$FeCl_3$ CATALYZED DEHYDRATIVE CYCLISATION of 1, 3 – (DIARYL DIKETONES) to FLAVONES

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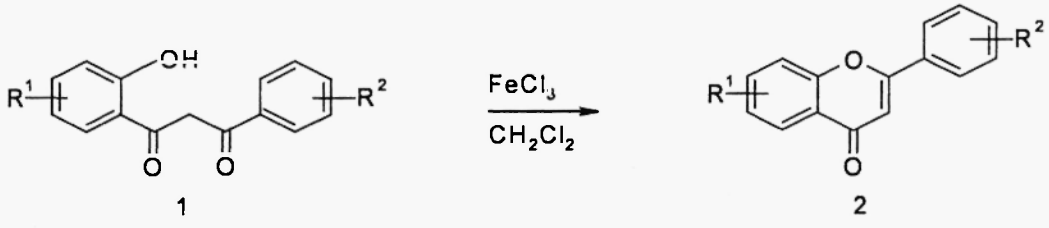
Abstract : $FeCl_3$ in catalytic amount effects smooth conversion of substituted 1- (2-hydroxy phenyl) - 3 - phenyl - 1, 3 - propanediones to the corresponding flavones in high yields.

Introduction : Flavones comprise the most abundant and significant class of flavonoids and exhibit wide spectrum of biological activities.[1] Recent interest in flavones stems from their ability to inhibit retroviral transcriptases as well as their capacity to inhibit protein tyrosine kinases[2] and serine/ threonine kinases[3]. Our interest in the study of flavones as aldose reductase inhibitors required synthesis of substituted flavones on large scale. Currently there are number of methods available to synthesize flavones,[4] among them Baker – Venkatraman strategy represents the most convenient route from 2-hydroxy acetophenone. In this method, acid induced dehydrative cyclisation of 1,3 - (diaryl diketones) obtained by intramolecular Claisen condensation of O - benzoyl acetophenone to flavones in 75% yield.[5] Recent developments for the above dehydrative cyclisation include use of Amberlyst 15,[6] Co^{III}(Sulpr) OH,[7] $Br_2/CHCl_3$,[8] EtOH/HCl,[9] Clay,[10] NaOAc/AcOH[11] and H_2SO_4 under MW irradiation.[12] These procedures suffer with respect to operational simplicity, reaction times, yields and cost of the reagent. Herein we would like to disclose our finding that $FeCl_3$[13] in catalytic amount effects the same in short period and in high yields (Scheme1).



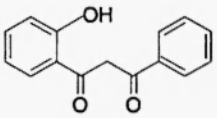
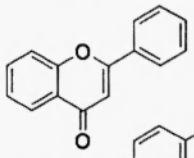
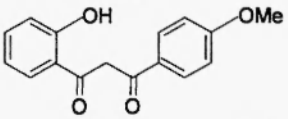
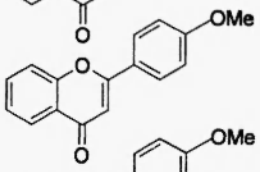
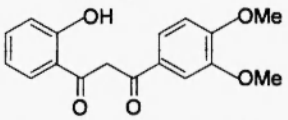
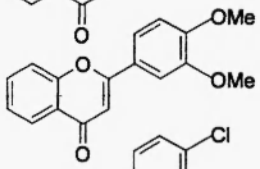
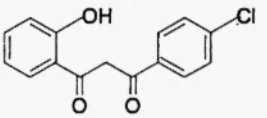
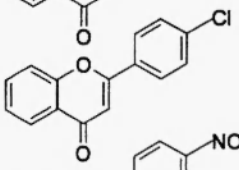
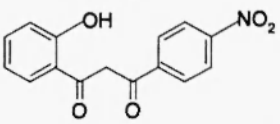
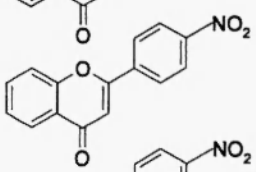
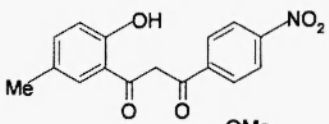
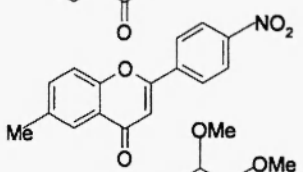
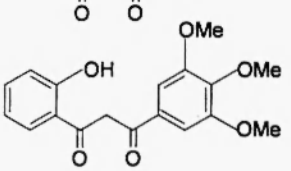
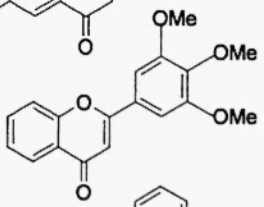
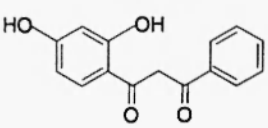
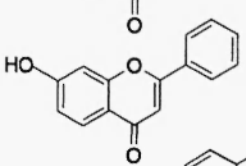
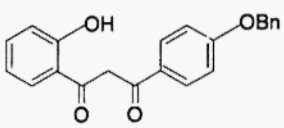
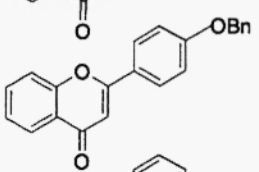
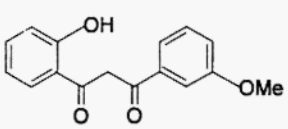
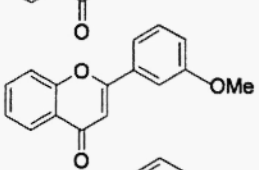
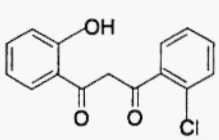
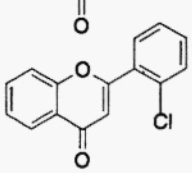
1 2

Scheme 1

Results and Discussion : In a typical reaction, the 1,3 diketones **1** in CH_2Cl_2 was treated with catalytic amount of $FeCl_3$ (10 %) and stirred at room temperature. The progress of the reaction was monitored by TLC. After completion, aqueous work-up followed by evaporation of the solvent afforded pure flavone **2** in almost quantitative yield. To evaluate the synthetic utility of the procedure, several substituted diketones were prepared by the established procedure[5] and subjected to the reaction conditions. The results are presented in Table-1.

The reaction proceeds very cleanly to afford flavones bearing NO_2, Cl, methoxy and hydroxyl groups on the aromatic ring in high yields. No undesirable side reactions were observed and the products obtained required little or no purification for most practical purposes. As is obvious from the table, the substituents on the aromatic ring had little

Table-1: Products synthesized and data.

Entry	Substrate	Product	Yield [a] (%)	Time (hr)	M. P. (°C)
1			95	0.5	97[4a]
2			96	1	156[4a]
3			95	1	153[4a]
4			91	1	187[4a]
5			90	1	245[15]
6			93	1	277[14]
7			87	1	176[2a]
8			92	1	241[4a]
9			87	1	192[1d]
10			94	1	129[16]
11			90	1	117[6]

a : Identification were made by ^1H NMR, ^{13}CNMR and comparision with authentic samples, yields were calculated from the isolated flavone.

effect on the yield and the protocol offers advantages in terms of the simple procedure and work- up, fast reaction rate, mild reaction condition and excellent yield. Application of this method to synthesize flavones bearing sensitive functional group is underway in our laboratory.

In summary, we have demonstrated that $FeCl_3$ is a superior catalyst for dehydrative cyclisation of 1, 3 - (diaryl diketones) to flavones. We hope this simplified procedure finds wide spread use in organic synthesis.

Experimental Section :

Melting points were determined in open glass capillaries on a mettler FP51 melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded at room temperature on a Varian Inova spectrometer in $CDCl_3$ using TMS as internal standard.

General Procedure : To the diketone 1 (1 mmole) in CH_2Cl_2 (10 ml) was added $FeCl_3$ (10 mol %) and stirred at room temperature for 30 minutes (TLC). Work-up with water and concentration of dichloromethane extract afforded flavone 2 in (87 - 96 %) yield.

The spectral data of some selected compounds :

3', 4'- Dimethoxyflavone (3) : ^1H NMR (300 MHz, $CDCl_3$) δ 3.95 (s, 3H), 3.97 (s, 3H), 6.73 (s, 1H), 6.96 (d, J = 8.1 Hz, 1H), 7.36 (d, J = 1.8 Hz, 1H), 7.40 (dd, J = 7.2, 7.5 Hz, 1H), 7.52 (dd, J = 1.8, 8.1 Hz, 1H), 7.53 (d, J = 7.5 Hz, 1H), 7.67 (ddd, J = 1.5, 7.2, 7.8 Hz, 1H), 8.20 (dd, J = 1.5, 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.1, 106.4, 108.8, 111.2, 118.0, 111.2, 118.0, 120.0, 123.9, 124.2, 125.6, 133.6, 149.3, 152.1, 156.1, 163.3, 178.3.

4'-Chloroflavone (4) : ^1H NMR (300 MHz, $CDCl_3$) δ 6.73 (s, 1H), 7.32 - 7.58 (m,4H), 7.61 - 7.70 (m, 1H), 7.77 - 7.88 (m, 2H), 8.12 - 8.22 (m, 1H); ^{13}CNMR (100 MHz, $CDCl_3$). δ 107.6, 117.8, 123.9, 125.7, 127.5, 129.3, 130.2, 133.9, 137.8, 156.1, 162.8, 178.2.

6-Methyl-4'-nitroflavone (6) : ^1H NMR (300 MHz, $CDCl_3$) δ 2.43 (s, 3H), 7.21 (s, 1H), 7.68 (dd, 1H, J = 8.9, 2.1 Hz), 7.72 (d, 1H, J = 8.6 Hz), 7.85 (m, 1H), 8.37 (s, 4H); ^{13}CNMR (100 MHz, $CDCl_3$) 21.4, 109.9, 119.4, 125.0, 125.0, 128.6, 136.4, 136.6, 138.1, 149.9, 154.9, 160.9, 177.1.

7- Hydroxyflavone (8) : ^1H NMR (300 MHz, $CDCl_3$) δ 6.91 (s, 1H), 6.95 (dd, J = 1.8, 9.0 Hz, 1H), 7.02 (d, J = 1.8 Hz, 1H), 7.57-7.59 (m, 3H), 7.91 (d, J = 9.0 Hz, 1H), 8.05-8.08 (m, 2H), 10.8 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 102.6, 106.6, 115.1, 116.2, 126.2, 126.5, 129.1,131.3, 131.5, 157.5, 161.2, 162.8, 176.4.

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