

# Simple and Improved Procedure for the Regioselective Acylation of Aromatic Ethers with Carboxylic Acids on the Surface of Graphite in the Presence of Methanesulfonic Acid

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**Abstract:** Friedel–Crafts acylation of aromatic compounds such as anisole has been successfully carried out using the combination of graphite with MeSO<sub>3</sub>H. Both aromatic and aliphatic carboxylic acids reacted smoothly under the conditions to afford the corresponding aromatic ketones in high yield.

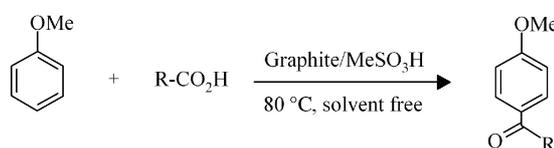
**Keyword:** Friedel–Crafts acylation, acylations, graphite, regioselectivity, carboxylic acids

The Friedel–Crafts acylation of aromatic compounds is one of the most fundamental and useful reactions in organic synthesis.<sup>1</sup> The disadvantages associated with the classical procedures include the use of toxic acid chloride as the acylating agent and stoichiometric amounts of aluminium trichloride as a Lewis acid, which entails environment pollution. In order to minimize this problem, some catalytic Friedel–Crafts acylations have been developed recently.<sup>2</sup> In addition, acylations involving carboxylic acids and less toxic Lewis acids<sup>3</sup> or apparently non-hazardous acid catalysts<sup>4</sup> have been studied, although these procedures are not quite successful as practical and general synthetic methods. For instance, a methodology<sup>4b</sup> of acylation of anisole with carboxylic acids over HZSM-5 zeolite, although environmentally safe, has limitations with regard to generality (no reaction with higher acids) and efficiency (reaction time of 48 h and concomitant O-acylation). Recently, it was also shown that alumina promotes the acylation of reactive aromatics such as anisole and thiophene with carboxylic acid in the presence of trifluoroacetic anhydride.<sup>5</sup> Thus, a reliable general method for this useful reaction involving non-hazardous reagents is in demand.

One of the most important objectives now is to adapt classical processes so that pollution effects are kept to a minimum, with both a reduction in energy and consumption of raw materials. In this respect, dry-media reactions are promising, and a new approach has been undertaken using graphite chemistry. The exceptional ability of graphite to adsorb organic molecules is well known.<sup>6</sup> Diels–Alder and ene reactions,<sup>7a–g</sup> decarboxylations,<sup>7a,b</sup> decompositions,<sup>8</sup> rearrangements,<sup>7a,b,9</sup> keto carboxylation<sup>10</sup> and con-

version of aldehydes into nitriles<sup>11</sup> were effected using such conditions.

As a part of our continued efforts to utilize surface-mediated reactions for useful synthetic transformations,<sup>12</sup> we wish to disclose here a very simple and highly efficient method for regioselective acylation of aromatic ethers with carboxylic acids in the presence of MeSO<sub>3</sub>H on the surface of graphite (Scheme 1).



**Scheme 1**

To exploit a simple and suitable condition for the Friedel–Crafts acylation of aromatic ethers, the reaction of anisole with acetic acid was chosen as a model, and its behavior was studied under a variety of conditions via TLC and <sup>1</sup>H NMR spectroscopy (Table 1).

According to Table 1, the best results were obtained using a mixture of graphite and MeSO<sub>3</sub>H in a 2:1 molar ration, when carried out at 80 °C for 20 min. The results also show that the importance of using both graphite and MeSO<sub>3</sub>H. In the absence of graphite (entry 3) or MeSO<sub>3</sub>H (entry 4), the attempted acylation did not afford the corresponding product.

In a typical reaction, carboxylic acid and aromatic ether were added to a mixture of graphite and MeSO<sub>3</sub>H and mixed uniformly with shaking. The mixture was kept at 80 °C in an oil bath with occasional shaking for a certain period of time until the reaction was completed. The product was isolated by simple extraction of the solid mass by diethyl ether followed by usual work-up. Several structurally varied aromatic ethers underwent acylations with a wide range of carboxylic acids including cyclic, acyclic, and aromatic ones. The results are presented in Table 2.

The reactions are remarkably clean, and no chromatographic separation is necessary to get the spectra-pure compounds. Acylation occurs exclusively *para* to the OMe group for all of the ethers studied, in high yields. However, in cases where the *para* position is blocked (Table 2, entry 11), the acyl group is introduced *ortho* to the ether moiety. This procedure is also good enough for

**Table 1** Friedel Crafts Acylation of Anisole (1 mmol) with Acetic Acid (1 mmol) under Various Reaction Conditions

Entry	Conditions	Time (min)	Yield (%) <sup>a</sup>
1	H <sub>2</sub> SO <sub>4</sub> , 80 °C	120	10
2	PPA, 80 °C	60	10
3	MeSO <sub>3</sub> H (1 mL), 80 °C	60	trace
4	graphite (0.1 g), 80 °C	120	No reaction
5	graphite (0.1 g); MeSO <sub>3</sub> H (1.5 mL), 100 °C	10	80
6	graphite (0.1 g); MeSO <sub>3</sub> H (0.5 mL), 100 °C	5	75
7	graphite (0.1 g); MeSO <sub>3</sub> H (0.3 mL), 100 °C	10	82
8	graphite (0.1 g); MeSO <sub>3</sub> H (1.5 mL), 80 °C	10	85
9	graphite (0.1 g); MeSO <sub>3</sub> H (0.5 mL), 60 °C	60	70
10	graphite (0.1 g); MeSO <sub>3</sub> H (0.3 mL), 80 °C	20	98

<sup>a</sup> Isolated yields.

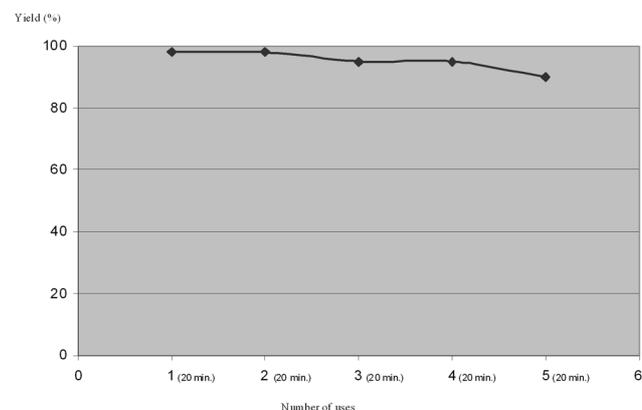
the acylation of heterocyclic compounds such as furan (Table 1, entry 9), producing the corresponding 2-acylated product in excellent yield. The reactions are reasonably fast even with the higher acids and cyclohexanecarboxylic acid; however, aromatic carboxylic acids with electron-withdrawing groups (Table 2, entries 6, 7, 8) react rather slowly. The reaction conditions are mild enough not to induce any dealkylation of an ether residue *ortho* to the introduced acyl group (Table 2, entry 11) as observed in the acylation reaction with carboxylic acid catalyzed by BF<sub>3</sub>.<sup>3</sup>

Although the use of graphite for acylation of active aromatic compounds has been reported previously,<sup>13</sup> our new method, using a mixture of graphite and MeSO<sub>3</sub>H, offers significant improvements over the earlier method, reducing the reaction time considerably (20 minutes compared to eight hours), minimizing the amount of graphite from 1 g to 0.1 g, increasing the yield remarkably, and above all, using both electron donating and specially withdrawing substituted carboxylic acids instead of using the expensive and polluting acid halides that require special procedures in handling and working up.

Therefore, graphite–MeSO<sub>3</sub>H has been shown to have a remarkable high activity for the acylation of aromatic compounds with both aromatic and aliphatic carboxylic acids to give the corresponding acylated compounds in

high yields, without any of the environmental disadvantages of using toxic homogeneous reagents such as anhydrous AlCl<sub>3</sub>.

Another interesting behaviour of graphite lies in the fact that it can be re-used after simple washing with ethyl acetate and water, rendering thus process more economic. The results of this study are shown in Figure 1.



**Figure 1** Re-use studies on the graphite-mediated synthesis of 4-methoxyacetophenone using anisole (1 mmol) and acetic acid (1 mmol). The reaction was carried out in an oil bath at 80 °C. In parenthesis reaction time is given.

In conclusion, the present method provides a very convenient and efficient procedure for acylation of aromatic ethers. The notable advantages of this methodology are direct use of a wide variety of carboxylic acids, fast reaction, operational simplicity, generality, excellent regioselectivity, no side reaction, and quantitative yields, and thus it offers significant improvements over other procedures involving Friedel–Crafts acylation of aromatic ethers.<sup>2–4,14,15</sup>

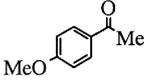
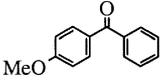
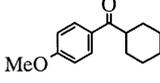
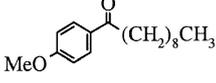
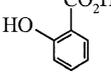
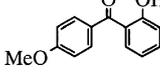
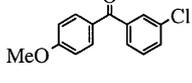
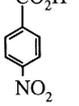
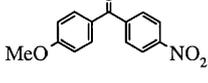
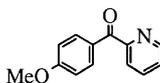
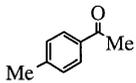
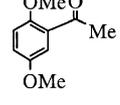
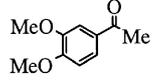
Starting materials were obtained from Fluka Company. Melting points were determined using a Büchi 510 apparatus and are uncorrected. IR spectra were measured on a Perkin-Elmer spectrometer. NMR [<sup>1</sup>H (250 MHz), <sup>13</sup>C (62.9 MHz)] spectra were recorded on a Bruker Advance DPX FT 250 MHz instrument in CDCl<sub>3</sub> with TMS as the internal standard.

#### Acylation of Aromatic Ethers (Table 2); Typical Procedure

To a mixture of graphite (powder type; 0.1 g, 8 mmol) and MeSO<sub>3</sub>H (0.3 mL, 4 mmol) at 80 °C in an oil bath, aromatic ether (1 mmol) and carboxylic acid (1 mmol) were added. The reaction mixture was kept at 80 °C with occasional shaking for a certain period of time (Table 2) as required to complete the reaction (monitored by TLC). The reaction mixture was extracted with CHCl<sub>3</sub> (2 × 20 mL). The organic layer was washed with sat. aq NaHCO<sub>3</sub>, dried (Na<sub>2</sub>SO<sub>4</sub>). Evaporation of solvent furnished practically pure product. This was further purified by recrystallization with suitable solvent (Et<sub>2</sub>O or MeOH).

The structure of the products was confirmed by <sup>1</sup>H NMR, IR and comparison with authentic samples obtained commercially or prepared by reported methods.

**Table 2** Acylation of Aromatic Ethers with Carboxylic Acids Using Graphite–MeSO<sub>3</sub>H in Molar Ratio of 2:1

Entry	Substrate	Acid	Product	Time (min)	Yield (%) <sup>a</sup>
1		MeCO <sub>2</sub> H		20	98
2				20	95
3				5	98
4		Me(CH <sub>2</sub> ) <sub>8</sub> CO <sub>2</sub> H		20	90
5				60	85
6				120	85
7				180	80
8				240	85
9		MeCO <sub>2</sub> H		20 <sup>b</sup>	98
10		MeCO <sub>2</sub> H		50	90
11		MeCO <sub>2</sub> H		30	95
12		MeCO <sub>2</sub> H		30	90

<sup>a</sup> Yields are the isolated compounds.<sup>b</sup> The reaction was carried out at r.t., and better at 0–10 °C.

### Acknowledgment

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