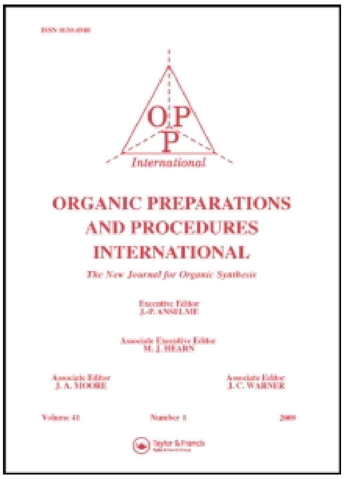

ORGANIC PREPARATIONS
AND PROCEDURES
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Volume 41 Number 1 2009

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

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

W. K. Su[a]; X. Y. Zhu[a]; Z. H. Li[a]
[a] College of Pharmaceutical Sciences, Zhejiang Key Laboratory of Pharmaceutical Engineering, Zhejiang University of Technology, Hangzhou, P. R. China

To cite this Article Su, W. K. , Zhu, X. Y. and Li, Z. H.(2009) 'First Vilsmeier-Haack Synthesis of Flavones using *bis*-(Trichloromethyl) Carbonate/Dimethylformamide', Organic Preparations and Procedures International, 41: 1, 69 — 75

To link to this Article: DOI: 10.1080/00304940802710947

URL: http://dx.doi.org/10.1080/00304940802710947

Organic Preparations and Procedures International, 41:69–75, 2009
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ISSN: 0030-4948 print
DOI: 10.1080/00304940802710947

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

W. K. Su, X. Y. Zhu, and Z. H. Li

College of Pharmaceutical Sciences, Zhejiang University of Technology,
Zhejiang Key Laboratory of Pharmaceutical Engineering, Hangzhou, P. R. China

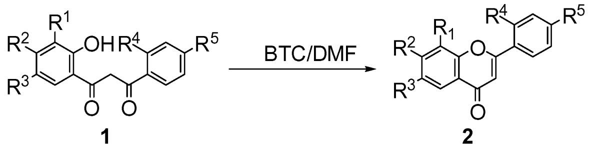
Flavones are a class of naturally occurring compounds with various biological activities.[1–4] One of the most commonly used methods for the synthesis of flavones is the cyclodehydration of 1-(2-hydroxyphenyl)-3-aryl-1,3-propanediones. Many of these procedures use strong acids such as H_2SO_4,[5-6] HCl,[7] HBr or HI,[8] catalysts such as $NaHSO_4/SiO_2$,[9] $H_3PMo_{12}O_{40}\cdot nH_2O/SiO_2$,[10] $H_3PW_{12}O_{40}\cdot nH_2O/SiO_2$,[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 Br_2 or I_2 under irradiation conditions,[13] ionic liquid $[EtNH_3]NO_3$,[14] $CuCl_2$,[15] or montmorillonite K-10 clay[16] 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/dime-thylformamide (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 dramati-cally. Several conventional organic solvents such as DMF, diethyl ether, THF, toluene, and halohydro-carbons 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

Received February 21, 2008; in final form September 26, 2008

Address correspondence to W.K. Su, Zhejiang University of Technology, College of Pharmaceutical Sciences, Zhejiang Key Laboratory of Pharmaceutical Engineering Hangzhou 310014, P. R. China. E-mail: suweike@zjut.edu.cn



(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 ^{13}C NMR spectra were obtained on a Varian Mercury plus-400 spectrometer using $CDCl_3$ 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 $ClCH_2CH_2Cl$ (10 mL) was added dropwise to a solution of DMF (4 mL, 4 mmol) in $ClCH_2CH_2Cl$ (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, $J = 8.0$ Hz, 1 H, ArH), 7.94 (d, $J = 8.0$ Hz, 2 H, ArH), 7.71 (t, $J = 8.0$ Hz, 1 H, ArH), 7.53–7.60 (m, 4 H, ArH), 7.43 (t, $J = 8.0$ 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, $J = 8.0$ Hz, 1 H, ArH), 7.84 (d, $J = 8.0$ Hz, 2 H, ArH), 7.70 (t, $J = 8.0$ Hz, 1 H, ArH), 7.54 (d, $J = 8.0$ Hz, 1 H, ArH), 7.48 (d, $J = 8.0$ Hz, 2 H, ArH), 7.42 (t, $J = 8.0$ 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, $J = 8.0$ 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, $J = 8.0$ Hz, 1 H, ArH), 7.70–7.74 (m, 1 H, ArH), 7.60 -7.61 (m, 2 H, ArH), 7.51 (d, $J = 8.0$ 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, $J = 8.0$ 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, $J = 8.0$ Hz, 2H, ArH), 7.53 (d, $J = 8.0$ 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, $J = 8.0$ 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, $J = 8.0$Hz, 1 H, ArH), 6.70 (s, 1 H, CH), 2.47 (s, 3 H, CH_3)

(Continued on next page)

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)
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, *J* = 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, *J* = 8.0 Hz, 2 H, ArH), 7.61 (d, *J* = 8.0 Hz, 1 H, ArH), 7.50 (d, *J* = 8.0 Hz, 1 H, ArH), 7.31 (d, *J* = 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, *J* = 8.0 Hz, 1 H, ArH), 7.78 (s, 2 H, ArH), 7.65 (t, *J* = 4.0 Hz, 1 H, ArH), 7.52 (s, 1 H, ArH), 7.27 (s, 1 H, ArH), 7.38 (t, *J* = 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, *J* = 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, *J* = 8.0 Hz, 2 H, ArH),7.51 (s, 3 H, ArH), 7.35 (s, 1 H, ArH), 7.22 (d, *J* = 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, *J* = 8.0 Hz, 2 H, ArH), 7.44–7.50 (m, 2 H, ArH), 7.31 (d, *J* = 8.0 Hz, 2 H, ArH), 6.77 (s, 1 H, CH), 2.46 (s, 3 H, CH$_3$), 2.43 2.46 (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, *J* = 8.0 Hz, 1 H, ArH), 7.85 (d, *J* = 8.4 Hz, 2 H, ArH), 7.65–7.69 (m, 1 H, ArH), 7.53 (d, *J* = 8.0 Hz, 1 H, ArH), 7.40 (t, *J* = 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, $J = 8.0$ Hz, 2 H, ArH), 7.61 (d, $J = 4.0$ Hz, 1 H, ArH), 7.45 (d, $J = 8.0$ Hz, 1 H, ArH), 7.29 (d, $J = 4.0$ Hz, 1 H, ArH), 7.03 (d, $J = 8.0$ 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, $J = 8.0$ Hz, 1 H, ArH), 7.93–7.95 (m, 2 H, ArH), 7.74 (d, $J = 4.0$ 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, $J = 8.0$ Hz, 2 H, ArH), 8.11 (d, $J = 8.0$ 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, $J = 8.0$ Hz, 2 H, ArH), 8.11 (t, $J = 4.0$ Hz, 2 H, ArH), 7.61 (d, $J = 4.0$ Hz, 1 H, ArH), 7.55 (d, $J = 8.0$ 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)

[a] Substrate **1** (2 mmol), BTC (1.33 mmol) and DMF (4 mL, 4 mmol) was used.

[b] Isolated yields.

[c] ^{13}C NMR ($CDCl_3$): 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 $C_{16}H_{11}ClO_2$: 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 CH_2Cl_2 (20 mL × 2). The combined organic extracts were washed with saturated $NaHCO_3$ solution (20 mL × 2), dried ($MgSO_4$) and evaporated. The crude product was purified by flash column chromatography to provide the corresponding product.

Acknowledgment

We are grateful to the Natural Science Foundation of Zhejiang province (No. 202095) and the Natural Science Foundation of China (No. 20676123) for financial help.

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