

Catalytic Friedel–Crafts Acylation of Alkoxybenzenes Mediated by Aluminum Hydrogensulfate in Solution and Solvent-Free Conditions

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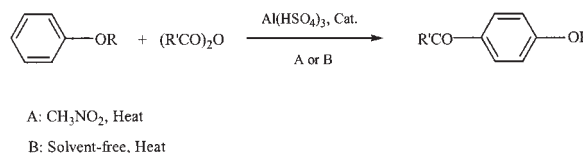
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Friedel–Crafts acylation of alkoxybenzenes was achieved efficiently by a reaction with aliphatic acid anhydrides in the presence of catalytic amounts of aluminum hydrogensulfate, $\text{Al}(\text{HSO}_4)_3$, in nitromethane and under solvent-free conditions. Alkylbenzenes and aryl halides, as well as aromatic anhydrides, remained intact under these conditions.

Friedel–Crafts acylation is one of the most important protocols for bringing about the formation of carbon–carbon bonds between aromatic rings and aliphatic moieties.¹ The traditional methods generally involve the use of stoichiometric amounts of aluminum chloride or sulfuric acid.² Many of the classic catalysts, such as metallic halides and Brønsted acids, are corrosive and some of them suffer from unavailability, instability or hygroscopicity.

Thus, the development of heterogeneous solid acid catalysts to replace the use of strongly acidic, homogeneous and corrosive reagents can be considered extensively.



Scheme 1.

Aluminum hydrogensulfate is a very stable and non-hygroscopic solid material that is insoluble in most organic solvents. To the best of our knowledge, there is not any report on its application in organic synthetic methodology. In continuation of our studies on the application of metallic hydrogensulfate salts in organic synthesis,³ we wish to report on a selective method for the acylation of alkoxybenzenes with aliphatic acid anhydrides in the presence of 0.15 molar amount of $\text{Al}(\text{HSO}_4)_3$ in nitromethane and also under solvent-free conditions (Scheme 1).

As shown in the Table 1, the catalytic acylation of alkoxybenzenes was proceeded well in solution with a high position selectivity for the formation of para-acylated products in good yields. Among the common organic solvents that have been used for Friedel–Crafts acylation, we found that nitromethane is the solvent of choice for these reactions.

We also conducted similar reactions in the absence of a solvent, and observed that at the same temperature omitting the solvent had a little effect in shortening the reaction times, but the product yields did not change significantly (Table 1).

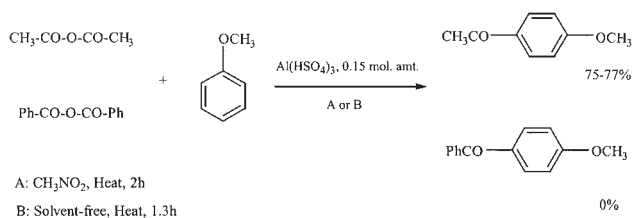
We also observed that aromatic acid anhydrides reacted sluggishly under the same conditions. Therefore, a competitive reaction between acetic anhydride and benzoic anhydride with anisole was studied and under both conditions; a high degree of chemoselectivity was observed (Scheme 2).

This method also permits us to conduct the selective acylation of alkoxybenzenes in the presence of the less reactive aromatic compounds, such as arenes and aryl halides.

In conclusion, aluminum hydrogensulfate is a stable, non-hygroscopic and heterogeneous catalyst for the selective acylation of alkoxybenzenes. Although aluminum chloride is also used for this purpose, its hygroscopic nature limits its applications in the laboratory. Moreover, AlCl_3 should be used in quantitative amounts. The catalytic nature of $\text{Al}(\text{HSO}_4)_3$ can be attributed to the presence of hydrogensulfate anion, which acts as a source of proton. The method also enjoys the chem-

Table 1. Friedel–Crafts Acylation of Alkoxybenzenes with Acid Anhydrides Mediated by $\text{Al}(\text{HSO}_4)_3$

Entry	R	R'	Reaction in CH_3NO_2			Solvent-free conditions		
			Time /h	Molar amount of the catalyst	Yield /%	Time /h	Molar amount of the catalyst	Yield /%
1	$-\text{CH}_3$	$-\text{CH}_3$	2	0.15	78	1.3	0.15	77
2	$-\text{CH}_2\text{CH}_3$	$-\text{CH}_3$	3	0.15	77	2.1	0.15	79
3	$-\text{CH}_2(\text{CH}_2)_2\text{CH}_3$	$-\text{CH}_3$	4	0.15	75	3.3	0.15	75
4	$-\text{CH}_2\text{CH}(\text{CH}_3)_2$	$-\text{CH}_3$	5.8	0.15	72	5	0.15	78
5	$-\text{CH}_2(\text{CH}_2)_4\text{CH}_3$	$-\text{CH}_3$	5	0.15	77	4.5	0.15	82
6	$-\text{CH}_3$	$-\text{CH}_2\text{CH}_3$	2	0.15	80	1.5	0.15	78
7	$-\text{CH}_2\text{CH}_3$	$-\text{CH}_2\text{CH}_3$	2.5	0.15	75	2	0.15	75
8	$-\text{CH}_2(\text{CH}_2)_2\text{CH}_3$	$-\text{CH}_2\text{CH}_3$	4.9	0.15	75	4	0.15	79
9	$-\text{CH}_2\text{CH}(\text{CH}_3)_2$	$-\text{CH}_2\text{CH}_3$	5	0.15	80	4	0.15	82
10	$-\text{CH}_2(\text{CH}_2)_4\text{CH}_3$	$-\text{CH}_2\text{CH}_3$	4	0.15	83	3.5	0.15	83



Scheme 2.

ical and environmental advantages of solvent-free reactions.⁴ $\text{Al}(\text{HSO}_4)_3$ is proposed as a very good successor for AlCl_3 in other organic reactions.

Experimental

The products were characterized by comparison of their spectral data (^1H NMR, IR) and physical properties with those reported in the literature. ^1H NMR spectra were run on a Bruker Avance 200 MHz spectrometer. IR spectra were obtained by a Shimadzu 470 spectrophotometer. The progress of the reactions was followed by TLC using silica gel Polygrams SIL G/UV 254 Sheets. All yields refer to isolated products.

Preparation of Aluminum Hydrogensulfate. A 500 mL suction flask was equipped with a constant-pressure dropping funnel. The gas outlet was connected to a vacuum system through an adsorbing solution (water) and an alkali trap. Anhydrous aluminum chloride (33.4 g, 0.25 mol) was charged in the flask and concentrated sulfuric acid (98%, 73.5 g, 0.75 mol) was added dropwise over a period of 30 min at room temperature. HCl evolved immediately. After completion of the addition, the mixture was shaken for 30 min, while the residual HCl was eliminated by suction. Finally, a pale-brown solid material was obtained in 77 g. $\text{Al}(\text{HSO}_4)_3$ was characterized by the determination of its H^+ content by titration with NaOH (Calcd 0.95%, Found 0.96%) and SO_4^{2-} by precipitation with Ba^{2+} (Calcd 90.57%, Found 90.48%). Al^{3+} was determined by two methods; conversion to Al_2O_3 (Calcd 8.48%, Found 8.31%) and spectrophotometric determination by complex formation with aluminon (Calcd 8.48%, Found 8.38%).⁵

General Procedure for the Acylation of Alkoxybenzenes in Nitromethane. Aluminum hydrogensulfate (0.45 mmol) was added to a solution of alkoxybenzene (3 mmol) and acid anhydride (6 mmol) in nitromethane (10 mL). The mixture was stirred magnetically at 65–70 °C for an appropriate period of time (Table 1). The progress of the reaction was monitored by TLC (eluent: hexane/diethyl ether: 2/1). Then, nitromethane was evaporated under reduced pressure and a solution of NaHCO_3 (5%, 20 mL) was added. The aqueous mixture was extracted with diethyl ether (3×20 mL). The organic layer was dried (Na_2SO_4) and concentrated. Final purification on a silica gel column afforded the desired products in 72–83% yields.

General Procedure for Acylation Reactions under Solvent-Free Conditions. Alkoxybenzene (3 mmol), acid anhydride (3.6 mmol) and aluminum hydrogensulfate (0.45 mmol) were placed in a mortar and mixed. The mixture was heated at 65–70 °C in an oven for an appropriate period of time (Table 1). Progress of the reaction was followed by dissolving a sample in dichloromethane and monitoring by TLC (eluent: hexane/diethyl ether: 2/1). The mixture was cooled to room temperature and a

solution of NaHCO_3 (5%, 20 mL) was added. The aqueous mixture was extracted with diethyl ether (3×20 mL). The organic layer was dried (Na_2SO_4) and concentrated. Final purification on a silica gel column afforded the desired products in 75–83% yields.

Spectral and Physical Data of the Products. Entry 1: Mp 35 °C (lit.⁶ 37 °C), mp of semicarbazone derivative 195–197 °C (lit.⁶ 197–198 °C).

Entry 2: Mp 34 °C (lit.⁶ 36–37 °C), mp of semicarbazone derivative 178–180 °C (lit.⁶ 179–180 °C).

Entry 3: Mp 23 °C (lit.⁷ 22 °C), mp of oxime derivative 83 °C (lit.⁷ 86 °C).

Entry 4: Mp of oxime derivative 105–106 °C (lit.⁸ 107 °C).

Entry 5: Mp of oxime derivative 77 °C (lit.⁸ 78 °C).

Entry 6: Mp 25–27 °C (lit.⁶ 26–27 °C), mp of semicarbazone derivative 170–172 °C (lit.⁶ 171–172 °C).

Entry 7: Mp 28–30 °C (lit.⁶ 29–30 °C), mp of semicarbazone derivative 182 °C (lit.⁶ 181–183 °C).

Entry 8: Mp 27–29 °C (lit.⁹ 28 °C), mp of oxime derivative 77 °C (lit.⁹ 79 °C).

Entry 9: IR (KBr), ν (cm^{-1}): 3050(w), 2950(s), 2910(s), 1673(s), 1600(s), 1472(m), 1255(s), 1230(s), 1020(s), 795(s); ^1H NMR (CDCl_3), δ 7.9 (2H, d, $J = 8.8$ Hz), 6.9 (2H, d, $J = 8.8$ Hz), 3.8 (2H, d, $J = 6.5$ Hz), 3.0 (2H, q, $J = 7.3$ Hz), 2.1 (1H, m, $J = 6.8$ Hz), 0.8–1.5 (9H, m); mp 44 °C, mp of 2,4-dinitrophenylhydrazone derivative 155–157 °C.

Entry 10: IR (neat), ν (cm^{-1}): 3050(w), 2930(s), 1675(s), 1600(s), 1460(m), 1250(s), 1220(s), 795(m); ^1H NMR (CDCl_3), δ 7.8 (2H, d, $J = 8.7$ Hz), 6.8 (2H, d, $J = 8.7$ Hz), 3.9 (2H, t, $J = 6.7$ Hz), 2.9 (2H, q, $J = 7.3$ Hz), 0.7–1.6 (14H, m); mp of 2,4-dinitrophenylhydrazone derivative 161–163 °C.

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References

- 1 G. A. Olah, "Friedel–Crafts and Related Reactions," Vol. 1, John Wiley & Sons, New York (1963).
- 2 J. A. Hyatt and P. W. Reynolds, *J. Org. Chem.*, **49**, 384 (1984).
- 3 a) P. Salehi, M. M. Khodaei, M. A. Zolfigol, and A. Keyvan, *Synth. Commun.*, **31**, 1947 (2001). b) P. Salehi, M. M. Khodaei, M. A. Zolfigol, and A. Keyvan, *Monatsh. Chem.*, **133**, 1291 (2002), and references cited therein.
- 4 K. Tanaka and F. Toda, *Chem. Rev.*, **100**, 1025 (2000).
- 5 A. I. Vogel, "Quantitative Inorganic Analysis," Longman, London (1972), pp. 462, 472, 792.
- 6 X. A. Dominguez, B. Gomez, J. Slim, D. Giesecke, and E. Ureta, *J. Am. Chem. Soc.*, **76**, 5150 (1954).
- 7 R. E. Lutz, R. K. Allison, G. Ashburn, P. S. Bailey, M. T. Clark, J. F. Codrington, A. J. Deinet, J. A. Freek, R. H. Jordan, N. H. Leake, T. A. Martin, K. C. Nicodemus, R. J. Towlett, N. H. Shearer, J. D. Smith, and J. W. Wilson, *J. Org. Chem.*, **12**, 617 (1947).
- 8 E. Eckhart and J. Varga, *Mag. Kem. Foly.*, **67**, 509 (1961); *Chem. Abstr.*, **56**, 15557e (1962).
- 9 E. Hanning and G. Leuschner, *Pharm. Zentralhalle*, **96**, 570 (1957); *Chem. Abstr.*, **52**, 14078d (1958).