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A green procedure for the synthesis of cinnamate esters using Aliquat®336

Tanusri Mahapatra, Amarendra Patra* and Alok Kumar Mitra†

Department of Chemistry, University of Calcutta, University College of Science and Technology, 92, Acharya Prafulla Chandra Road, Calcutta 700 009, India

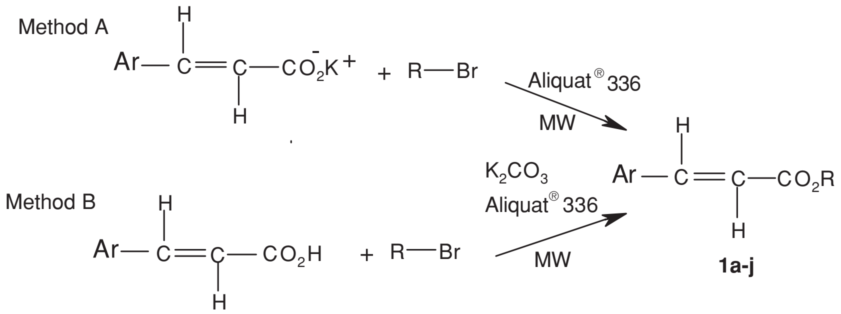
As an effective solid-liquid phase-transfer catalyst as well as an ionic liquid medium Aliquat® 336 has been applied in the synthesis of cinnamate esters under mild green chemistry procedures involving microwave irradiation.

Keywords: cinnamate esters, aliquat®336, phase-transfer catalysis, ionic liquid, solvent-free microwave heating

The diverse applications of cinnamate esters as raw materials for hair tonics,[1] perfumes and agrochemicals,[2] potent non-steroidal inhibitors of fungal 17β-hydroxysteroid dehydrogenase enzyme,[3] anti-inflammatory[4] and anthelmintic,[5] compounds in oxyuriasis therapy,[6] as plasticising and modifying agents for vinyl resins, ethyl cellulose, cellulose acetate *etc.* and as synthetic intermediates for lignans and for pharmaceuticals[7] have attracted the attention of organic chemists in the development of simple, convenient and improved methods for their synthesis. Several syntheses[3,8-16] of cinnamate esters have thus been reported. However, in spite of their potential utility, most of these methods suffer from one or other disadvantages *viz.*, requiring expensive reagents like tungstogermanic acid,[9] $LaMgO/EtO_2CCH_2P(:O)(OEt)_2$,[10] $RuCl_3.3H_2O$[11] or $Pd(OAc)_2/2P(o\text{-}Tol)_3$,[12] strongly basic conditions using reagents like alkyl acetate/alkali or alkali-earth $C_{1\text{-}4}$ alkoxides,[13] long reaction times[2b,8a,9,10,11,12,14] as well as use of mixtures of corrosive and toxic reagents and solvents such as Ac_2O/Fe^{III}-salts[15] and $SnCl_4.5H_2O$/toluene.[16]

The use of environmentally friendly reagents and solvents in organic synthesis is one of the trends in recent years in the growth of green chemistry,[17] which inevitably avoids solvent emission and/or waste. In this context, the uses of room temperature ionic liquids are the subject of current interest as novel reaction media mainly owing to their unique properties of very low vapour pressure, non-volatility, non-combustibility, dissolving polar compounds *etc*, making them potential greener-alternatives to classical organic solvents in chemical transformations. As a result many catalytic reactions proceeding in ionic liquids as reaction media have been reported with excellent results.[18]

The synthesis of cinnamate esters under microwave irradiation (MW) has been reported using conc. H_2SO_4 as catalyst[19] which besides being highly corrosive, leads to the emission of toxic vapours into the environment. Methods for synthesis under solid-liquid phase-transfer catalysis (PTC)[20] of aromatic carboxylic esters have been reported. Herein we report the facile microwave-assisted synthesis of a series of cinnamate esters **1a–j** (Scheme 1) in fair to excellent yield in short times (Table 1) using a room temperature ionic liquid and an effective phase-transfer catalyst Aliquat®336 which has not been reported to have been used for the synthesis of cinnamate esters.



Scheme 1

Table1 Microwave-assisted esterification of substituted cinnamic acids using Aliquat®336 under two different PTC conditions

Product*	Time		Yield[a]		% Composition	
	Method A	Method B	Method A	Method B	Found	Calculated
t-$C_6H_5CH{=}CHCOOCH_2CH_2C_6H_5$ (**1a**)	15	10	90	98	–	–
t-$C_6H_5CH{=}CHCOOBu^n$ (**1b**)	12	10	88	91	–	–
t-4-$MeOC_6H_4CH{=}CHCOOCH_2CH_2C_6H_5$ (**1c**)	12	10	86	87	C, 76.7; H, 6.4	C, 76.6 ; H, 6.4
t-4-$MeOC_6H_4CH{=}CHCOOBu^n$ (**1d**)	10	8	85	88	–	–
t-4-$ClC_6H_4CH{=}CHCOOCH_2CH_2C_6H_5$ (**1e**)	12	8	87	89	C, 71.0; H, 5.2	C, 71.2; H, 5.3
t-4-$ClC_6H_4CH{=}CHCOOBu^n$ (**1f**)	10	7	85	86	–	–
t-3,4-$OCH_2OC_6H_3CH{=}CHCOOCH_2CH_2C_6H_5$ (**1g**)	11	8	80	83	C, 72.85: H, 5.4	C, 73.0; H, 5.4
t-3,4-$OCH_2OC_6H_3CH{=}CHCOOBu^n$ (**1h**)	10	8	90	92	C, 67.8; H, 6.6	C, 67.7; H, 6.5
t-3-$NO_2C_6H_4CH{=}CHCOOCH_2CH_2C_6H_5$ (**1i**)	17	14	78	80	C, 68.6; H, 5.0; N, 4.7	C, 68.7; H, 5.1; N, 4.7
t-3-$NO_2C_6H_4CH{=}CHCOOBu^n$ (**1j**)	16	12	81	84	C, 62.6; H, 6.0; N, 5.5	C, 62.6; H, 6.1; N, 5.6

[a]Yield of isolated products

1c**, **1d**[5], **1h**** and **1b** (obs. b.p. 290–295°C; lit.[6,8c,21b] b.p. 160–168°C/10 torr) are viscous liquids; **1a**[21a] (m.p. 54–56 °C), **1e**** (m.p. 62–64 °C), **1f**[5] (m.p. 40 °C) , **1g**** (m.p. 70–72 °C), **1i**** (m.p. 46–48 °C), **1j**** (m.p. 56–58 °C) are solids.

**New compounds

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* Correspondent. E-mail: amarendra@satyam.net.in

† Since deceased.

Table 2 Recycling studies for the reaction of potassium cinnamate with *n*-BuBr and $PhCH_2CH_2Br$

Number of cycles	Amount of catalyst used	Isolated yield of ester using	
		n-BuBr	$PhCH_2CH_2Br$
1	0.25 mmol	88 %	90 %
2	0.25 mmol	86 %	88 %
3	0.25 mmol	83 %	85 %

Alkylation using preformed potassium cinnamates (method A) and *in situ* generated potassium cinnamates (method B) led to comparable yields of esters (Table 1) and hence the preformed potassium salts of the acids are not necessary. Recycling of Aliquat®336 was then tested using potassium cinnamate and *n*-BuBr or $PhCH_2CH_2Br$ (Table 2). After each run, the reaction mixture was extracted with diethyl ether for 3–4 times to separate the products. The residue portion contains Aliquat®336 (and KBr), which after removal of trace of solvent under vaccum was reused directly for the next runs. It was found that the Aliquat®336 can be recycled at least 3 times with little loss of activity. Further the reaction has been carried out with a reasonably large quantity of reactants to examine its prospect for scale-up preparation. It has been observed that the reaction of potassium cinnamate (2 g) and *n*-BuBr (1.47 g) in the presence of the same quantity of Aliquat®336 (0.25 mmol) took 20 min to give maximum conversion into *n*-butyl cinnamate (85 %). Therefore, this process has also prospects for industrial applications.

In this reaction alkylating agents (*e.g.*, $PhCH_2CH_2Br$ and *n*-BuBr) play the role of organic non-polar liquid and consequently can act both as electrophile and organic phase for the reaction. Aliquat®336 (essentially $Oct_3MeN^+Cl^-$) can serve as a good ionic liquid medium and an effective solid-liquid

Table 3 IR, ^1H NMR and ^{13}C NMR spectroscopic data for cinnamate esters

Compounds	IR ν/cm^{-1}	^1H NMR (δ_H)	^{13}C NMR (δ_C)
1a	3029, 2927, 2855, 1714, 1638, 1495, 1452, 1311, 1274, 1168, 768, 700	7.68 (d, *J* = 16.0 Hz, 1H), 7.54–7.24 (m,10H), 6.43 (d, *J* = 16.0 Hz, 1H), 4.43 (t, *J* = 7.1 Hz, 2H), 3.03 (t, *J* = 7.1 Hz, 2H)	166.7 (s), 144.7 (d), 137.7 (s), 134.3 (s), 130.1 (d), 128.8 (2d), 128.7(2d), 128.4 (2d), 127.9 (2d), 126.4 (d), 117.9 (d), 64.9 (t), 35.1 (t)
1b	2950, 2869, 1714, 1639, 1457, 1385, 1312, 1269, 1173, 1067, 984, 768, 711, 686	7.68 (d, *J* = 16.0 Hz, 1H), 7.54–7.37 (m, 5H), 6.44 (d, *J* = 16.0 Hz, 1H), 4.21 (t, *J* = 6.6 Hz, 2H), 1.67 (m, 2H), 1.41 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H)	166.9 (s), 144.4 (d), 134.3 (s),130.0 (d), 128.7 (2d), 127.9 (2d), 118.1(d), 64.2 (t), 30.6 (t), 19.0 (t), 13.6 (q)
1c	3029, 2932, 2855, 1709, 1634, 1604, 1511, 1456, 1254, 1165, 1030, 830, 749, 700	7.64 (d, *J* = 16.0 Hz, 1H), 7.45 (d, *J* = 8.6 Hz, 2H), 7.35–7.22 (m, 5H), 6.91 (d, *J* = 8.6 Hz, 2H), 6.31 (d, *J* = 16.0 Hz, 1H), 4.42 (t, *J* = 7.0 Hz, 2H), 3.84 (s, 3H), 3.02 (t, *J* = 7.0 Hz, 2H).	167.2 (s), 161.3 (s), 144.5 (d), 137.9 (s), 129.7 (2d), 128.9 (2d), 128.4 (2d), 127.1 (s), 126.5 (d), 115.5 (d), 114.3 (2d), 64.8 (t), 55.3 (q), 35.2 (t)
1d	2960, 2934, 2873, 1710, 1635, 1605, 1576, 1513, 1463, 1423, 1254, 1169, 1031, 984, 829	7.64 (d, *J* = 15.9 Hz, 1H), 7.45 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 6.31 (d, *J* = 16.0 Hz, 1H), 4.19 (t, *J* = 6.6 Hz, 2H), 3.84 (s, 3H), 1.66 (m, 2H), 1.43 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H)	167.1 (s), 161.1 (s), 143.9 (d), 129.4 (2d), 126.9 (s), 115.5 (d), 114.0 (2d), 63.9 (t), 55.0 (q), 30.6 (t), 19.0 (t), 13.5 (t)
1e	3028, 2930, 1712, 1634, 1489, 1454, 1307, 1271, 1158, 1085, 955, 825, 743, 699	7.61 (d, *J* = 16.0 Hz, 1H), 7.46–7.23 (m, 9H), 6.39 (d, *J* = 16.0 Hz, 1H), 4.43 (t, *J* = 7.1 Hz, 2H), 3.02 (t, *J* = 7.1 Hz, 2H)	166.5 (s), 143.3 (d), 137.7 (s), 136.1 (s), 132.8 (s), 129.2 (2d), 129.1 (2d), 128.8 (2d), 128.5 (2d), 126.4 (d), 118.5 (d), 65.1 (t), 35.2 (t)
1f	3034, 2959, 2867, 1702, 1637, 1553, 1476, 1404, 1315, 1264, 1174, 1087, 1022, 815, 820	7.62 (d, *J* = 16.0 Hz, 1H), 7.46 (d, *J* = 8.6 Hz, 2H), 7.40 (d, *J* = 8.6 Hz, 2H), 6.41 (d, *J* = 16.0 Hz, 1H), 4.21 (t, *J* = 6.6 Hz, 2H), 1.69 (m, 2H), 1.42 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H)	166.7 (s), 143.0 (d), 136.0 (s), 132.9 (s), 129.1 (2d), 129.0 (2d), 118.8 (d), 64.3 (t), 30.7 (t), 19.1 (t), 13.7 (q)
1g	3027, 2907, 1704, 1630, 1495, 1448, 1304, 1251, 1173, 1104, 1030, 702	7.58 (d, *J* = 15.9 Hz, 1H), 7.35–7.22 (m, 5H), 7.03–6.98 (m, 2H), 6.81 (d, *J* = 7.9 Hz, 1H), 6.25 (d, *J* = 15.9 Hz, 1H), 6.00 (s, 2H), 4.41 (t, *J* = 7.0 Hz, 2H)	166.8 (s), 149.6 (s), 148.3 (s), 144.4 (d), 137.9 (s), 128.8 (2d), 128.4 (2d), 128.2 (s), 126.5 (d), 124.2 (d), 116.1 (d), 108.4 (d), 106.6 (d), 101.4 (t), 64.8 (t), 36.2 (t)
1h	3073, 2960, 1708, 1634, 1608, 1494, 1448, 1359, 1250, 1171, 1038, 980, 931, 811	7.58 (d, *J* = 15.9 Hz, 1H), 7.02–6.98 (m, 2H), 6.80 (d, *J* = 7.0 Hz, 1H), 6.26 (d, *J* = 15.9 Hz, 1H), 6.00 (s, 2H), 4.19 (t, *J* = 6.7 Hz, 2H), 1.66 (m, 2H), 1.43 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H)	167.1 (s), 149.4 (s), 148.2 (s),144.1 (d), 128.8 (s), 124.2 (d),116.1 (d), 108.4 (d), 106.3 (d), 101.4 (t), 64.2 (t), 30.7 (t), 19.1 (t), 13.6 (q)
1i	3030, 2929, 1715, 1643, 1532, 1454, 1351, 1316, 1175, 745, 702	8.35 (t, *J* = 1.7 Hz, 1H), 8.22 (dd, *J* = 7.3 Hz, *J* = 0.9 Hz, 1H), 7.80 (d, *J* = 7.7 Hz, 1H), 7.69 (d, *J* = 16.0 Hz, 1H), 7.56 (t, *J* = 8.0 Hz, 1H), 7.36–7.25 (m, 5H), 6.55 (d, *J* = 16.0 Hz, 1H), 4.45 (t, *J* = 7.0 Hz, 2H), 3.03 (t, *J* = 7.0 Hz, 2H)	165.9 (s), 148.6 (s), 141.8 (d),137.6 (s), 136.0 (s), 133.6 (d), 129.9 (d),128.8 (2d), 128.5 (2d), 126.6 (d), 124.4 (d), 122.3 (d), 121.1 (d), 65.3 (t), 35.0 (t)
1j	3069, 2927, 2860, 1714, 1641, 1529, 1464, 1179, 810, 743, 665	8.38 (br.s, 1H), 8.22 (br.d, *J* = 8.0 Hz, 1H), 7.82 (d, *J* = 7.7 Hz, 1H), 7.71 (d, *J* = 16.0 Hz, 1H), 7.58 (t, *J* = 7.9 Hz, 1H), 6.56 (d, *J* = 16.0 Hz, 1H), 4.23 (t, *J* = 6.6 Hz, 2H), 1.69 (m, 2H), 1.47 (m, 2H), 0.97 (t, *J* = 7.3 Hz, 3H)	166.0 (s), 148.8 (s), 141.5 (d), 136.3 (s), 133.4 (d), 129.8 (d), 124.3 (d), 122.3 (d), 121.6 (d), 64.7 (t), 30.7 (t), 19.1 (t), 13.5 (q).

phase-transfer catalyst between the liquid organic phase and the solid potassium salts of cinnamic acids. Consequently, the esterification process is facile affording fair to excellent yield of products : 78–90% and 80–98% respectively in the two methods in reasonably short times (Table 1) under microwave heating. Again, K_2CO_3 being a weak non-nucleophilic base, the fear of easy saponification of the esters and competitive etherification of the alkylating agents are removed in the one pot reaction conditions under microwave heating. By conventional heating methods (120 °C in an oil bath) in the presence of Aliquat®336 the same reactions required 2 h to complete and in the absence of the catalyst did not occur at all.

In conclusion, we have reported a reliable, rapid and environmentally benign method for the synthesis of substituted cinnamate esters which involves the use of less toxic reagents under microwave irradiation in the absence of added solvent. In addition, high yields of the products, short reaction times, easy work up procedure and catalyst recycling make this method advantageous in comparison to other existing methods. This work is a significant addition in the area of Green Chemistry.

Experimental

Typical procedure for esterification with preformed K-salts of cinnamic acids: To the potassium cinnamates (2.5 mmol) were added in a 50 ml Erlenmeyer flask 2-phenylethyl bromide or *n*-butyl bromide (2.5 mmol) and Aliquat®336 (0.25 mmol). After shaking, the flask was placed inside a BPL-SANYO, 700T domestic microwave oven and was irradiated for a specified time (Table 1) at 720 W. After completion of reaction (monitored by TLC), the reaction mixture was diluted with 50 ml diethylether. The ether layer was then collected and subsequently filtered over florisil. The crude products were finally purified by silica column chromatography with EtOAc/hexane as the eluent and characterised by IR spectra taken of the neat compound and ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra in $CDCl_3$ (Table 3) and in the case of novel compounds elemental analysis (Table 1).

Typical procedure for esterification in one-pot: To the cinnamic acids (2.5 mmol) were added in a 50 ml Erlenmeyer flask K_2CO_3 (2.5 mmol), 2-phenylethyl bromide or *n*-butyl bromide (2.5 mmol) and Aliquat®336 (0.25 mmol). After shaking, the flask was placed inside a BPL-SANYO, 700T microwave oven and was irradiated for a specified time (Table 1) at 720 W. After completion (monitored by TLC), the reaction mixture was worked up as above to get the product.

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