

## An Efficient Method for Aromatic Friedel–Crafts Acylation Reactions

Mohammad Mehdi Khodaei,<sup>\*1,2</sup> Kiumars Bahrami,<sup>\*1,2</sup> and Fomeida Shahbazi<sup>1</sup>

<sup>1</sup>Department of Chemistry, Razi University, Kermanshah 67149, Iran

<sup>2</sup>Nanoscience and Nanotechnology Research Center (NNRC), Razi University, Kermanshah 67149, Iran

(Received March 4, 2008; CL-080236; E-mail: mmkhoda@razi.ac.ir)

Friedel–Crafts acylation of aromatic compounds was carried out using FeCl<sub>3</sub>-based ionic liquid. This liquid serves as an efficient media as well as a Lewis acid catalyst. The significant advantages of this methodology are excellent yields, short reaction times, mild reaction conditions, environmentally friendly method, simple work-up procedure, low cost, and easy preparation and handling of the catalyst.

One of the main tasks of contemporary industrial chemistry is the search for catalysts for the production of fine and intermediate chemicals.<sup>1</sup> Friedel–Crafts acylation and benzylation reactions lead to aromatic ketones, which are important intermediates in a very wide field of chemistry, including pharmacologicals, dyes, fragrances, and agrochemicals, such as fungicides, herbicides, and insecticides. Many of the industrial processes still use HF or AlCl<sub>3</sub> as catalysts for this kind of reaction, producing a high amount of contaminated waste. Considering the ecological and economical problems associated with waste management in most civilized countries,<sup>2</sup> an alternative, salt-free synthesis would be of high interest.<sup>3</sup>

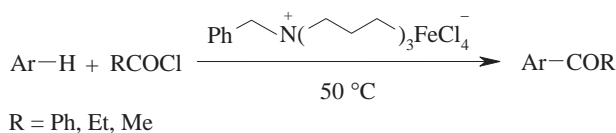
Recently, much attention has been focused on the use of ionic liquids as environmentally benign reaction media.<sup>4</sup> This fact is attributed to some intriguing properties of ionic liquids, such as high thermal stability, negligible vapor pressure, high loading capacity, and tunable polarity. In view of these distinct advantages, ionic liquids have become an exciting area of research.

Many organic chemical transformations have been carried out in ionic liquids, for example, hydrogenation,<sup>5,6</sup> oxidation,<sup>7</sup> epoxidation,<sup>8</sup> and hydroformylation<sup>9</sup> reactions.

In continuation of our recent work on the acylation reactions,<sup>10</sup> with a view towards developing reactions for clean synthesis in ionic liquids,<sup>11</sup> we now wish to introduce the FeCl<sub>3</sub>-based ionic liquid as effective and highly chemoselective catalysts for Friedel–Crafts acylation and benzylation of aromatic compounds under mild reaction conditions (Scheme 1).

To study the effect of increasing amounts of the Lewis acid in the ionic liquid, acylation of methoxybenzene, as a model substrate, with benzoyl chloride was carried out in benzyltributylammonium chloride ([BTBA]Cl) at 50 °C. As shown, the best result was obtained with [BTBA]Cl–FeCl<sub>3</sub>, *N* = 0.5 (Table 1).

We also investigated benzylation of methoxybenzene with benzoyl chloride in the presence of several Lewis acids in



Scheme 1.

**Table 1.** Effect of increasing amount of FeCl<sub>3</sub> on benzylation reaction of methoxybenzene, using [BTBA]Cl–FeCl<sub>3</sub> ionic liquid<sup>a</sup>

[BTBA]Cl–FeCl <sub>3</sub>	Molar fraction of FeCl <sub>3</sub> / <i>N</i>	Yield/% <sup>b</sup>
1:0.4	0.28	20
1:0.5	0.33	40
1:0.7	0.41	50
1:0.9	0.47	80
1:1	0.5	95

<sup>a</sup>Reaction conditions: The reactions were performed with benzoyl chloride (1 mmol), methoxybenzene (1 mmol), and ionic liquid (1 mmol) for 3 min, at 50 °C. <sup>b</sup>Isolated yield.

**Table 2.** Benzylation of methoxybenzene with benzoyl chloride in the presence of several Lewis acids in [BTBA]Cl–Lewis acids, *N* = 0.5

Entry	[BTBA]Cl–Lewis acid	Time/min	Yield/% <sup>a</sup>
1	[BTBA]Cl–ZrCl <sub>4</sub>	3	10
2	[BTBA]Cl–ZnCl <sub>2</sub>	3	30
3	[BTBA]Cl–AlCl <sub>3</sub>	3	90 <sup>b</sup>
4	[BTBA]Cl–FeCl <sub>3</sub>	3	95

<sup>a</sup>Isolated yields. <sup>b</sup>Ortho/para ratio 40:60 (by <sup>1</sup>H NMR).

[BTBA]Cl–Lewis acids, *N* = 0.5. The results show that only FeCl<sub>3</sub> is effective for this purpose (Table 2).

To generalize our reagent system, the applicability of the [BTBA]Cl–FeCl<sub>3</sub> system was then examined for the reactions of a series of aromatic compounds with acyl chloride or benzoyl chloride under the optimized reaction conditions<sup>12</sup> (Table 3).

It was observed that electron-donating groups such as alkyl and methoxy on the aromatic compound gave rise to excellent yields of the product (Entries 1–3). Also, deactivated arenes such as fluorene, chlorobenzene, bromobenzene, and nitrobenzene underwent acylation with good to excellent yields (Entries 8–11). As shown in Table 3, a tremendous enhancement of para selectivity was observed in each case.

Methyl phenyl sulfide (Entry 5) was benzylation with benzoyl chloride, and only 8% of ortho isomer was obtained.

In order to show the efficiency of this method, the results of the acylation and benzylation reactions of methoxybenzene by this method are compared with those reported by other methods. The results show that this method is superior to some previously reported methods in terms of yields and reaction times (Table 4).

In conclusion, the use of [BTBA]Cl–FeCl<sub>3</sub><sup>19</sup> in the Friedel–Crafts acylation and benzylation of aromatic compounds can be considered as an interesting alternative to the existing homogeneous catalysts. The significant advantages of this methodology are excellent yields, short reaction times, mild reaction conditions, high selectivity of the products, low cost, and easy preparation and handling of the catalyst.

**Table 3.** Acylation and benzylation of aromatic compounds using [BTBA]Cl-FeCl<sub>3</sub> ionic liquid (*N* = 0.5), with acyl chloride or benzoyl chloride

Entry	Ar	R	Time/min	Yield/% <sup>a,b</sup> [o:p]
1	4-MeOC <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	3	95 [5:95]
2	4-MeC <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	6	91 [7:93]
3	2,4,6-(Me) <sub>3</sub> C <sub>6</sub> H <sub>2</sub>	C <sub>6</sub> H <sub>5</sub>	3	92
4	2-Thienyl	C <sub>6</sub> H <sub>5</sub>	2	90
5	4-MeSC <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	8	90 [8:92]
6	2-Methoxynaphthyl	C <sub>6</sub> H <sub>5</sub>	3	94
7	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	12	90
8	4-BrC <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	15	91
9	4-ClC <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	20	92
10	4-FC <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	30	90
11	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	40	70
12	4-MeOC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	1	95 [10:90]
13	4-MeOC <sub>6</sub> H <sub>4</sub>	Et	6	93 [7:93]
14	4-MeC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	5	91 [10:90]
15	2,4,6-(Me) <sub>3</sub> C <sub>6</sub> H <sub>2</sub>	CH <sub>3</sub>	4	94
16	2-Thienyl	CH <sub>3</sub>	2	90
17	2-Methoxynaphthyl	CH <sub>3</sub>	3	92
18	9-Anthracenyl	CH <sub>3</sub>	6	90

<sup>a</sup>The products were characterized by comparison of their spectroscopic and physical data with those reported in literature.<sup>13-16</sup>

<sup>b</sup>Yields refer to pure isolated products.

**Table 4.** Comparison of the acylation of methoxybenzene using [BTBA]Cl-FeCl<sub>3</sub> with methods reported in the literature

Conditions	Yield/%
[BTBA]Cl-FeCl <sub>3</sub> /CH <sub>3</sub> COCl/50 °C/1 min	95
[BTBA]Cl-FeCl <sub>3</sub> /PhCOCl/50 °C/3 min	95
[bmim]Cl-FeCl <sub>3</sub> /Ac <sub>2</sub> O/100 °C/1 h <sup>17</sup>	0.31 <sup>a</sup>
Cu(OTf) <sub>2</sub> /PhCOCl/50 °C/8 h <sup>14</sup>	83
CF <sub>3</sub> SO <sub>3</sub> H/PhCOOMe/85 °C/2 h <sup>15</sup>	76
Cu(OTf) <sub>2</sub> /[bmim][BF <sub>4</sub> ]/CH <sub>3</sub> COCl/80 °C/overnight <sup>16</sup>	87
The Nafion resin (Nafion NR 50)/PhCOCl/100 °C/2 h <sup>18</sup>	59

<sup>a</sup>Conversion%.

The authors are thankful to the Razi University Research Council for financial support for this research.

## References and Notes

- W.-F. Hölderich, *Stud. Surf. Sci. Catal.* **1993**, *75*, 127.
- J. N. Armor, *Appl. Catal.*, A **1999**, *189*, 153.
- J. H. Clark, *Green Chem.* **1999**, *1*, 1.
- H. Zhao, S. V. Malhotra, *Aldrichim. Acta* **2002**, *35*, 75.
- C. J. Adams, M. J. Earle, K. R. Seddon, *Chem. Commun.* **1999**, 1043.
- Y. Chauvin, L. Mussmann, H. Olivier, *Angew. Chem., Int. Ed. Engl.* **1996**, *34*, 2698.
- J. Howarth, *Tetrahedron Lett.* **2000**, *41*, 6627.
- G. S. Owens, M. M. Abu-Omar, *Chem. Commun.* **2000**, 1165.
- C. C. Brasse, U. Englert, A. Salzer, H. Waffenschmidt, P. Wasserscheid, *Organometallics* **2000**, *19*, 3818.
- M. M. Khodaei, A. Alizadeh, E. Nazari, *Tetrahedron Lett.*

**2007**, *48*, 4199.

- K. Bahrami, M. M. Khodaei, F. Shahbazi, *Tetrahedron Lett.* **2008**, *49*, 3931.
- General procedure for acylation reactions: To a weighed quantity of ionic liquid (*N* = 0.5, 1 mmol), acylating reagent (1 mmol) and an aromatic compound (1 mmol) were added. The reaction mixture was stirred magnetically at 50 °C. After complete conversion, as indicated by TLC, the reaction mixture was quenched by adding water (10 mL) and extracted with diethyl ether (4 × 8 mL), and the extract was dried with anhydrous MgSO<sub>4</sub>. The filtrate was evaporated and the corresponding product was obtained in excellent yield (Table 3). Selected characterization data of: 2-Benzoylthiophene (Entry 4). White solid; mp 54–55 °C (ref 20, 52–55 °C); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz): δ 7.2–8.2 (m, 8H); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>): δ 127.9, 128.4, 129.1, 132.1, 133.7, 134.1, 138.1, 143.6, 189.0. 4-Methoxyacetophenone (Entry 12). Colorless crystals; mp 35–36 °C (ref 21, 36.5–38 °C); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz): δ 2.57 (s, 3H), 3.87 (s, 3H), 6.97 (d, *J* = 8.7 Hz, 2H), 7.93 (d, *J* = 8.7 Hz, 2H); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>): δ 26.4, 55.7, 113.9, 130.5, 130.9, 163.6, 197.1. 1-(4-Methoxyphenyl)propan-1-one (Entry 13). Oil (ref 22, 26–27 °C); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz): δ 2.47 (t, *J* = 7.3 Hz, 3H), 2.9 (q, *J* = 7.3 Hz, 2H), 3.8 (s, 3H), 6.9 (d, *J* = 8.6 Hz, 2H), 7.9 (d, *J* = 8.6 Hz, 2H); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>): δ 8.40, 31.37, 55.40, 113.63, 129.97, 130.20, 163.26, 199.45. 2-Acetylthiophene (Entry 16). Colorless liquid; (ref 20, colorless liquid); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz): δ 2.74 (s, 3H), 7.14 (d, *J* = 3.8 Hz, 1H), 7.65 (d, *J* = 1.13 Hz, 1H) 7.71 (d, *J* = 1.13 Hz, 1H); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>): δ 26.9, 128.1, 132.4, 133.8, 144.6, 190.7. 1-Acetyl-2-methoxynaphthalene (Entry 17). Pale yellow solid; mp 56–57 °C (ref 23, 57–58 °C); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz): δ 2.70 (s, 3H), 3.94 (s, 3H), 7.30 (d, *J* = 9.2 Hz, 1H), 7.37–7.48 (m, 2H), 7.78 (d, *J* = 8.1 Hz, 1H), 7.83 (d, *J* = 8.1 Hz, 1H), 7.90 (d, *J* = 9.2 Hz, 1H); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>): δ 32.9, 56.7, 112.9, 123.8, 124.5, 125.4, 127.5, 128.3, 128.9, 130.5, 131.7, 154.1, 205.4.
- a) W.-B. Yi, C. Cai, *J. Fluorine Chem.* **2005**, *126*, 1191. b) *Aldrich Catalog Handbook of Fine Chemicals*, **2006–2007**. c) S. Paul, P. Nanda, R. Gupta, A. Loupy, *Synthesis* **2003**, 2877.
- R. P. Singh, R. M. Kamble, K. L. Chandra, P. Saravanan, V. K. Singh, *Tetrahedron* **2001**, *57*, 241.
- J. P. Hwang, G. K. S. Prakash, G. A. Olah, *Tetrahedron* **2000**, *56*, 7199.
- J. Ross, J. Xiao, *Green Chem.* **2002**, *4*, 129.
- M. H. Valkenberg, C. deCastro, W. F. Hölderich, *Appl. Catal., A* **2001**, *215*, 185.
- A. Heidekum, M. A. Harmer, W. F. Hoelderich, *J. Catal.* **1999**, *188*, 230.
- The [BTBA]Cl-FeCl<sub>3</sub> ionic liquid was prepared by grinding of benzyltributylammonium chloride (311.94 mg, 1 mmol) with FeCl<sub>3</sub> (162.2 mg, 1 mmol) for 2 min.
- H. D. Hartough, A. I. Kosak, *J. Am. Chem. Soc.* **1947**, *69*, 1012.
- K. Smith, Z. Zhenhua, P. K. G. Hodgson, *J. Mol. Catal. A: Chem.* **1998**, *134*, 121.
- N. Ono, R. Tamura, A. Kaji, *J. Am. Chem. Soc.* **1983**, *105*, 4017.
- C. R. Noller, R. Adams, *J. Am. Chem. Soc.* **1924**, *46*, 1889.