An environmentally benign synthesis of flavones from 1,3-diketones using silica gel supported $NaHSO_4$ catalyst

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A simple and enviromentaly benign method for synthesis of flavones is described via dehydrative cyclisation of *o*-hydroxydibenzoylmethane using silica gel supported $NaHSO_4$ catalyst.

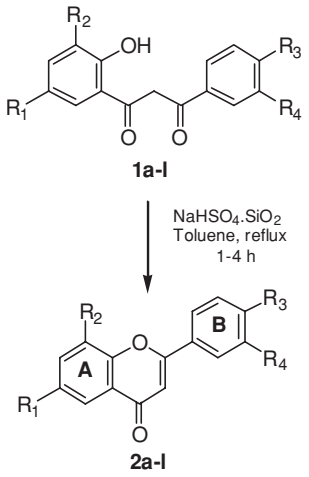
Keywords: flavones, 1,3-diketones, silica gel, $NaHSO_4$

Flavonoids are a group of naturally occurring phenolic compounds widely distributed in the plant kingdom, the most abundant being the flavones. Usually these compounds have diverse biological activities, including, among others, antihypertensive,[1] broncodilatory,[2] antitumor,[3] and antibacterial activities.[4]

There are a number of methods available for the synthesis of flavones and their derivatives.[5] The cyclodehydration of 1-(*o*-hydroxyphenyl)-1,3 diketones is one of the most commonly used methods for the synthesis of subtituted flavones.[6] The basic aproach of the synthesis of the 1,3-diketones consists of acylation of *o*-hydroxyacetophenone using different acylating agent and experimental conditions.[7-9] In Baker-Venkataraman synthesis, the rearrangement of o-aryloxy-acetophenone to β-diketone is utilised.[10] Conventional methods for the synthesis of flavones **2** include the cyclodehydration of diketones **1** or equivalent intermediates catalysed by strong acids or bases, where the yields of flavones are not always good.[11-13] Thus, there is a need for development of a milder protocol for the cyclisation process.

Recently, the use of solid supported reagents[14] has received considerable importance in organic synthesis because of their ease of handling, enhanced reaction rates, high selectivity, simple work up, and recoverability of catalysts. Particularly, silica gel impregnated with $NaHSO_4$[15,16] has advantages of low cost, ease of preparation, and catalyst recycling. Since the reaction is heterogeneous in nature, the catalyst can conveniently be separated by simple filtration.

Herein, we describe an environmentally friendly procedure for the synthesis of flavones catalysed by $NaHSO_4$–SiO_2. This method not only afforded the products in high yields but also avoided the problems associated with catalyst cost, handling, safety, and pollutions (Scheme 1).



Scheme 1

Several examples illustrating this novel and general method for the synthesis of flavones are summarised in Table 1. Various flavones carrying either electron-donating or –withdrawing substituents in rings A and B were synthesised in good yields from 1,3 diketones. Among the different solvents acetonitrile, *n*-hexane, THF, benzene, and toluene used for this transformation, toluene was the solvent of choice as it yielded the best results. $NaHSO_4{\cdot}SiO_2$ may be regenerated easily as an active catalyst by washing with acetone, followed by drying at 120 ° for 4 h, and be reused. Reusability of the catalyst was examined with the 1,3-diketone **1a** and resulted in 95, 94, 94, 93% yields over four cycles.

Table 1 Synthesis of flavones from *o*-hydroxydibenzoyl methanes using $NaHSO_4.SiO_2$ catalyst

Entry	R^1	R^2	R^3	R^4	Time/h	Yield[a]/%	M.p./°C	
							Observed	Reported
2a	H	H	H	H	1	93[b]	95–96	95–97[7]
2b	H	H	CH_3	H	1	92	109–111	110–112[17a]
2c	H	H	OCH_3	OCH_3	1	95	152–154	154–155[5e]
2d	H	H	NO_2	H	4	92	242–244	244–245[17b]
2e	OCH_3	H	H	H	1	93	161–162	163–164[17c]
2f	OCH_3	H	CH_3	H	1	86	160–161	161–162[17d]
2g	OCH_3	H	OCH_3	OCH_3	1	90	199–200	–
2h	OCH_3	H	NO_2	H	4	93	198–200	–
2i	CH_3	H	H	H	1	90	120–121	122[8]
2j	CH_3	H	NO_2	H	4	93	263–264	–
2k	Cl	Cl	H	H	3	92	167–168	–
2l	Cl	Cl	NO_2	H	4	54	290–293	–

[a]Isolated yields, [b]Yield after four cycles

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In conclusion, we have devoloped a mild and easy process for the synthesis of flavones using $NaHSO_4 \cdot SiO_2$ as the catalyst. This method offers several advantages including high yields, short reaction times, and simple work up procedure. The catalyst can be prepared easily with readily available inexpensive reagents, which is heterogenous and nontoxic.

Experimental

General: M.p.s are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury NMR at 300 MHz instrument in $CDCl_3$. The mass spectral analyses were carried out on a Micromass Quattro LC-MS/MS spectrometer. The starting materials were prepared via Baker-Venkataraman rearrangement wherein *o*-hydroxy acetophenone was acylated to form the benzoyl ester which is treated with base (KOH/pyridine) to form 1,3-diketone.[18]

Preparation of the catalyst: The catalyst was prepared by mixing silica gel (10 g , Merck grade 60, 200–400 mesh) with a solution of $NaHSO_4 \cdot H_2O$ (4.14 g, 0.03 mol) in 20 ml of distilled water. The mixture was well mixed and then gently heated on a hot plate to give a free-flowing white solid. The catalyst was dried in an oven maintained at 120 °C for 48 h and stored under dry conditions.

Typical procedure, Synthesis of flavone **2a**: 1-(2-hydroxyphenyl)-3-(phenyl)-propane-1,3-dione **1a** (0.24 g, 1 mmol) was dissolved in toluene (3 ml) and catalyst (0.33 g, 0.7 eq) was added. The mixture was refluxed for 1 h. Completion of the reaction was monitored by TLC. After cooling to room temperature, 20 ml of acetone was added and the mixture was filtered. Evaporation of the solvent gave almost pure product. Further purification was carried out by recrystallisation from *n*-hexane and column chromatography on silica gel using hexane:ethyl acetate (9:1) as eluent to afford **2a** in 95% yield, m.p. 95–96 °C; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.82 (1H, s, CH=C), 7.38–7.44 (1H, m, Ar), 7.51–7.57 (3H, m, Ar), 7.66–7.72 (1H, m, Ar), 7.89–7.93 (2H, m, Ar), 8.21–8.24 (1H, m, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 107.7, 118.3, 124.1, 125.4, 125.9, 126.5, 129.3, 131.8, 131.9, 134.0, 156.5, 163.6, 178.7; *m/z*:calcd. for $C_{15}H_{10}O_2$, 222.24; found, 222.87.

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