t, 1H, *J*=7.2 Hz, CH), 6.81–7.57 (m, 12H), 7.96 (d, 2H, *J*=7.2 Hz), 8.00 (s, 1H, NH); Elemental analysis: found: C, 80.98; H, 6.08; N, 3.8 Calcd. for $C_{24}H_{21}NO_2$: C, 81.1; H, 5.96; N, 3.94%.

3e: ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 3.70 (dd, 1H, J_1=7.6 Hz, J_2=16.8 Hz, CH_2), 3.80 (dd, 1H, J_1=6.8 Hz, J_2=16.8 Hz, CH_2), 3.88 (s, 3H, CH_3), 5.09 (t, 1H, *J*=7.2 Hz, CH),6.93 (d, 2H, *J*=8.8 Hz), 7.02–7.45 (m, 10H), 7.95 (d, 2H, *J*=8.4 Hz), 8.00(s, 1H, NH); Elemental analysis: found: C, 80.9; H, 5.94; N, 3.83. Calcd for $C_{24}H_{21}NO_2$: C, 81.1; H, 5.96; N, 3.94%.

3f: ^{1}H NMR (CD_3COCD_3, 400 MHz) δ_H: 3.87 (dd, 1H, J_1=7.6 Hz, J_2=16.8 Hz, CH_2), 3.96 (dd, 1H, J_1=6.8 Hz, J_2=16.8 Hz, CH_2), 5.03 (t, 1H, *J*=7.2 Hz, CH), 6.91–7.48 (m, 10H), 7.54 (d, 2H, *J*=8.0 Hz), 8.07(d, 2H, *J*=8.0 Hz), 10.12(s, 1H, NH); Elemental analysis: found: C, 76.86; H, 5.14; N, 3.8 Calcd for $C_{23}H_{18}NOCl$: C, 76.77; H, 5.04; N, 3.9%.

3g: ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 3.66 (dd, 1H, J_1=8.0 Hz, J_2=16.4 Hz, CH_2), 3.77 (s, 4H), 3.88 (s, 3H, CH_3), 5.03(t, 1H, *J*=8.0 Hz, CH), 6.81 (d, 2H, *J*=7.2 Hz), 6.92(d, 2H, *J*=7.2 Hz) 7.01–7.46 (m, 7H), 7.95(d, 2H, *J*=7.6 Hz), 8.00(s, 1H, NH); Elemental analysis: found: C, 77.75; H, 6.08. N, 3.52. Calcd for $C_{25}H_{23}NO_3$: C, 77.9; H, 6.01; N, 3.63%.

3h: ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 3.80-3.94 (m, 2H, CH_2), 5.20(s, 1H, CH), 6.90–7.64(m, 12H), 8.06(s, 2H), 8.31(s, 1H, NH); Elemental analysis: found: C, 76.76; H, 5.18; N, 3.74 Calcd for $C_{23}H_{18}NOCl$: C, 76.77; H, 5.04; N, 3.89%.

3i: ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 3.74 (dd, 1H, J_1=7.6 Hz, J_2=16.8 Hz, CH_2), 3.87 (dd, 1H, J_1=6.4 Hz, J_2=16.8 Hz, CH_2), 5.12 (t, 1H, *J*=6.8 Hz, CH), 6.92 (s, 1H) 7.11–7.61 (m, 11H), 8.00 (d, 2H, *J*=7.6Hz), 8.19 (s, 1H, NH); Elemental analysis: found: C, 68.21; H, 4.63; N, 3.37 Calcd for $C_{23}H_{18}NOBr$ C, 68.33; H, 4.49; N, 3.46%.

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