

## Solventless Friedel-Crafts Acylation under Microwave Activation

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**Abstract:** A novel catalytic system, ZnCl<sub>2</sub> supported on alumina, was found to be an efficient and readily available medium for the solvent-free Friedel-Crafts acylation reactions under microwave irradiation. Good yields and high catalytic efficiencies were observed within short reaction times. Comparing with silica gel, alumina was more efficient under the same conditions.

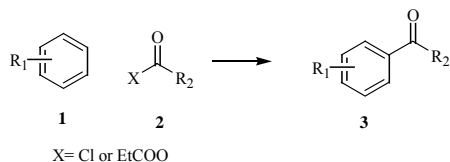
**Keywords:** Friedel-Crafts acylation, microwave irradiation, solvent-free.

Traditional Friedel-Crafts reaction is widely used in industrial processes to synthesize medicines and chemicals. Many kinds of Lewis acids<sup>1</sup>, *e.g.* AlCl<sub>3</sub>, FeCl<sub>3</sub>, *etc.*, were employed to promote the reaction. However, there are some serious problems, such as the requirement of more than a stoichiometric amount of Lewis acid and the inconvenient treatment of the residue after the reactions. For the importance of the Friedel-Crafts reaction in industry, a variety of catalysts such as Hf(OTf)<sub>4</sub><sup>2a</sup>, LiClO<sub>4</sub>-MeNO<sub>2</sub><sup>2b</sup>, Ln(OTf)<sub>3</sub>-LiClO<sub>4</sub><sup>2c</sup> and Cu(OTf)<sub>2</sub><sup>2d</sup> and synthetic methods have been reported in the literatures. However, with these catalysts a long reflux time is required and the catalysts are not readily available. Lewis acid supported on montmorillonite clay<sup>3</sup>, silica gel<sup>4</sup>, zeolite<sup>5</sup> and alumina<sup>6</sup> have also been used. All of these reaction systems needed harmful solvent like benzene.

Recently, microwave-assisted synthesis in organic chemistry is quickly growing<sup>7</sup>. Many organic reactions proceed much faster with higher yields under microwave irradiation compared to conventional heating. Supported reagents on solid surface have been widely employed in organic synthesis. Reagents impregnated on solid materials present advantages over the conventional solution phase reactions, for good dispersion of active sites leading to improve reactivity and milder reaction conditions. A solvent-free reaction with microwave irradiation would shorten the reaction time, and provide easier work-up procedures. In contrast to the traditional application of solid phase in synthesis, microwave technology does not involve the solid phase. The recycling of the inorganic solid support makes the procedure more environmentally benign. It has been reported that for a heterogeneous medium, MW heating greatly increased the catalytic activities of AlCl<sub>3</sub> in the redistribution of organometallics and FeCl<sub>3</sub> and graphite in the acylation reactions<sup>8</sup>.

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**Scheme 1** Friedel-Crafts acylation reaction**Table 1** Microwave-assisted solvent-free Friedel-Crafts acylation reaction catalyzed by ZnCl<sub>2</sub>

Entry	R-H	Product	Time	TON	Yield (%)
<b>3a</b>	MeOPh		0.25	1.2	87
			0.5	1.8	89
			1.0	2.1	90
			3	2.5	90 <i>p</i> : <i>m</i> / 99.8 : 1
			5.0	2.4	80
<b>3b<sup>a</sup></b>			3	1.0	97
<b>3c</b>	MeOPh		0.75	2.2	85
			1.0	2.6	82
			3.0	2.5	88 <i>p</i> : <i>m</i> / 99.8 : 0.2
			5.0	2.3	70
<b>3d<sup>a</sup></b>			3	0.9	93
<b>3e</b>	1,2-(MeO) <sub>2</sub> Ph		3	2.0	91
<b>3f</b>	1,2-(MeO) <sub>2</sub> Ph		4	2.2	90
<b>3g</b>	1,3-(MeO) <sub>2</sub> Ph		3	2.1	80
<b>3h</b>	1,3-(MeO) <sub>2</sub> Ph		3	2.2	83
<b>3i</b>	1,3-(HO) <sub>2</sub> Ph		2	1.5	75
<b>3j</b>	MePh		4	1.0	97 <i>p</i> : <i>o</i> : <i>m</i> / 78.7 : 2.3 : 18.9

<sup>a</sup> The reaction was catalyzed by ZnCl<sub>2</sub> / silica gel.

Herein, we wish to report a novel catalytic system containing ZnCl<sub>2</sub>/alumina, which can efficiently promote the Friedel-Crafts acylation reactions. Christopher and David<sup>9</sup> have shown that carrier size was important for this reaction, in the present work 200~300 mesh alumina was used as carrier. The solid support was prepared as follows: 10 g Al<sub>2</sub>O<sub>3</sub> was heated for 8 hrs at 825 °C, and cooled to the room temperature. Then the Al<sub>2</sub>O<sub>3</sub> was added in a solution of 3 g ZnCl<sub>2</sub> in 20 mL methanol and mixed thoroughly. Methanol was allowed to evaporate under reduced pressure. Then the residue was heated for 24 hrs at 100 °C.

From **Table 1**, it was shown that compared to the conventional method, the reaction time was shortened greatly (from at least 30 min to 3-4 min) and the TONs (turn-over number) were increased with high yield. And when resorcinol was used as starting material, which is sensitive to oxygen, good result can be obtained too (entry **3i**). But for the starting material with low boiling point, the TON is not good enough (entry **3j**). Probably it was vaporated when the reaction took place in open flask. For entries **3a**, **3c** and **3j**, it can be seen that the acylation was almost regiospecific and the *para*-isomers were the exclusive products. There was no apparent steric effects for various starting materials (entry **3g**, **3h**, **3i**).

It was noted that the reaction time was very important. If the heating time was too long, the yield decreased, the substituted acetophenone could form dimer as by-product and the substituted dibenzoyl ketone (entry **3a**, **3e**, **3g**) transferred the methoxy to hydroxyl. When the mixture of anisole with benzoylchloride was irradiated for two more minutes, the yield decreased by 10%. When the mixture of anisole with acetic anhydride was irradiated for 5 min, three kinds of dimers, corresponding to the two isomers, were obtained in 18% yield. It was worthy to mention that the power of the irradiation was important too. Too high power would make the reaction boil acutely and get more the by-products. However lower power would prolong the reaction time. In our reaction system, the optimum power was 160 W. Electron donating substitute such as methoxyl could greatly activate this reaction, and made the TON increased. While electron-drawing group on aromatic rings such as bromobenzene inhibited the reactions and the target products could not be obtained.

Comparing entries **3a** with **3b**, and **3c** with **3d**, it was seen that alumina enhanced the TON but reduced yield as carrier. At the same time, when the reaction was finished on alumina without  $ZnCl_2$  under microwave irradiation, no expected compound was produced.

In summary,  $ZnCl_2$  supported on alumina and silica gel has been shown to be an efficient medium for Friedel-Crafts reactions with microwave activation. And alumina was especially suitable carrier. It can greatly promote the efficiency of catalysts, shorten the reaction time. Alumina and  $ZnCl_2$  are readily available. And  $ZnCl_2$  could be washed away easily just by water after the reaction.

General Procedure: A mixture of anisole (25 mmol, 2.7 mL), benzoylchloride (25 mmol, 2.9 mL) and solid support (4 g) was mixed thoroughly in a flask (50 mL) covered with a beaker, and irradiated in a domestic microwave oven at 160 W (Galanz WD 800B Microwave Oven with 20% power). The reaction was quenched with water (50 mL), and the organic compounds were extracted with ether (3×50 mL), besides resorcinol with acetic acid (entry **3i**). The combined organic layers were washed with aqueous NaOH solution, dried over anhydrous  $CaCl_2$  and filtered. The solvent was evaporated *in vacuo* and the residue was purified by chromatography to afford the pure product.

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10. Spectra data: **3a** white solid; m.p. 55-57 °C; IR (KBr) 1649, 1261, 792 cm<sup>-1</sup>; <sup>1</sup>HNMR (CDCl<sub>3</sub>, δ ppm): 7.75 (d, 2H, J=8.8 Hz), 7.69 (d, 2H, J=7.4 Hz), 7.64 (d, 1H, J=7.4 Hz), 7.55 (t, 2H, J=7.4 Hz), 7.09 (d, 2H, J=8.8 Hz), 3.87 (s, 3H); Calcd. for C<sub>14</sub>H<sub>12</sub>O<sub>2</sub>: C 79.23, H 5.698; Found: C 79.35, H 5.370. **3c** white solid; m.p. 36-37 °C; IR (KBr) 1673, 1259, 837 cm<sup>-1</sup>; <sup>1</sup>HNMR (CDCl<sub>3</sub>, δ ppm): 7.93 (d, 2H, J=8.1 Hz), 7.03 (d, 2H, J=8.2 Hz), 3.84 (s, 3H), 2.51 (s, 3H); Calcd. for C<sub>9</sub>H<sub>10</sub>O<sub>2</sub>: C 71.97, H 6.715; Found: C 72.10, H 6.410. **3e** white solid; m.p. 99-100 °C; IR (KBr) 1644, 1270, 795 cm<sup>-1</sup>; <sup>1</sup>HNMR (CDCl<sub>3</sub>, δ ppm): 7.76 (m, 2H), 7.57 (m, 1H), 7.49 (m, 3H), 7.38 (dd, 1H, J=8.3, 2.0 Hz), 6.89 (d, 1H, J=8.3 Hz), 3.96 (s, 1H), 3.94 (s, 1H); Calcd. for C<sub>15</sub>H<sub>14</sub>O<sub>3</sub>: C 74.36, H 5.824; Found: C 74.05, H 5.728. **3f** white solid; m.p. 47-48 °C; IR (KBr) 1673, 1269, 810 cm<sup>-1</sup>; <sup>1</sup>HNMR (CDCl<sub>3</sub>, δ ppm): 7.58 (dd, 1H, J=8.3, 2.0 Hz), 7.53 (d, 1H, J=2.0 Hz), 6.89 (d, 1H, J=8.4 Hz), 3.99 (s, 3H), 3.95 (s, 3H), 2.57 (s, 3H); Calcd. for C<sub>10</sub>H<sub>12</sub>O<sub>3</sub>: C 66.65, H 6.712; Found: C 66.72, H 6.688. **3g** white solid; m.p. 82-83 °C; IR (KBr) 1650, 1277, 800 cm<sup>-1</sup>; <sup>1</sup>HNMR (CDCl<sub>3</sub>, δ ppm): 7.77 (m, 2H), 7.52 (m, 1H), 7.41 (m, 3H), 6.54 (dd, 2H, J=8.4, 2.2 Hz), 3.87 (s, 3H), 3.70 (s, 3H); Calcd. for C<sub>15</sub>H<sub>14</sub>O<sub>3</sub>: C 74.36, H 5.824; Found: C 74.15, H 5.838. **3h** white solid; m.p. 39-40 °C; IR (KBr) 1664, 1268, 827 cm<sup>-1</sup>; <sup>1</sup>HNMR (CDCl<sub>3</sub>, δ ppm): 7.83 (d, 1H, J=8.7 Hz), 6.52 (dd, 1H, J=8.7, 2.3 Hz), 6.46 (s, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 2.58 (s, 3H); Calcd. for C<sub>10</sub>H<sub>12</sub>O<sub>3</sub>: C 66.65, H 6.712; Found: C 66.48, H 6.701. **3i** red solid; IR (KBr) 1606, 1208, 786 cm<sup>-1</sup>; <sup>1</sup>HNMR (CDCl<sub>3</sub>, δ ppm): 12.6 (s, 1H), 10.6 (s, 1H), 7.75 (d, 1H, J=8.8 Hz), 6.38 (dd, 1H, J=8.8, 2.3 Hz), 6.24 (d, 1H, J=2.3 Hz), 2.51 (s, 3H). **3j** white solid; m.p. 54-54.5 °C; IR (KBr) 1655, 1277, 787 cm<sup>-1</sup>; <sup>1</sup>HNMR (CDCl<sub>3</sub>, δ ppm): 7.79 (m, 2H), 7.73 (d, 2H, J=8.0 Hz), 7.59 (t, 1H, J=7.6 Hz), 7.48 (t, 2H, J=7.6 Hz), 7.29 (d, 2H, J=8.0 Hz), 2.45 (s, 3H); Calcd. for C<sub>14</sub>H<sub>12</sub>O: C 85.68, H 7.190; Found: C 85.76, H 7.037.

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