Solvent-Free Catalytic *Friedel–Crafts* Acylation of Aromatic Compounds with Carboxylic Acids by Using a Novel Heterogeneous Catalyst System: *p*-Toluenesulfonic Acid/Graphite

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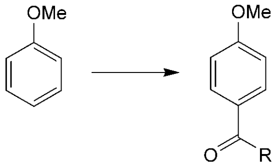
TsOH/graphite was found to be an effective catalyst system for the *Friedel–Crafts* acylation of aromatic compounds with carboxylic acids. Both aliphatic and aromatic carboxylic acids reacted smoothly under TsOH/graphite catalysis to afford the corresponding aromatic ketones in high yields. The graphite was easily recovered by simple extraction and could be reused without decrease of activity in the presence of fresh TsOH.

Introduction. – Recently, many studies on catalytic *Friedel–Crafts* acylation reactions with acid chlorides or anhydrides as acylating agents have been reported [1–5]. However, only few studies on *Friedel–Crafts* acylations with carboxylic acids as acylating agents have been published [6].

Although numerous methods to achieve *Friedel–Crafts* acylation are known, newer methods continue to attract attention for their experimental simplicity and effectiveness. We were interested in the development of a method for *Friedel–Crafts* acylation that *a*) circumvents chromatographic purification, *b*) avoids the use of acid anhydrides or toxic acid chlorides, *c*) is easy to perform, *d*) is economical for application to large-scale preparations, and *e*) allows to use solvent-free conditions.

Results and Discussion. – During the course of our studies aimed at developing solvent-free procedures [7], we reasoned that an immobilized system, *via* the application of solid-phase reagents, could be a more-efficient and cleaner variant of the classical *Friedel–Crafts* reaction. So, we examined several reactions, focusing on high efficiency as well as generation of activated acylating species under catalytic conditions (*Table 1*). Finally we found that a mixture of graphite and *p*-toluenesulfonic acid (TsOH) accelerated the catalytic *Friedel–Crafts* acylation of anisole systematically. The effect of the amounts of graphite and TsOH in the acylation of anisole is summarized in *Table 1.* While no acylated products were obtained in the presence of TsOH and graphite alone (*Entries 5* and *6*), a 67% yield of 4-methoxybenzophenone was obtained when combining 0.3 g of graphite and 0.1 g of TsOH (*Entry 7*). The yield was improved when 0.3 g of graphite and 0.03 g of TsOH were used (*Entry 10*). In the presence of a large amount of graphite (*Entries 11* and *12*), the yield decreased due to adsorption of an appreciable amount of product and starting material on the graphite. The effect of solvents in this reaction was detrimental since only a trace amount of the product was detected in CH_2Cl_2 or $CHCl_3$ solutions (*Entries 13* and *14*).

Table 1. Friedel–Crafts *Acylation of Anisole* (1 mmol) *under Various Reaction Conditions*



Entry	Conditions	Acylating agent	Time [h]	Yield[a] [%]
1	H_2SO_4, 80°	$PhCO_2H$	3	trace
2	polyphosphoric acid, 80°	$PhCO_2H$	3	10
3	$(CF_3CO)_2$, Al_2O_3, microwave	$PhCO_2H$	0.17	80
4	$[Eu(NTf_2)_3]$, 250°	$Me(CH_2)_5CO_2H$	6	87
5	TsOH (0.1 g), 90°	$PhCO_2H$	3	0
6	graphite (0.3 g), 90°	$PhCO_2H$	3	0
7	graphite (0.3 g), TsOH (0.1 g, 0.6 mmol), 90°	$PhCO_2H$	1	67
8	graphite (0.3 g), TsOH (0.05 g, 0.3 mmol), 90°	$PhCO_2H$	2	77
9	graphite (0.3 g), TsOH (0.04 g, 0.25 mmol), 90°	$PhCO_2H$	2.5	80
10	graphite (0.3 g), TsOH (0.03 g, 0.19 mmol), 90°	$PhCO_2H$	3	86
11	graphite (0.5 g), TsOH (0.03g, 0.19 mmol), 90°	$PhCO_2H$	6	60
12	graphite (1 g), TsOH (0.03g, 0.19 mmol), 90°	$PhCO_2H$	6	54
13	graphite (0.3 g), TsOH (0.03g, 0.19 mmol), CH_2Cl_2	$PhCO_2H$	6	trace
14	graphite (0.3 g), TsOH (0.03g, 0.19 mmol), $CHCl_3$	$PhCO_2H$	6	trace

[a]) Yield of isolated material.

Several examples of the *Friedel–Crafts* acylation of aromatic compounds with various types of carboxylic acids in the presence of a catalytic amount of TsOH and graphite are shown in *Table 2* (→ **1**–**14**). In a typical experimental procedure, anisole (1 mmol) and benzoic acid (1 mmol) were added to TsOH (0.03 g) and graphite (0.3 g) at 90° (oil bath). After 3 h, the product was isolated by simple extraction of the solid mass with $CHCl_3$. In all cases (except for *Entries 6–9*), the reactions proceeded smoothly giving the corresponding aromatic ketones in high yields (see *Table 2*) and purities. No chromatographic separation was necessary, except in a few cases (*Entries 2* and *4*) where the product contained some starting material, the conversion being incomplete. Acylation occurred exclusively at the position *para* to the MeO or Me group of the aromatic compounds studied. The acetylation of benzene, anthracene, and unactivated benzenes with acetic acid, themselves volatile and less reactive, seemed more difficult to perform (*Entries 6–9*). Even after vigorous stirring for 8 h, the reaction did not occur since no acylated products were obtained, the reactants were not partially consumed, and no side reaction took place. In addition, it was very exciting to find that unactivated carboxylic acids such as 4-nitrobenzoic acid reacted smoothly in the presence of TsOH and graphite to afford the corresponding aromatic ketones in high yields (*Entry 12*). Furthermore, the reaction was reasonably fast even with the higher acids and cyclohexanecarboxylic acid (*Entries 14* and *15*).

The use of graphite for the acylation of activated aromatic compounds has been reported previously [8], but our new method using a mixture of graphite and TsOH offers significant improvements over the earlier method, *i.e.*, a considerable decrease of

Table 2. Friedel–Crafts *Acylation of Aromatic Compounds* (1 mmol) *with Carboxylic Acids* (1 mmol) *in the Presence of a Catalytic Amount of TsOH and Graphite at 90°*

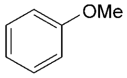
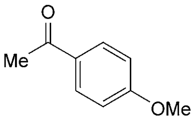
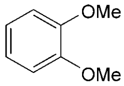
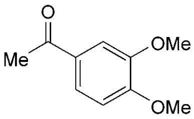
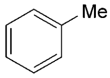
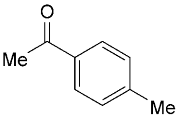
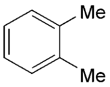
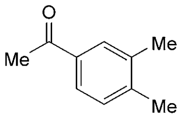
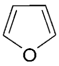
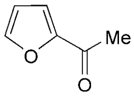
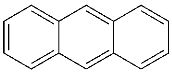
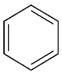
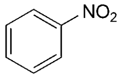
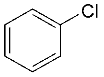
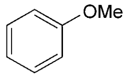
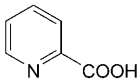
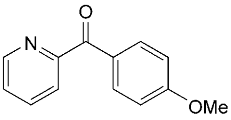
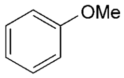
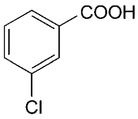
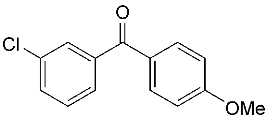
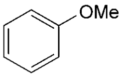
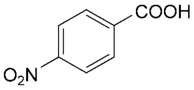
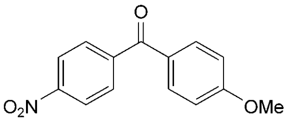
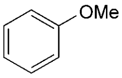
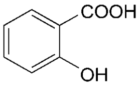
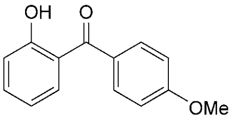
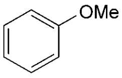
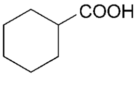
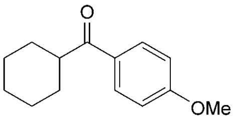
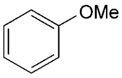
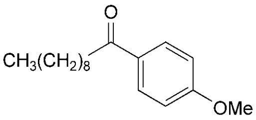
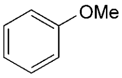
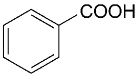
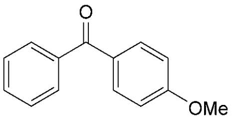
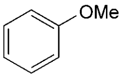
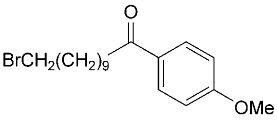
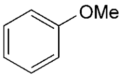
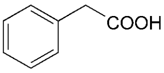
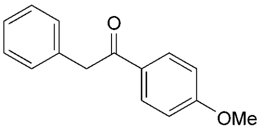
Entry	ArH	RCOOH	Product[a])	Time [h]	Yield [%][b])	M.p. or b.p. [°/Torr]
1		$MeCO_2H$	**1** 	3	96	129/637 ([9]: 154/760)
2		$MeCO_2H$	**2** 	6	87	48 ([9]: 51)
3		$MeCO_2H$	**3** 	6	85	89/637 ([9]: 113/760)
4		$MeCO_2H$	**4** 	5	81	186/637 ([9]: 213/740)
5		$MeCO_2H$	**5** 	0.5	97[c])	46/637 ([9]: 67/760)
6		$MeCO_2H$	No reaction	8		
7		$MeCO_2H$	No reaction	8		
8		$MeCO_2H$	No reaction;	8		
9		$MeCO_2H$	No reaction	8		
10			**6** 	2.5	90	165
11			**7** 	1.5	95	125 ([9]: 127.5–128)

Table 2 (cont.)

Entry	ArH	RCOOH	Product[a])	Time [h]	Yield [%][b])	M.p. or b.p. [°/Torr]
12			**8** 	4	90	125
13			**9** 	3.5	85	220
14			**10** 	1	90	92.5
15		$Me(CH_2)_8COOH$	**11** 	3	92	110
16			**12** 	3	86	55 ([9]: 56)
17		$BrCH_2(CH_2)_9COOH$	**13** 	4	84	190
18			**14** 	3.5	92	120

[a]) Products were characterized by their melting points, IR, and NMR spectra; for **13** and **14**, see *Exper. Part.* [b]) Yields refer to pure isolated products. [c]) The reaction was carried out at room temperature.

the reaction time (3 h *vs.* to 8 h), a minimization of the amount of graphite (1 g *vs.* 0.3 g), remarkable increase of the yield, solvent-free conditions, and above all, the use of both electron-donating and specially electron-withdrawing substituted carboxylic acids as starting materials instead of the expensive and polluting acid halides that require special cares in handling and workup.

Another interesting behavior of graphite lies in the fact that it can be reused after simple washing with AcOEt and H_2O, thus rendering the process more economic. The yields of 4-methoxyacetophenone (**1**) in the 2nd, 3rd, 4th, and 5th use of the graphite were almost the same as that in the 1st use (*Table 3*). It should be noted that TsOH was not adsorbed on the graphite during the reaction and, after extraction with AcOEt, TsOH was not found on the graphite; thus, it is necessary to add TsOH again for the 2nd use of recovered graphite. No attempt was made to probe the mechanism of the reaction and further understanding of the catalysis by graphite.

Table 3. *Reuse of Graphite in the Acetylation of Anisole with Acetic Acid*

Number of use	Yield of **1** [%]	Recovery of graphite [%]
1	95	94
2	90	87
3	87	85

In conclusion, catalytic *Friedel–Crafts* acylation was successfully carried out in the presence of a new heterogeneous catalyst system, TsOH/graphite. The presented method provides a very convenient and efficient procedure for the acylation of aromatic ethers. The notable advantages are the direct use of a wide variety of carboxylic acids, fast reaction, operational simplicity, generality, excellent regioselectivity, no side reactions, solvent-free conditions, and more or less quantitative yields. Thus, a higher turnover is expected, and this report may be the answer to the long-term *Friedel–Crafts* acylation problems. The application of graphite to other synthetic reactions is now under investigation.

The authors are thankful to the *Shiraz University Research Council* for the partial support of this work.

Experimental Part

General. Chemicals were purchased from *Fluka*, *Merck*, *B. D. H.,* and *Aldrich Chemical Companies.* TLC Monitoring: silica gel *Polygrams SIL G/UV 254* plates. GC Monitoring: *Shimadzu* gas chromatograph *GC-14A*, flame ionization detector 3-m glass column packed with *DC-200* stationary phase; N_2 as the carrier gas. IR Spectra: *Perkin-Elmer 781* or *Nicolet Impact-400-D* FT-IR spectrophotometers; in cm^{-1}. NMR Spectra: *Bruker-DPX*-250-MHz instrument; δ in ppm rel. to $SiMe_4$. MS: in *m/z* (rel. %).

Acylation of Aromatic Compounds, General Procedure: To a mixture of graphite (CAS No. 7782-42-5; fine powder extra pure, from *Merck*; 0.3 g, 25 mmol) and anh. TsOH (0.03 g, 0.17 mmol) at 90° in an oil bath the aromatic compound (1 mmol) and carboxylic acid (1 mmol) were added. The mixture was kept at 90° while stirring with a mechanical stirrer for the time required to complete the reaction (see *Table 2*; TLC or GC monitoring). The solid mass (graphite) was then extracted with AcOEt (20 ml) and the AcOEt extract washed with aq. $NaHCO_3$ soln., dried (Na_2SO_4) and evaporated: practically pure product. The structure of the products was confirmed by ^{1}H-NMR, IR, m.p. or b.p., and comparison with authentic samples obtained commercially or prepared by reported methods. Data for new compounds (see *Table 2*, *Entries 17* and *18*) are given below.

11-Bromo-1-(4-methoxyphenyl)undecan-1-one (**13**): IR (KBr): 1676. ^{1}H-NMR ($CDCl_3$): 1.19–1.30 (*m*, 6 CH_2); 1.65 (*m*, CH_2CH_2Br); 1.99 (*m*, $COCH_2CH_2$); 2.87 (*t*, $COCH_2$); 3.75 (*s*, MeO); 4.07 (*t*, CH_2Br); 6.87 (*d*, 2 arom. H); 7.89 (*d*, 2 arom. H). ^{13}C-NMR ($CDCl_3$): 28.17; 33.20; 40.97; 55.15; 112.61; 129.80; 163.10; 195.40. MS: 354 (100, M^+), 356.12 (97.2), 355.12 (20.2). Anal. calc. for $C_{18}H_{27}BrO_2$; C 60.85, H 7.66; found: C 60.60, H 7.40.

1-(4-Methoxyphenyl)-2-phenylethan-1-one (**14**). IR (KBr): 1679. ^{1}H-NMR ($CDCl_3$): 3.87 (*s*, MeO); 4.35 (*s*, $COCH_2$); 6.94 (*d*, 2 arom. H); 7.26–7.39 (*m*, 5 arom. H); 8.03 (*d*, 2 arom. H). ^{13}C-NMR ($CDCl_3$): 50.48; 56.17; 113.44; 114.66; 120.51; 126.97; 128.72; 130.06; 162.12; 191.10. MS: 226 (100, M^+). Anal. calc. for $C_{15}H_{14}O_2$: C 79.62, H 6.24; found: C 79.41, H 6.08.

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