Simple and Improved Procedure for Regioselective Acylation of Aromatic Ethers with Carboxylic Acids on the Solid Surface of Alumina in the Presence of Trifluoroacetic Anhydride

Brindaban C. Ranu,* Keya Ghosh, and Umasish Jana

Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Calcutta 700 032, India

Received August 7, 1996

The Friedel−Crafts acylation of aromatic rings is one of the most fundamental and useful reactions in organic synthesis.[1] The disadvantages associated with the classical procedures include the use of toxic acid chloride as the acylating agent and stoichiometric amounts of aluminum trichloride as a Lewis acid, which entails environment pollution. In order to minimize this problem, some catalytic Friedel−Crafts acylations have been developed recently.[2] In addition, acylations involving carboxylic acids and less toxic Lewis acids[3] or apparently nonhazardous acid catalysts[4] have been studied, although these procedures are not quite successful as practical and general synthetic methods. For instance, a recent methodology[4b] 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). Thus, a reliable general method for this useful reaction involving nonhazardous reagents is in demand. As a part of our continued efforts to utilize surface-mediated reactions for useful synthetic transformations[5] 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 trifluoroacetic anhydride on the surface of alumina without any solvent (Scheme 1).

In a typical reaction, a mixture of carboxylic acid and trifluoroacetic anhydride was added to an aromatic ether adsorbed on the surface of activated acidic alumina and mixed uniformly with shaking. The mixture was kept at room temperature with occasional shaking for a certain period of time until the reaction was complete. The product was isolated by simple extraction of the solid mass by ether followed by usual workup. Several structurally varied aromatic ethers underwent acylations with a wide range of carboxylic acids including acyclic, cyclic, and aromatic ones. The results are presented in Table 1. The reactions are remarkably clean, and no chromatographic separation is necessary to get the spectra-pure compounds except in a few cases (Table 1, entries 8, 11, and 13) where some starting ethers remained, the conversion being less than 100%. Acylation occurs exclusively at the position para to −OMe for all of the ethers studied in almost quantitative yields. However, in cases where the para positions are blocked (Table 1, entries 11 and 13) the acyl group is introduced ortho to the ether moiety. This procedure is also good enough for the acylation of thioethers like thioanisole (Table 1, entry 14), giving 4-acylthioanisole, as well as thiophene and furan (Table 1, entries 15 and 16), producing the corre-

Scheme 1

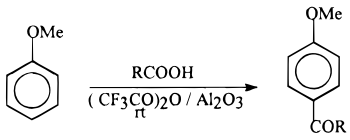
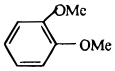
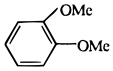
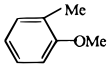
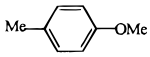
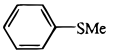


Table 1. Acylation of Aromatic Ethers with Carboxylic Acids on the Surface of Alumina

entry	aromatic ethers	RCOOH	time(min)	yield (%)[a]	ref
1	anisole	R = Me	10	96	7
2	anisole	R = Et	20	95	4b
3	anisole	R = Pr^n	20	92	4b
4	anisole	R = Pr^i	40	90	8
5	anisole	R = n-C_7H_{15}	120	94	4b
6	anisole	R = n-$C_{15}H_{31}$	180	92	9
7	anisole	R = 	40	95	10
8	anisole	R = Ph	10[b]	80	4b
9		R = Me	25	96	2f
10		R = Pr^n	25	95	11
11		R = Me	180	60[c]	7
12		R = Me	25	94	12
13		R = Me	150	80[d]	12
14		R = Me	15[b]	94	2f
15		R = Me	25	95[e]	4b
16		R = Me	180	75[f]	4b

[a] All yields refer to pure isolated products, fully characterized by IR and ^{1}H NMR. [b] The reaction was carried out in a microwave oven. [c] The product is 2,5-dimethoxyacetophenone. [d] The product is 2-methoxy 5-methylacetophenone. [e] The product is 2-acetylthiophene. [f] The product is 2-acetylfuran, and the reaction was carried out at 0−5 °C.

(1) (a) Olah, G. A. *Friedel−Crafts and Related Reactions*; Interscience: New York, 1964; Vol. III, Part 1. (b) Heaney, H. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, p 753.

(2) (a) Nomita, K.; Sugaya, Y.; Sasa, S.; Miwa, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 2089. (b) Yamaguchi, T.; Mitoh, A.; Tanabe, K. *Chem. Lett.* **1982**, 1229. (c) Mukaiyama, T.; Nagaoka, H.; Ohshima, M.; Murakami, M. *Chem. Lett.* **1986**, 165. (d) Mukaiyama, T.; Ohno, T.; Nishimura, T.; Han, S. J.; Kobayashi, S. *Chem. Lett.* **1991**, 1059. (e) Mukaiyama, T.; Suzuki, K.; Han, S. J.; Kobayashi, S. *Chem. Lett.* **1992**, 432. (f) Kawada, A.; Mitamura, S.; Kobayashi, S. *Synlett* **1994**, 545. (g) Hachiya, I.; Moriwaki, M.; Kobayashi, S. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 2053. (h) Kobayashi, S.; Nagayama, S. *J. Org. Chem.* **1996**, *61*, 2256.

(3) Schiemenz, G. P.; Schmidt, U. *Liebigs Ann. Chem.* **1976**, 1514.

(4) (a) Chiche, B.; Finiels, A.; Gauthier, C.; Geneste, P. *J. Org. Chem.* **1986**, *51*, 2128. (b) Wang, Q. L.; Ma, Y.; Ji, X.; Yan, H.; Qiu, Q. *J. Chem. Soc., Chem. Commun.* **1995**, 2307.

(5) (a) Ranu, B. C.; Bhar, S.; Sarkar, D. C. *Tetrahedron Lett.* **1991**, *32*, 2811. (b) Ranu, B. C.; Bhar, S. *Tetrahedron* **1992**, *48*, 1327. (c) Ranu, B. C.; Bhar, S.; Chakrabori, R. *J. Org. Chem.* **1992**, *57*, 7349. (d) Ranu, B. C.; Bhar, S. *J. Chem. Soc., Perkin Trans. 1* **1992**, 365. (e) Ranu, B. C.; Sarkar, D. C.; Chakraborty, R. *Synth. Commun.* **1992**, *22*, 1095. (f) Ranu, B. C.; Saha, M.; Bhar, S. *Tetrahedron Lett.* **1993**, *34*, 1989. (g) Ranu, B. C.; Chakraborty, R. *Tetrahedron* **1993**, *49*, 5333. (h) Ranu, B. C.; Chakraborty, R.; Saha, M. *Tetrahedron Lett.* **1993**, *34*, 4659. (i) Ranu, B. C.; Saha, M.; Bhar, S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2197. (j) Ranu, B. C.; Saha, M. *J. Org. Chem.* **1994**, *59*, 8269. (k) Ranu, B. C.; Majee, A.; Das, A. R. *Synth. Commun.* **1995**, *25*, 363. (l) Ranu, B. C.; Sarkar, A.; Saha, M.; Bhar, S. *Pure Appl. Chem.* **1996**, *68*, 775. (m) Ranu, B. C.; Saha, M.; Bhar, S. *Synth. Commun.*, in press.

S0022-3263(96)01541-1 CCC: $12.00

sponding 2-acylated products in excellent yields. The reactions are reasonably fast even with the higher acids and cyclohexane carboxylic acid; however, benzoic acid reacts rather slow, although satisfactory conversion was achieved by 10 min of microwave irradiation. The reaction conditions are mild enough not to induce any dealkylation of an ether residue ortho to the introduced acyl group (Table 1, entries 11 and 13) as observed in the acylation reaction with carboxylic acid catalyzed by BF_3.[3]

Although the use of trifluoroacetic anhydride for the acylation of anisole with carboxylic acid has been reported previously (only three examples), no attempt has been made for generalization.[6] Moreover, this procedure on the solid surface of alumina offers significant improvements over the earlier method,[6] reducing the reaction time considerably (10 min compared to 3 h), minimizing the amount of trifluoroacetic anhydride from 3−4 equiv to 1.5 equiv, and above all, increasing the yield remarkably; the most marked examples are thiophene and furan, where yields were raised from 50% and 39% to 95% and 75%, respectively.

For comparison, when silica gel (HF 254, activated) was used in place of alumina in the reactions of anisole with acetic acid and with propionic acid, both reactions were found to be very slow. In fact, only 5−10% progress was observed by the time at which the reactions were complete using alumina. Thus, alumina was found to be the better choice for this reaction.

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 carboxylic acid, mild conditions (room temperature), fast reaction (10 min to 3 h), operational simplicity, generality, excellent regioselectivity, no side reactions, and quantitative yields, and thus, it offers significant improvements over other procedures involving Friedel−Crafts acylation of aromatic ethers.[2−4,6,8] We believe this will find significant application in the field of organic synthesis.

Experimental Section

General Methods. General information regarding instruments and techniques used are the same as mentioned in our previous paper.[5j]

Alumina (acidic, Brockmann activity, grade 1 for column chromatography, SRL, India) was activated by heating at 200 °C for 4 h under vacuum followed by cooling under N_2 and was used for all the reactions. (Activated alumina can be stored under N_2 for 1 week for subsequent use without much loss of activity). The aromatic ethers and carboxylic acids are all commercial materials and were purified by distillation or recrystallization before use.

General Procedure for Acylation of Aromatic Ethers. Representative Procedure. A mixture of acetic acid (120 mg, 2 mmol) and trifluoroacetic anhydride (610 mg, 2.9 mmol, Fluka) was added to anisole (216 mg, 2 mmol) adsorbed on alumina (2 g) and mixed uniformly by shaking. Color (usually pink, but in few cases green or blue) developed immediately and darkened with progress of the reaction. The reaction mixture was kept under moisture guard at room temperature with occasional shaking for a certain period of time (Table 1) as required to complete the reaction (monitored by TLC). The solid mass was then eluted with Et_2O (50 mL), and the ether extract was then washed with an aqeuous solution of sodium bicarbonate and brine and dried over anhydrous sodium sulfate. Evaporation of solvent furnished practically pure (GC, 100%) 4-methoxyacetophenone (298 mg, 99%). This was further purified by filtering it through a short column of silica gel (eluted with 95/5 petroleum ether−ether mixture) to afford the analytically pure product (290 mg, 96%). The identity of this compound was easily established by comparison of its ^{1}H NMR spectrum with that of an authentic sample.[7]

All of the acylated products are known compounds and characterized easily by comparison with authentic samples (IR, ^{1}H NMR, mp) except one (Table 1, entry 7), whose spectral and analytical data are furnished.[10]

Although the results reported in Table 1 were based on mmol scale reactions, gram-scale reactions also afforded the corresponding products in analogously excellent yields.

Acknowledgment. Financial support from CSIR, New Delhi (01/1364/95), is gratefully acknowledged. K.G. and U.J. also thank CSIR for their fellowships.

JO9615413

(6) Bourne, E. J.; Stacey, M.; Tatlow, J. C.; Tedder, J. M. *J. Chem. Soc.* **1951**, 719.

(7) Pouchert, C. J. *The Aldrich Library of NMR Spectra*, 2nd ed.; Aldrich Chemical Co., Inc.: Milwaukee, 1983; Vol. 2.

(8) Effenberger, F.; Epple, G. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 300.

(9) Matsuda, S.; Ogawa, M.; Okazaki, T.; Benden, M. M. *Chem. Abst.* **1958**, *52*, 10930f.

(10) IR(neat): 1600, 1670 cm^{-1}. ^{1}H NMR δ: 1.12−2.22 (10H, m), 2.92−3.24 (1H, m), 3.82 (3H, s), 6.82 (2H, d, J = 9 Hz), 7.84 (2H, d, J = 9 Hz). Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.02; H, 8.31. Found: C, 76.91; H, 8.12.

(11) Awad, W. I.; EL-Neweihy, M. F.; Selin, S. F. *J. Org. Chem.* **1958**, *23*, 1783.

(12) Mathur, K. B. L.; Sharma, J. N.; Venkataramanan, K.; Krishnamurthy, H. G. *J. Am. Chem. Soc.* **1957**, *79*, 1957.