Microwave-Assisted *O*-Alkylation of Carboxylic Acids in Dry Media: Expeditious Synthesis of 2-Oxo-2-arylethyl Carboxylates

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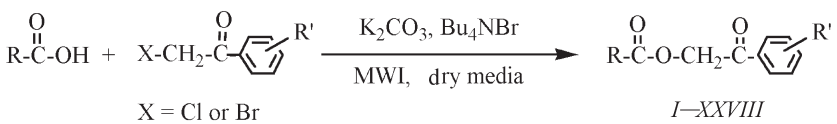
Microwave-assisted *O*-alkylation reactions of carboxylic acids, such as aryloxyacetic acids, 4-chlorobenzoic acid, (un)substituted furoic acids, and benzofuroic acid, with (un)substituted ω-haloacetophenones in dry media under phase-transfer catalysis are described. 2-Oxo-2-arylethyl carboxylates are expeditiously synthesized by this method in high yield using tetrabutylammonium bromide as catalyst.

O-Alkylation of diverse carboxylic acids has played an important role in preparation of esters. *O*-Alkylation of various carboxylic acids with (un)substituted ω-haloacetophenones is a major source of 2-oxo-2-arylethyl carboxylates [1], which are important intermediates for organic synthesis and biologically active compounds because of their antibacterial [2], anesthetic [3], anticonvulsive [4], and plant-growth regulating [5] activities. The present methods for obtaining 2-oxo-2-arylethyl carboxylates are usually performed by the reaction in toxic solvents, such as acetonitrile and chlorobenzene, at reflux temperature for at least 12 h, giving only middle yield. Furthermore, the carboxylic acids have to be converted into their potassium salts before reaction with ω-haloacetophenones [1, 6].

In recent years, the use of microwave irradiation in solvent-free reactions has received considerable attention. All microwave reactions reported exhibit dramatic rate enhancements compared to the classical methods. Meanwhile, the microwave reactions often afford high yield by convenient procedures [7, 8].

Based on the above facts, a rapid, simple, and high-yielding *O*-alkylation reaction of carboxylic acids with (un)substituted ω-haloacetophenones in the presence of phase-transfer catalyst under microwave irradiation and solvent-free conditions is reported.

Treatment of various carboxylic acids, such as phenyloxyacetic, 4-chlorophenyloxyacetic, 4-methyl-



Scheme 1

Table 1. The Effect of Microwave Power and Irradiating Time on the Yield of Compound *V* under Solvent-Free and Phase-Transfer Catalysis Conditions

The effect of microwave power on the yield					
Microwave power/W	70	210	350	490	700
Yield/%	60	67	83	90	33
The effect of irradiating time on the yield					
Irradiating time/min	1	2	3	4	5
Yield/%	60	75	80	90	50

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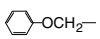
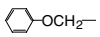
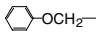
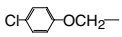
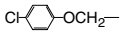
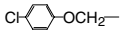
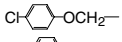
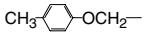
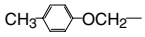
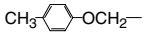
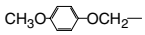
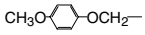
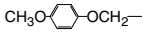
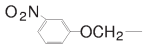
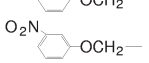
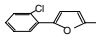
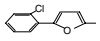
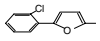
Table 2. Comparison of Solvent-Free Microwave Method with Conventional Solution Method for the Effect of Phase-Transfer Catalysts on the Yield of Compound *V*

Catalyst	Yield/%		Catalyst	Yield/%	
	Microwave method[a]	Conventional[b]		Microwave method[a]	Conventional[b]
TEAI	88	80	CTMAB	60	64
TMAB	78	69	CPB	74	65
TBAB	90	70	18-Crown-6	82	78
TBAI	60	73	PEG-400	50	40
TEAB	70	54	None	45	Traces

a) Microwave irradiation at 490 W for 4 min in solvent-free conditions.
b) Conventional heating at 110 °C for 12 h in chlorobenzene.

Table 3. The Microwave-Assisted Synthesis of *I*—*XXVIII* Catalyzed by TBAB in Dry Media

Compound	R	R′	Time	M.p. (Ref.[a])	Yield (Ref.[a])
			min	°C	%
I		H	4	72—73 (71—73)	85 (86)
II		4-Cl	4	144—145 (146—148)	92
III		4-OCH_3	4	80—81	97
IV		H	4	87—88 (88—90)	90 (88)
V		4-Cl	4	135—136 (134—135)	90 (92)
VI		4-OCH_3	4	135—136	98
VII		4-CH_3	3.5	129—130	94
VIII		H	3	101—102 (99—101)	87 (96)
IX		4-Cl	5	146—147	94
X		4-OCH_3	4	102—103	98
XI		H	3	103—104 (99—101)	83 (87)
XII		4-Cl	5	143—144	84
XIII		4-OCH_3	4	104—105	76
XIV		H	3.5	117—118 (117—118)	85 (65)
XV		4-Cl	5	120—121 (97—99)	88 (82.8)
XVI		4-OCH_3	3.5	110—111	92
XVII		H	6	128—129	85
XVIII		4-Cl	8	124—125	91
XIX		4-OCH_3	6	85—86	97
XX		H	10	87—88	87
XXI		4-Cl	10	125—126	90
XXII		4-OCH_3	10	116—117	95
XXIII		H	7	229—230	86
XXIV		4-Cl	7	154—155	92
XXV		4-OCH_3	7	157—158	90
XXVI		H	4	124—125	90
XXVII		4-Cl	5	145—146	95
XXVIII		4-OCH_3	6	136—137	92

a) The data for solution method reported by literature, see Refs. [1, 6].

phenyloxyacetic, 4-methoxyphenyloxyacetic, 3-nitrophenyloxyacetic, 4-chlorobenzoic, furoic, benzofuroic, and 5-(2-chlorophenyl)-2-furoic acid, with equivalent of (un)substituted ω-haloacetophenones in the presence of tetrabutylammonium bromide (TBAB) as phase-transfer catalyst and potassium carbonate as

Table 4. ^{1}H NMR, IR, and Elemental Analyses Data of Compounds *I*—*XXVIII*[a]

Compound	^{1}H NMR ($CDCl_3$, δ)			IR, $\tilde{\nu}$/cm^{-1}	w_i(found)/% (w_i(calc.)/%)	
	Ar-H and Fu-H	CH_2	CH_3	C═O	C	H
I	6.84—7.82 (m, 10H)	5.52 (s, 2H), 4.72 (s, 2H)		1700, 1760	70.86 (71.10)	5.35 (5.22)
II	6.84—7.93 (m, 9H)	5.61 (s, 2H), 4.75 (s, 2H)		1708, 1763	63.42 (63.06)	4.15 (4.30)
III	6.83—7.94 (m, 9H)	5.60 (s, 2H), 4.73 (s, 2H)	3.75 (s, 3H)	1710, 1760	68.08 (67.99)	5.29 (5.37)
IV	6.86—7.92 (m, 9H)	5.42 (s, 2H), 4.78 (s, 2H)		1700, 1770	63.28 (63.06)	4.34 (4.30)
V	6.89—8.22 (m, 8H)	5.51 (s, 2H), 4.77 (s, 2H)		1713, 1769	57.01 (57.01)	3.50 (3.57)
VI	6.86—8.20 (m, 8H)	5.57 (s, 2H), 4.76 (s, 2H)	3.76 (s, 3H)	1710, 1772	61.10 (61.00)	4.46 (4.52)
VII	6.87—7.80 (m, 8H)	5.30 (s, 2H), 4.76 (s, 2H)	2.26 (s, 3H)	1699, 1772	63.98 (64.06)	4.83 (4.74)
VIII	6.74—7.84 (m, 9H)	5.36 (s, 2H), 4.72 (s, 2H)	2.20 (s, 3H)	1696, 1760	71.65 (71.82)	5.38 (5.67)
IX	6.74—7.90 (m, 8H)	5.40 (s, 2H), 4.72 (s, 2H)	2.27 (s, 3H)	1713, 1762	64.12 (64.06)	4.79 (4.74)
X	6.73—8.01 (m, 8H)	5.42 (s, 2H), 4.73 (s, 2H)	3.78 (s, 3H) 2.27 (s, 3H)	1705, 1761	68.69 (68.78)	5.84 (5.77)
XI	6.82—7.84 (m, 9H)	5.38 (s, 2H), 4.72 (s, 2H)	3.68 (s, 3H)	1702, 1764	67.67 (67.99)	5.46 (5.37)
XII	6.81—8.20 (m, 8H)	5.52 (s, 2H), 4.73 (s, 2H)	3.76 (s, 3H)	1763, 1768	60.95 (61.00)	4.47 (4.52)
XIII	6.83—8.08 (m, 8H)	5.43 (s, 2H), 4.72 (s, 2H)	3.78 (s, 6H)	1697, 1768	65.36 (65.45)	5.58 (5.49)
XIV	7.30—8.03 (m, 9H)	5.50 (s, 2H), 4.96 (s, 2H)		1700, 1758	60.66 (60.95)	4.00 (4.16)
XV	7.32—8.15 (m, 8H)	5.52 (s, 2H), 4.97 (s, 2H)		1703, 1761	54.69 (54.95)	3.31 (3.46)
XVI	7.26—8.20 (m, 8H)	5.50 (s, 2H), 4.95 (s, 2H)	3.79 (s, 3H)	1711, 1759	59.22 (59.13)	4.45 (4.38)
XVII	7.26—7.75 (m, 9H)	5.25 (s, 2H)		1706, 1724	65.66 (65.59)	4.13 (4.04)
XVIII	7.24—7.78 (m, 8H)	5.26 (s, 2H)		1701, 1727	58.34 (58.28)	3.19 (3.26)
XIX	7.21—7.80 (m, 8H)	5.27 (s, 2H)	3.76 (s, 3H)	1718, 1725	63.17 (63.06)	4.22 (4.30)
XX	7.25—8.18 (m, 8H)	5.26 (s, 2H)		1709, 1746	67.93 (67.82)	4.28 (4.38)
XXI	7.28—8.20 (m, 7H)	5.29 (s, 2H)		1712, 1749	59.07 (59.00)	3.37 (3.43)
XXII	7.22—8.17 (m, 7H)	5.28 (s, 2H)	3.77 (s, 3H)	1716, 1750	64.55 (64.61)	4.73 (4.65)
XXIII	7.22—8.23 (m, 10H)	5.30 (s, 2H)		1711, 1762	72.78 (72.85)	4.39 (4.32)
XXIV	7.25—8.21 (m, 9H)	5.31 (s, 2H)		1715, 1768	64.95 (64.88)	3.48 (3.52)
XXV	7.26—8.24 (m, 9H)	5.29 (s, 2H)	3.78 (s, 3H)	1718, 1769	69.74 (69.67)	4.48 (4.55)
XXVI	6.78—8.20 (m, 11H)	5.28 (s, 2H)		1708, 1758	66.92 (66.97)	3.79 (3.85)
XXVII	6.73—8.22 (m, 10H)	5.32 (s, 2H)		1709, 1759	60.79 (60.82)	3.19 (3.22)
XXVIII	6.80—8.19 (m, 10H)	5.29 (s, 2H)	3.74 (s, 3H)	1712, 1760	64.83 (64.79)	4.15 (4.08)

a) The data for compounds *I, II, IV, V, VIII, XI, XIV, XV* reported by literature, see Refs. [1, 6].

base under microwave irradiation affords 2-oxo-2-arylethyl carboxylates (*I*—*XXVIII*) in high yield (Scheme 1).

In the *O*-alkylation reactions, according to the mechanism proved by *Loupy* and coworkers [8] the potassium carbonate acting as a weak nonnucleophilic base sequentially reacted with carboxylic acids to form potassium carboxylates first, then with TBAB to give tetrabutylammonium carboxylates by ion exchange, which further reacted with (un)substituted ω-haloacetophenones to afford 2-oxo-2-arylethyl carboxylates *via* releasing phase-transfer catalyst, quaternary ammonium salt.

In order to optimize the reaction conditions, we selected the synthesis of compound *V* as a typical example to investigate the effect of microwave power and irradiating time on the yield of the product. The results are listed in Table 1. The best yield of *V* is obtained by performing the reaction at 490 W of microwave power for 4 min using TBAB as phase-transfer catalyst in the studied scale.

We also selected the preparation of *V* as a representative to study the effect of various phase-transfer catalysts, such as tetraethylammonium iodide (TEAI), tetramethylammonium bromide (TMAB), TBAB, tetrabutylammonium iodide (TBAI), tetraethylammonium bromide (TEAB), *N*-cetylpyridinium bromide (CPB), cetyltrimethylammonium bromide (CTMAB), 18-crown-6 and poly(ethylene glycol)-400 (PEG-400), on the yield of *V* under the solvent-free conditions. The similar conventional solution reactions were also investigated. The main results are given in Table 2. It is shown that the use of phase-transfer catalyst can significantly improve the yield in all of the cases studied, but different phase-transfer catalysts can give different results. Among which, TBAB is the most suitable catalyst for the reaction studied. This result is similar to the Loupy's report for the phase-transfer catalyzed reaction of benzoic acid with octyl bromide [8]. Meanwhile, for the same phase-transfer catalyst, the solventless microwave method affords higher yield when compared to the conventional solution one.

However, all the reactions can be completed within 3—8 min at 490 W of microwave power giving 76—97 % yield under TBAB as phase-transfer catalyst except those concerning compounds *XX*—*XXII*, the syntheses of which need to perform the reactions at lower

microwave power (350 W) for longer time (10 min) in order to avoid the decomposition of furoic acid at higher microwave power (Table 3).

In summary, we have introduced a solvent-free *O*-alkylation method of carboxylic acids using (un)substituted ω-haloacetophenones under microwave irradiation and phase-transfer catalysis. The use of solvent-free technology efficiently eliminates the possibility of environmental pollution caused by using toxic and volatile organic solvents, and the applications of microwave irradiation and phase-transfer catalyst enormously speed up the reaction rate and enhance the yield of the product.

EXPERIMENTAL

Aryloxyacetic acids [9], 5-aryl-2-furoic acid [10], benzofuroic acid [11], and (un)substituted ω-haloacetophenones [12] were prepared according to the literature procedures.

The microwave reactions were carried out in a modified domestic microwave oven.

IR spectra were recorded using KBr pellets on Nicolet AVATAR 36 FT-IR spectrophotometer and ^{1}H NMR spectra on an Avanci-D2X-200 instrument using $CDCl_3$ as solvent and TMS as internal standard. Elemental analyses were performed on an Erba 1106 elemental analysis instrument. Melting points were determined with an electrothermal micromelting point apparatus.

Compounds *I*—*XXVIII*

The mixture of carboxylic acid (1 mmol), potassium carbonate (1 mmol), ω-haloacetophenone (1 mmol), and appropriate catalyst (0.1 mmol) was finely ground in a mortar for about 1 min. Then it was transferred into a 50 cm^3 flask and irradiated in a microwave oven for appropriate time under appropriate microwave power. The completion of the reaction was monitored by TLC using ethyl acetate, petroleum ether, and acetone ($\varphi_r = 1 : 4 : 1$) as eluent. Then the resulting mixture was cooled to room temperature and water (30 cm^3) was added. The precipitate was collected by filtration and recrystallized from ethanol to give the product. The analytical data are shown in Table 4.

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