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Ultrasound-Promoted Friedel-Crafts Acylation of Arenes and Cyclic Anhydrides Catalyzed by Ionic Liquid of [bmim]Br/$AlCl_3$[1]

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Abstract—A simple and efficient method of Friedel-Crafts acylation of arenes with succinic anhydride, phthalic anhydride and glutaric anhydride under the action of 1-butyl-3-ethylimidazolium ([bmim]Br/$AlCl_3$ ([bmim]$^+$) cation (ionic liquid) and ultrasound irradiation is presented. Thy purity of products was tested by GC-MS and their structures evaluated by IR and ^{1}H NMR spectroscopy.

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INTRODUCTION

Importance of the Friedel-Crafts reaction for laboratory and industrial organic synthesis cannot be overestimated. In most cases Friedel-Crafts acylation upon aliphatic or aromatic acid halides or acetic anhydrides catalysis in combination with Lewis or Bronsted acids leading to ketones is studied in depth [1, 2]. Synthesis of ketocarboxylic acids is of particular importance for synthesis of lactones [3, 4] and pyridazinones [5] as pharmaceutical compounds. Ketocarboxylic acids were used as structural blocks of biologically active compounds such as fenbufen, bucloxic acid, menbutone, trepibutone, florantyrone, and some more.

$AlCl_3$, H_2SO_4, HF and other Lewis acids are used as catalysts in conventional Friedel–Crafts reactions but such catalysts are not environmentally friendly and cannot be recycled. Therefore, replacement of these highly corrosive and hazardous acidic catalysts by alternative environmentally friendly catalysts was one of major objectives of our research. Ultrasound enhancement of the reactions is known as an efficient and economically pronounced method [6, 7].

Over recent years, ionic liquids had proven to have a distinctive potential as an alternative to conventional catalysts and reactions media [8–12]. Such compounds demonstrated high selectivity and could be readily recycled making.

To the best knowledge, this is the first report on the Friedel-Crafts reaction of cyclic anhydrides with arenas under the action of [bmim]Br/$AlCl_3$ ionic liquid promoted by ultrasound leading to ketoacids. Such process could be an efficient rout to pharmaceutical compounds [7, 13, 14].

RESULTS AND DISCUSSION

According to experimental data (Table 1) the molar fraction of $AlCl_3$ in [bmim]Br/$AlCl_3$ had significant influence on the acylation reaction of *m*-xylene with phthalic anhydride. Efficiency of the catalyst reached maximum at molar fraction 0.67 and decreased at higher molar fractions of $AlCl_3$. Depending on the rate of [bmim]Br to the Lewis acid $AlCl_3$, acidity of the ionic liquid system can vary within wide range. Actually Friedel–Crafts acylation was catalyzed more efficiently by an acidic catalyst than by a basic one. The ionic liquid was basic at the mole fraction of $AlCl_3$ in the ionic liquid being less than 0.5 and at higher content of the same the ionic liquid became acidic.

The molar ratio of ionic liquid to *m*-xylene equal to 2 : 1 and $X(AlCl_3)$ = 0.67 were determined to be the most efficient (Table 2).

Purity of all products was tested by GC-MS. Structures of those were scrutinized by IR and ^{1}H

[1] The text was submitted by the authors in English.

Table 1. Effect of molar fraction of $AlCl_3$ in ionic liquid on the acylation reaction of *m*-xylene with phthalic anhydride under ultrasound irradiation

$X(AlCl_3)$	$n(AlCl_3)$: n([bmim]Br)	Time, min	Yield, %
0.33	0.5:1.0	no reaction	0
0.50	1.0:1.0	120	51
0.60	1.5:1.0	90	63
0.67	2.0:1.0	25	85
0.71	2.5:1.0	25	80
0.75	3.0:1.0	25	73

Table 2. Influence of molar ratio of ionic liquid to *m*-xylene on the acylation reaction

n{[bmim]Br/$AlCl_3$}: n(*m*-xylene)	Reaction time, min	Yield, %
0.5	60	73
1.0	45	75
1.5	35	80
2.0	25	85
2.5	25	79
3.0	25	76

NMR spectroscopy. The reactions data are presented in Table 3.

$AlCl_3$ were irradiated in a water bath under silent condition by ultrasound (45 kHz) at 60°C for 45 min, yield 75%.

Upon completion of the process the organic components were extracted by chloroform and the residual [bmim]Br/$AlCl_3$ ionic liquid phase treated with ether. Upon vacuum drying the latter at 80–100°C for 30 min the recycled [bmim]Br/$AlCl_3$ had high catalytic activity. Activity of the recycled [bmim]Br/$AlCl_3$ is listed in Table 4.

Synthetic procedure involving [bmim]Br/$AlCl_3$ and following make up of the reaction mixtures were simple and hazardous free.

EXPERIMENTAL

Materials and measurements. All chemicals were purchased from Merck and Fluka and used without further purification. Ultrasound apparatus Astra 3D (9.5 dm^3, 45 kHz frequency, input power with heating, 305W) was used. Melting points were measured with an Electrothermal 9100 apparatus. FT–IR spectra were recorded by a Shimadzu FT–IR-8400S spectrometer. ^1H NMR spectra were measured with a Bruker DRX-500 spectrometer against TMS standard. ^{13}C NMR spectra were measured with a Bruker DRX-125 Avance spectrometer.

General method for ketocarboxylic acid (I–XIV). A mixture of an anhydride (10 mmol), an arene (10 mmol), and [bmim]Br/$AlCl_3$ (20 equiv) were charged into a Pyrex-glass open vessel and irradiated in a water bath under silent condition by ultrasound (45 kHz) at 60°C for the 20–30 min. Progress of the reaction was monitored by TLC (EtOAc : petroleum ether = 1 : 4). The reaction mixture was cooled down to room temperature and organic components extracted by chloroform. Upon evaporation of the solvent the residual crystalline products were collected.

Compound I. White solid, mp 114–116°C; FT–IR (KBr), ν, cm^{-1}: 2400–3400, 1680, 1590, 1440, 1220. ^1H NMR spectrum (500 MHz, $CDCl_3$), δ_H, ppm: 2.9 t (2H, J = 6.5 Hz), 3.4 t (2H, J = 6.5 Hz), 7.5 m (3H), 8.00 m (2H), 11.5 s (1H).

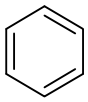
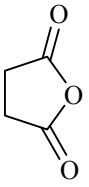
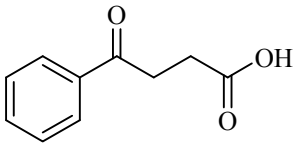
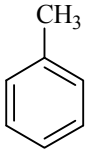
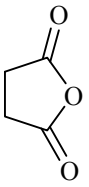
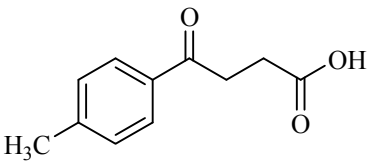
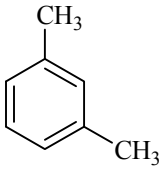
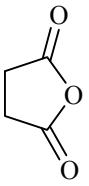
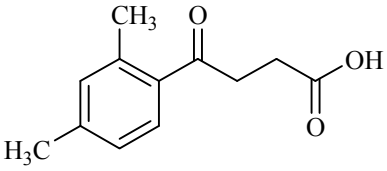
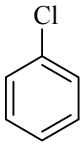
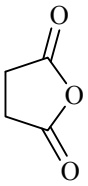
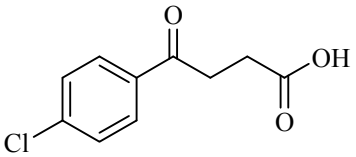
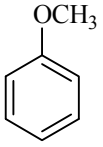
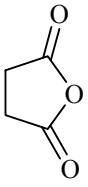
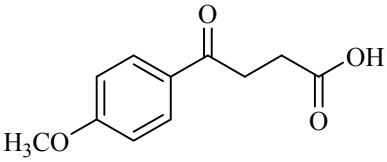
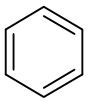
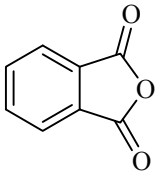
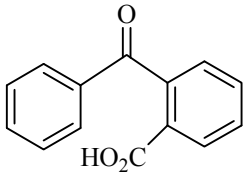
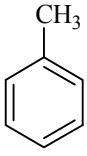
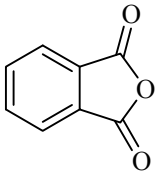
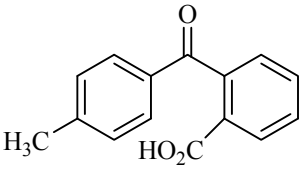
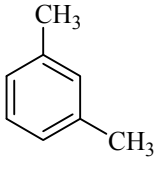
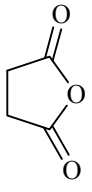
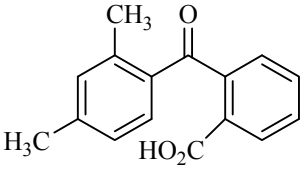
Compound II. White solid, mp 122–124°C; FT–IR (KBr), ν, cm^{-1}: 2400–3400, 1680, 1600, 1400, 1230. ^1H NMR spectrum (500 MHz, $CDCl_3$), δ_H, ppm: 2.45 s (3H), 2.8 t (2H, J = 6.6 Hz), 3.3 t (2H, J = 6.6 Hz), 7.30 d (2H, J = 8.2 Hz), 7.92 d (2H, J = 8.2 Hz), 11.5 s (1H).

Compound III. White solid, mp 108–110°C; FT–IR (KBr), ν, cm^{-1}: 2400–3400, 1690, 1600, 1440, 1257. ^1H NMR spectrum (500 MHz, $CDCl_3$), δ_H, ppm: 2.39 s (3H), 2.53 s (3H), 2.8 t (2H, J = 6.5 Hz), 3.2 t (2H, J = 6.5 Hz), 7.11 d (1H, J = 8.0 Hz), 7.30 s (1H), 7.69 d (1H, J = 7.6 Hz), 10.41 s (1H).

Compound IV. White solid, mp 124–126°C; FT–IR (KBr), ν, cm^{-1}: 2400–3400, 1676, 1600, 1596, 1232. ^1H NMR spectrum (500 MHz, $CDCl_3$), δ_H, ppm: 2.8 t (2H, J = 6.5 Hz), 3.3 t (2H, J = 6.5 Hz), 7.49 d (2H, J = 8.5 Hz), 7.96 d (2H, J = 8.5 Hz), 10.41 s (1H).

Compound V. White solid, mp 136–138°C; FT–IR (KBr), ν, cm^{-1}: 2400–3400, 1695, 1660, 1600, 1565, 1240. ^1H NMR spectrum (500 MHz, $CDCl_3$), δ_H, ppm:

Table 3. Resulting data of ketocarboxylic acid derivatives synthesis under optimized conditions

Substrate	Anhydride	Product	Yield, %[a,b]	Purity, %
			85	99.5
			95	99.6
			87	99.9
			83	99.4
			95	99.5
			85	99.7
			97	98.6
			3(85)[c]	99.5

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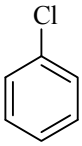
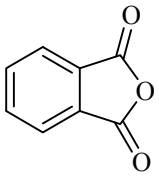
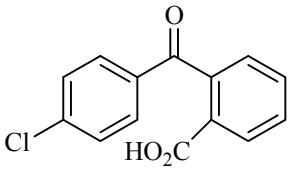
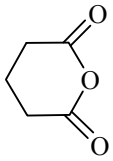
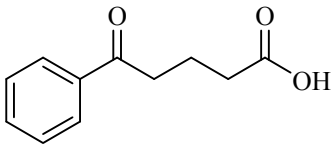
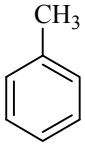
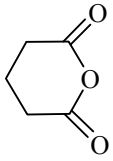
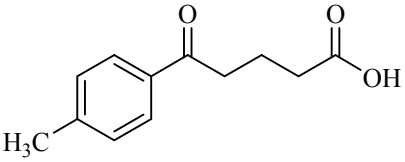
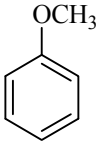
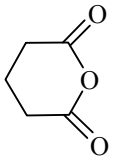
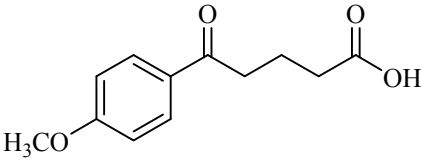
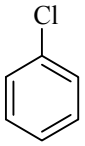
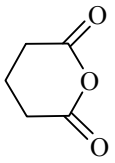
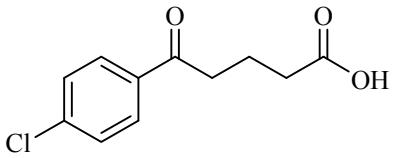
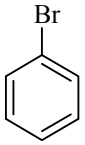
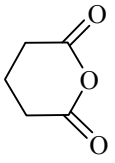
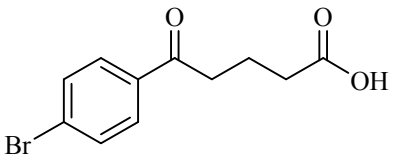
			86	99.7
			85	99.0
			94	99.2
			96	99.5
			85	98
			85	98.8

[a] Isolated yield. [b] Identified by IR and ^{1}H NMR spectroscopy. [c] Equimolar amounts of methaxylene (10 mmol), Phthalic anhydride (10 mmol) and 20 equiv.

Table 4. Activity data of the recycled [bmim]Br/$AlCl_3$ in the reaction of *m*-xylene with phthalic anhydride

Cycles	Yield, %
1	85
2	85
3	84
4	82
5	83

2.5 t (2H, J = 6.7 Hz), 3.0 t (2H, J = 6.7 Hzt), 3.7 s (3H), 6.78 d (2H, J = 8.9 Hz), 7.80 d (2H, J = 8.9 Hz).

Compound VI. White solid, mp 93–94°C; FT–IR (KBr), ν, cm^{-1}: 3200–3400, 1680, 1660, 1595, 1440, 1260. ^{1}H NMR (500 MHz, $CDCl_3$), δ_H, ppm: 7.41 t (2H, J = 7.3 Hz), 7.54–7.60 m (2H), 7.68 t (1H, J = 7.4 Hz), 7.73 d (2H, J = 7.3 Hz), 8.08 d (2H, J = 7.7 Hz). ^{13}C NMR (125 MHz, $CDCl_3$), δ_C, ppm: 127.98, 128.59, 128.89, 129.82, 130.00, 131.18, 133.54, 133.58, 137.39, 142.99, 170.80.

Compound VII. White solid, mp 99–101°C; FT–IR (KBr), ν, cm^{-1}: 3200–3400, 1680, 1660, 1595, 1440, 1280. ^1H NMR spectrum (500 MHz, $CDCl_3$), δ_H, ppm: 2.4 s (3H), 6.0 s (1H), 7.24 d (2H, *J* = 8.0 Hz), 7.38 d (1H, *J* = 7.5 Hz), 7.58 t (1H, *J* = 7.5 Hz), 7.64–7.69 m (3H), 8.10 d (1H, *J* = 7.8 Hz).

Compound VIII. White solid, mp 133–135°C; FT–IR (KBr), ν, cm^{-1}: 3200–3400, 1693, 1680, 1580, 1480, 1280. ^1H NMR spectrum (500M Hz, $CDCl_3$), δ_H, ppm: 2.37 s (3H), 2.65 s (3H), 6.93 d (1H, *J* = 7.8 Hz), 7.09 d (1H, *J* = 7.9 Hz), 7.12 s (1H), 7.44 d (1H, *J* = 7.5 Hz), 7.58 t (1H, *J* = 7.5 Hz), 7.64–7.69 m (3H), 8.06 d (1H, *J* = 8.6 Hz), 10 s (1H). ^{13}C NMR (125M Hz, $CDCl_3$), δ_C, ppm: 21.79, 21.89, 126.25, 128.44, 128.54, 129.88, 131.19, 132.35, 133.26, 133.36, 134.34, 140.84, 142.97, 144.50, 171.72, 198.85.

Compound IX. White solid, mp 228–230°C; FT–IR (KBr), ν, cm^{-1}: 3200–3400, 1693, 1680, 1580, 1480, 1280, 1100. ^1H NMR spectrum (500 MHz, $CDCl_3$), δ_H, ppm: 7.40 t (1H, *J* = 7.5 Hz), 7.44 d (1H, *J* = 7.7 Hz), 7.55–7.60 m (2H), 7.68 t (1H, *J* = 7.5 Hz), 7.74 d (2H, *J* = 7.5 Hz), 8.09 d (1H, *J* = 7.8 Hz).

Compound X. White solid, mp 126–128°C; FT–IR (KBr), ν, cm^{-1}: 2400–3400, 1695, 1674, 1596, 1412, 1287. ^1H NMR spectrum (500 MHz, $CDCl_3$), δ_H, ppm: 1.90–1.97 m (2H), 2.31 t (2H, *J* = 7.2 Hz), 2.97 t (2H, *J* = 7.2 Hz), 7.34 t (2H, *J* = 7.8 Hz), 7.45 t (2H, *J* = 7.5 Hz), 7.83 d (2H, *J* = 7.8 Hz).

Compound XI. White solid, mp 122–124°C; FT–IR (KBr), ν, cm^{-1}: 2400–3400, 1698, 1676, 1606, 1451, 1286. ^1H NMR spectrum (500 MHz, $CDCl_3$), δ_H, ppm: 1.80–1.85 m (2H), 2.19 t (2H, *J* = 7.2 Hz), 2.22 s (3H), 2.84 t (2H, *J* = 7.2 Hz), 7.06 d (2H, *J* = 7.9 Hz), 7.65 d (2H, *J* = 8.1 Hz).

Compound XII. White solid, mp 144–146°C; FT–IR (KBr), ν, cm^{-1}: 2400–3400, 1705, 1668, 1601, 1510, 1413, 1264. ^1H NMR spectrum (500 MHz, $CDCl_3$), δ_H, ppm: 1.93–1.99 m (2H), 2.33 t (2H, *J* = 7.1 Hz), 2.94 t (2H, *J* = 7.2 Hz), 3.80 s (3H), 6.85 d (2H, *J* = 8.8 Hz), 7.87 d (2H, *J* = 8.8 Hz).

Compound XIII. White solid, mp 112–114°C; FT–IR (KBr), ν cm^{-1}: 2400–3400, 1705, 1684, 1601, 1590, 1490, 1403, 1283, 1195. ^1H NMR spectrum (500 MHz, $CDCl_3$), δ_H, ppm: 2.10–2.16 m (2H), 2.56 t (2H, *J* = 7.1 Hz), 3.09 t (2H, *J* = 7.1 Hz), 7.47 d (2H, *J* = 8.4 Hz), 7.94 d (2H, *J* = 8.5 Hz).

Compound XIV. White solid, mp 112–114°C; FT–IR (KBr), ν cm^{-1}: 2400–3400, 1684, 1676, 1606, 1590, 1490, 1408, 1286, 1185. ^1H NMR spectrum: (500 MHz, $CDCl_3$), δ_H, ppm: 2.10–2.14 m (2H), 2.54 t (2H, *J* = 7.1 Hz), 3.08 t (2H, *J* = 7.1 Hz), 7.64 d (2H, *J* = 8.5 Hz), 7.86 d (2H, *J* = 8.5 Hz).

CONCLUSIONS

An optimized and facile protocol for acylation of arenes by cyclic anhydride under the action of $AlCl_3$ and ultrasound irradiation was developed. The mechanism of acylation reaction catalyzed by [bmim] $Br/AlCl_3$ ionic liquids is not clear yet. The current study indicated [bmim]$Br/AlCl_3$ as a novel environmentally friendly catalyst and media for *m*-xylene's acylation reaction.

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