

First Vilsmeier-Haack Synthesis of Flavones using *bis*-(Trichloromethyl) Carbonate/Dimethylformamide

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Flavones are a class of naturally occurring compounds with various biological activities.^{1–4} One of the most commonly used methods for the synthesis of flavones is the cyclodehydration of 1-(2-hydroxyphenyl)-3-aryl-1,3-propanediones. Many of these procedures use strong acids such as H₂SO₄,^{5–6} HCl,⁷ HBr or HI,⁸ catalysts such as NaHSO₄/SiO₂,⁹ H₃PMO₁₂O₄₀·nH₂O/SiO₂,¹⁰ H₃PW₁₂O₄₀·nH₂O/SiO₂,¹⁰ non-aqueous cation-exchange resin,¹¹ or supported trifluoromethanesulfonic acid.¹² All of these agents require high temperatures to complete the reaction. Other methods include the use of Br₂ or I₂ under irradiation conditions,¹³ ionic liquid [EtNH₃]NO₃,¹⁴ CuCl₂,¹⁵ or montmorillonite K-10 clay¹⁶ as the catalyst by microwave-assisted synthesis have been reported in various yields.

The Vilsmeier-Haack reaction was initially used for the formylation of activated aromatic substrates and carbonyl compounds.¹⁷ It is now used as a powerful synthetic tool for the construction of many heterocyclic compounds such as quinolines, indoles, pyridines, and quinazoline derivatives.^{18–23} However, its application to cyclodehydration reactions has not been reported. Following our recent work,^{24–29} we carried out an investigation on the feasibility of cyclodehydration of 1-(2-hydroxyphenyl)-3-aryl-1,3-propanediones under Vilsmeier-Haack conditions with *bis*-(trichloromethyl) carbonate/dimethylformamide (BTC/DMF) to synthesize flavones (*Scheme 1*).

Firstly, the ratio of reactants was investigated. It was shown that using 1,2-dichloroethane as the solvent, BTC/DMF/1-(2-hydroxyphenyl)-3-aryl-1,3-propanedione = 1:3:1.5 was optimum to obtain the desired product in good yields. If the ratio was decreased, the yield was reduced dramatically. Several conventional organic solvents such as DMF, diethyl ether, THF, toluene, and halohydrocarbons were used to optimize the reaction conditions. 1,2-dichloroethane and DMF were found to be more suitable solvents for the reaction under similar conditions because of their excellent solvating properties. When

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(a) $R^1 = R^2 = R^3 = R^4 = R^5 = H$; (b) $R^1 = R^2 = R^3 = R^4 = H, R^5 = Cl$; (c) $R^1 = R^2 = R^3 = R^5 = H, R^4 = Cl$; (d) $R^1 = R^2 = R^3 = H, R^4 = R^5 = Cl$; (e) $R^1 = R^2 = R^4 = H, R^3 = R^5 = Cl$; (f) $R^2 = R^4 = H, R^1 = R^3 = Br, R^5 = Cl$; (g) $R^1 = R^3 = R^4 = H, R^2 = CH_3, R^5 = Cl$; (h) $R^1 = R^2 = R^4 = H, R^3 = CH_3, R^5 = Cl$; (i) $R^1 = R^2 = R^4 = H, R^3 = Cl, R^5 = CH_3$; (j) $R^1 = R^2 = R^3 = R^4 = H, R^5 = CH_3$; (k) $R^1 = R^2 = R^4 = R^5 = H, R^3 = CH_3$; (l) $R^1 = R^3 = R^4 = R^5 = H, R^2 = CH_3$; (m) $R^1 = R^2 = R^4 = H, R^3 = R^5 = CH_3$; (n) $R^1 = R^2 = R^3 = R^4 = H, R^5 = OCH_3$; (o) $R^1 = R^2 = R^4 = H, R^3 = R^5 = OCH_3$; (p) $R^1 = R^2 = R^3 = R^4 = H, R^5 = NO_2$; (q) $R^1 = R^2 = R^4 = R^5 = H, R^3 = NO_2$; (r) $R^1 = R^2 = R^4 = H, R^3 = CH_3, R^5 = NO_2$; (s) $R^1 = R^2 = R^4 = H, R^3 = OCH_3, R^5 = NO_2$.

Scheme 1

other solvents were used, the reaction proceeded slowly and gave low yields. In addition, we used *N,N*-diethyl-4-methylbenzamide instead of DMF to accomplish the reaction and also obtained good yields.

On the basis of the above results, to extend the scope and generality of the reaction, this procedure was applied to other structurally diverse 1-(2-hydroxyphenyl)-3-aryl-1,3-propanediones under similar conditions. The results are listed in *Table 1*. It could be seen that all the substrates easily underwent cyclodehydration to give flavones with short reaction times and good yields. It is worthwhile noting that electron-withdrawing and electron-donating groups on the aromatic ring did not seem to affect the reaction significantly, either in the yield of product or the rate of the reaction.

In conclusion, the present version of the Vilsmeier-Haack reaction with BTC/DMF provides an efficient and rapid synthesis of flavones by the cyclodehydration of the corresponding 1-(2-hydroxyphenyl)-3-aryl-1,3-propanediones. High yields, mild reaction conditions, and short reaction times are the notable advantages of this procedure. We believe that this procedure will provide a better scope and a more practical alternative to the existing methods for the synthesis of flavones.

Experimental Section

1-(2-Hydroxyphenyl)-3-aryl-1,3-propanediones were prepared by procedures reported previously.³⁰⁻³¹ Other reagents were from commercial sources. Melting points (mps) were determined on a WRS-1B digital melting point apparatus and are uncorrected. Infrared spectra were recorded on a Thermo Nicolet Avatar 370 spectrophotometer. ¹H NMR and ¹³C NMR spectra were obtained on a Varian Mercury plus-400 spectrometer using CDCl₃ as the solvent with TMS as the internal standard. Mass spectra were measured with a Finnigan Trace DSQ spectrometer. Elemental analyses were measured on a Thermo Finnigan Flash EA 1112 elemental analyzer.

Typical Procedure

A solution of BTC (0.4 g, 1.33 mmol) in ClCH₂CH₂Cl (10 mL) was added dropwise to a solution of DMF (4 mL, 4 mmol) in ClCH₂CH₂Cl (10 mL) in an ice-water bath,

Table 1
Preparation of Flavones with BTC/DMF in 1,2-Dichloroethane^a

Entry	Product	Time (h)	Yield ^b (%)	mp (°C) (lit. mp)	IR (cm ⁻¹)	¹ H NMR (δ)
1	2a	2	94	96–97 (96–97 ³²)	1646, 1605, 1568, 1128, 768	8.24 (d, <i>J</i> = 8.0 Hz, 1 H, ArH), 7.94 (d, <i>J</i> = 8.0 Hz, 2 H, ArH), 7.71 (t, <i>J</i> = 8.0 Hz, 1 H, ArH), 7.53–7.60 (m, 4 H, ArH), 7.43 (t, <i>J</i> = 8.0 Hz, 1 H, ArH), 6.86 (s, 1 H, CH)
2	2b	2	93	185–187 (185–188 ³³)	1641, 1466, 1090, 828, 772	8.21 (d, <i>J</i> = 8.0 Hz, 1 H, ArH), 7.84 (d, <i>J</i> = 8.0 Hz, 2 H, ArH), 7.70 (t, <i>J</i> = 8.0 Hz, 1 H, ArH), 7.54 (d, <i>J</i> = 8.0 Hz, 1 H, ArH), 7.48 (d, <i>J</i> = 8.0 Hz, 2 H, ArH), 7.42 (t, <i>J</i> = 8.0 Hz, 1 H, ArH), 6.78 (s, 1 H, CH)
3	2c	2.5	90	193–195 (192–193 ³⁴)	1651, 1368, 1153, 1066, 909, 767	8.26 (d, <i>J</i> = 8.0 Hz, 1 H, ArH), 7.62–7.71 (m, 2 H, ArH), 7.39–7.53 (m, 5 H, ArH), 6.67 (s, 1 H, CH)
4	2d	2.5	91	172–175 (172–174 ³⁵)	1650, 1467, 1381, 1365, 823, 775, 753	8.25 (d, <i>J</i> = 8.0 Hz, 1 H, ArH), 7.70–7.74 (m, 1 H, ArH), 7.60–7.61 (m, 2 H, ArH), 7.51 (d, <i>J</i> = 8.0 Hz, 1 H, ArH), 7.40–7.46 (m, 2 H, ArH), 6.66 (s, 1 H, CH)
5	2e	3	92	226–227 (226–227 ³⁶)	1658, 1492, 1438, 1092, 906, 831, 664	8.19 (s, 1 H, ArH), 7.85 (d, <i>J</i> = 8.0 Hz, 2 H, ArH), 7.64–7.67 (m, 1 H, ArH), 7.51–7.54 (m, 3 H, ArH), 6.79 (s, 1 H, CH)
6	2f	3	91	248–251 (249–250 ³⁷)	1649, 1612, 1492, 1092, 839, 699	8.29 (s, 1H, ArH), 8.04 (s, 1H, ArH), 7.93 (d, <i>J</i> = 8.0 Hz, 2H, ArH), 7.53 (d, <i>J</i> = 8.0 Hz, 2H, ArH), 6.84 (s, 1H, CH)
7	2g^c	2.5	94	179–180	1638, 1490, 1410, 1092, 906, 827, 813, 477	8.05 (d, <i>J</i> = 8.0 Hz, 1 H, ArH), 7.77–7.80 (m, 2 H, ArH), 7.43–7.46 (m, 2 H, ArH), 7.29 (s, 1 H, ArH), 7.19 (d, <i>J</i> = 8.0 Hz, 1 H, ArH), 6.70 (s, 1 H, CH), 2.47 (s, 3 H, CH ₃)

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Table 1
Preparation of Flavones with BTC/DMF in 1,2-Dichloroethane^a (Continued)

Entry	Product	Time (h)	Yield ^b (%)	mp (°C) (<i>lit.</i> mp)	IR (cm ⁻¹)	¹ H NMR (δ)
8	2h	2.5	93	198–199 (198–199 ³⁶)	1643, 1621, 1483, 1089, 902, 820, 707	7.99 (s, 1 H, ArH), 7.83 (d, <i>J</i> = 8.4 Hz, 2 H, ArH), 7.43–7.51 (m, 4 H, ArH), 6.76 (s, 1 H, CH), 2.46 (s, 3 H, CH ₃)
9	2i	2.5	90	183–184 (183–184 ³⁶)	1641, 1613, 1465, 1436, 1358, 816, 670	8.16 (s, 1 H, ArH), 7.78 (d, <i>J</i> = 8.0 Hz, 2 H, ArH), 7.61 (d, <i>J</i> = 8.0 Hz, 1 H, ArH), 7.50 (d, <i>J</i> = 8.0 Hz, 1 H, ArH), 7.31 (d, <i>J</i> = 8.0 Hz, 2 H, ArH), 6.79 (s, 1 H, CH), 2.43 (s, 3 H, CH ₃)
10	2j	2	95	108–111 (108–111 ³⁵)	1637, 1465, 1371, 1227, 817, 752, 634	8.21 (d, <i>J</i> = 8.0 Hz, 1 H, ArH), 7.78 (s, 2 H, ArH), 7.65 (t, <i>J</i> = 4.0 Hz, 1 H, ArH), 7.52 (s, 1 H, ArH), 7.27 (s, 1 H, ArH), 7.38 (t, <i>J</i> = 8.0 Hz, 2 H, ArH), 6.76 (s, 1 H, CH), 2.40 (s, 3 H, CH ₃)
11	2k	2	94	121–122 (122 ³⁶)	1638, 1615, 1482, 1359, 1044, 883, 814, 778	8.00 (s, 1 H, ArH), 7.90 (d, <i>J</i> = 8.0 Hz, 2 H, ArH), 7.43–7.52 (m, 5 H, ArH), 6.79 (s, 1 H, CH), 2.45 (s, 3 H, CH ₃)
12	2l	2	93	129–131 (128–130 ³⁴)	1637, 1606, 1449, 1371, 1157, 866, 772	8.14 (s, 1 H, ArH), 7.91 (d, <i>J</i> = 8.0 Hz, 2 H, ArH), 7.51 (s, 3 H, ArH), 7.35 (s, 1 H, ArH), 7.22 (d, <i>J</i> = 8.0 Hz, 1 H, ArH), 6.81 (s, 1 H, CH), 2.50 (s, 3 H, CH ₃)
13	2m	2.5	95	151–152 (150–151 ³⁶)	1643, 1613, 1483, 817	8.00 (s, 1 H, ArH), 7.80 (d, <i>J</i> = 8.0 Hz, 2 H, ArH), 7.44–7.50 (m, 2 H, ArH), 7.31 (d, <i>J</i> = 8.0 Hz, 2 H, ArH), 6.77 (s, 1 H, CH), 2.46 (s, 3 H, CH ₃), 2.43 (s, 3 H, CH ₃)
14	2n	1.5	97	157–159 (157–158 ³⁶)	1649, 1608, 1465, 1380, 1133, 827, 767	8.21 (d, <i>J</i> = 8.0 Hz, 1 H, ArH), 7.85 (d, <i>J</i> = 8.4 Hz, 2 H, ArH), 7.65–7.69 (m, 1 H, ArH), 7.53 (d, <i>J</i> = 8.0 Hz, 1 H, ArH), 7.40 (t, <i>J</i> = 7.2 Hz, 1 H, ArH), 6.98–7.01 (m, 2 H, ArH), 6.72 (s, 1 H, CH), 3.87 (s, 3 H, CH ₃)

Table 1
Preparation of Flavones with BTC/DMF in 1,2-Dichloroethane^a (Continued)

Entry	Product	Time (h)	Yield ^b (%)	mp (°C) (lit. mp)	IR (cm ⁻¹)	¹ H NMR (δ)
15	2o	1.5	95	196.1–196.2 (194–195 ³⁸)	1649, 1608, 1515, 1466, 1382, 1268, 1195, 1026, 827, 768	7.88 (d, <i>J</i> = 8.0 Hz, 2 H, ArH), 7.61 (d, <i>J</i> = 4.0 Hz, 1 H, ArH), 7.45 (d, <i>J</i> = 8.0 Hz, 1 H, ArH), 7.29 (d, <i>J</i> = 4.0 Hz, 1 H, ArH), 7.03 (d, <i>J</i> = 8.0 Hz, 2 H, ArH), 6.76 (s, 1 H, CH), 3.92 (s, 3 H, OCH ₃), 3.90 (s, 3 H, OCH ₃)
16	2p	3.5	90	241–243 (242–244 ³⁴)	1659, 1520, 1467, 1346, 1130, 857, 750, 692	8.11–8.40 (m, 5 H, ArH), 7.48–7.76 (m, 3 H, ArH), 6.92 (s, 1 H, CH)
17	2q	3	87	194.6–195.1 (193 ³⁹)	1646, 1610, 1454, 1340, 1135, 922, 841, 772, 679, 627	9.12 (s, 1 H, ArH), 8.52 (d, <i>J</i> = 8.0 Hz, 1 H, ArH), 7.93–7.95 (m, 2 H, ArH), 7.74 (d, <i>J</i> = 4.0 Hz, 1 H, ArH), 7.55–7.63 (m, 3 H, ArH), 6.90 (s, 1 H, CH)
18	2r	3.5	89	276–278 (275–277 ³⁶)	1639, 1617, 1522, 1343, 1138, 850, 823, 691	8.39 (d, <i>J</i> = 8.0 Hz, 2 H, ArH), 8.11 (d, <i>J</i> = 8.0 Hz, 2 H, ArH), 8.03 (s, 1 H, ArH), 7.50–7.58 (m, 2 H, ArH), 6.90 (s, 1 H, CH), 2.49 (s, 3 H, CH ₃)
19	2s	2	93	200.1–201.8 (198–200 ⁹)	1642, 1607, 1518, 1488, 1347, 1020, 853, 826, 697	8.39 (d, <i>J</i> = 8.0 Hz, 2 H, ArH), 8.11 (t, <i>J</i> = 4.0 Hz, 2 H, ArH), 7.61 (d, <i>J</i> = 4.0 Hz, 1 H, ArH), 7.55 (d, <i>J</i> = 8.0 Hz, 1 H, ArH), 7.33–7.36 (m, 1 H, ArH), 6.90 (s, 1 H, CH), 3.96 (s, 3 H, CH ₃)

^aSubstrate **1** (2 mmol), BTC (1.33 mmol) and DMF (4 mL, 4 mmol) was used.

^bIsolated yields.

^c¹³C NMR (CDCl₃): δ 177.89, 161.60, 156.05, 145.11, 137.55, 130.11, 129.14, 127.24, 126.66, 125.25, 121.46, 117.63, 107.36, 21.69; IR (KBr): 1638, 1490, 1410, 1092, 906, 827, 813, 477 cm⁻¹; MS (EI): *m/z* (%) = 270 (5) [M⁺], 242 (100), 178 (90), 152 (70), 78 (6); *Anal.* Calcd for C₁₆H₁₁ClO₂: C, 70.99; H, 4.10; Found: C, 70.92; H, 4.04.

and the mixture was stirred at 0°C for 10 min and at 20°C for 30 min. The temperature was reduced to 0–5°C and the substituted 1-(2-hydroxyphenyl)-3-aryl-1,3-propanedione (2 mmol) was added. The reaction proceeded at room temperature and was monitored by TLC. After completion, the mixture was washed with water (20 mL), and the organic layer was isolated. The aqueous layer was extracted by CH₂Cl₂ (20 mL × 2). The combined

organic extracts were washed with saturated NaHCO₃ solution (20 mL × 2), dried (MgSO₄) and evaporated. The crude product was purified by flash column chromatography to provide the corresponding product.

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