

## Catalytic Friedel-Crafts Acylation Reactions Using Hafnium Triflate as a Catalyst in Lithium Perchlorate-Nitromethane

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**Abstract:** Catalytic Friedel-Crafts acylation reactions were performed by using hafnium trifluoromethanesulfonate (hafnium triflate,  $\text{Hf}(\text{OTf})_4$ ) as a catalyst. The catalytic activity of the Lewis acid catalyst was much improved in lithium perchlorate-nitromethane ( $\text{LiClO}_4\text{-MeNO}_2$ ) and the yield was up to 250,000% based on the catalyst. Various substituted benzenes reacted with acid anhydrides in the presence of a catalytic amount of  $\text{Hf}(\text{OTf})_4$  to give the corresponding aromatic ketones in high yields.

Many kinds of Lewis acid-promoted reactions have been developed to realize unique reactivities and selectivities, and some of them have been applied in industrial processes.<sup>1</sup> In most of these reactions, however, more than a stoichiometric amount of a Lewis acid is required and it is desired to decrease the amount of the acid by developing an efficient catalyst and catalytic processes. The Friedel-Crafts acylation reactions, which are one of the most important processes in organic synthesis, are generally carried out by using aluminum trichloride ( $\text{AlCl}_3$ ) as a Lewis acid.<sup>2</sup> The  $\text{AlCl}_3$ -promoted reactions have some disadvantages such as the requirement of more than a stoichiometric amount of the Lewis acid and of treatment of the  $\text{AlCl}_3$  residue after the reactions. Although several catalytic Friedel-Crafts acylation reactions have been reported so far, they are not satisfactory in terms of yield, scope of the substrates, and turnover of the catalyst.<sup>3,4</sup> In this paper, we would like to report two important findings in this field. 1) The turnover of Lewis acid catalysts in Friedel-Crafts acylation reactions is 5-20 times improved in lithium perchlorate-nitromethane ( $\text{LiClO}_4\text{-MeNO}_2$ ). 2) Hafnium triflate ( $\text{Hf}(\text{OTf})_4$ ) was first synthesized and it was found to be the most effective catalyst we tested in the Friedel-Crafts acylation reactions.<sup>5</sup>

**Table 1.** Effect of Lewis Acids in  $\text{MeNO}_2$  and  $\text{LiClO}_4\text{-MeNO}_2$  Media

entry	Lewis acid	yield (%)	
		$\text{MeNO}_2$	4 M $\text{LiClO}_4\text{-MeNO}_2$
1	$\text{BF}_3\cdot\text{OEt}_2$	1	25
2	$\text{SnCl}_4$	5	50
3	$\text{Sc}(\text{OTf})_3$	5	40
4	$\text{SbCl}_5$	6	59
5	$\text{Zr}(\text{OTf})_4$	18	68
6	$\text{Hf}(\text{OTf})_4$	16	76

**Table 2.** Hf(OTf)<sub>4</sub>-Catalyzed Friedel-Crafts Acylation Reactions in LiClO<sub>4</sub>-MeNO<sub>2</sub> Media <sup>a)</sup>

entry	aromatic compound	acid anhydride	product	yield (%)
1	anisole	acetic anhydride	4-methoxyacetophenone	95
2	1,2-dimethoxybenzene		3,4-dimethoxyacetophenone	90
3	mesitylene		2,4,6-trimethylacetophenone	92
4	o-xylene		3,4-dimethylacetophenone	90
5	m-xylene		2,4-dimethylacetophenone	91
6	p-xylene		2,5-dimethylacetophenone	66
7	toluene		4-methylacetophenone	85 <sup>b)</sup>
8	benzene		acetophenone	17
9	naphthalene		acetylnaphthalene	99 <sup>c)</sup>
10	anisole	isopropionic anhydride	isopropyl 4-methoxyphenyl ketone	quant.
11		tert-butylic anhydride	tert-butyl 4-methoxyphenyl ketone	91
12		propionic anhydride	4-methoxyphenyl propyl ketone	93
13	mesitylene		2,4,6-trimethylphenyl propyl ketone	84
14	m-xylene		2,4-dimethylphenyl propyl ketone	83
15		benzoic anhydride	2,4-dimethylbenzophenone	88
16	mesitylene		2,4,6-trimethylbenzophenone	94

a) The reactions were carried out using 5 mol% Hf(OTf)<sub>4</sub> except for entry 3 (1 mol%) and entries 6, 7, and 8 (10 mol%). The reactions were carried out at room temperature except for entry 2 (0 °C) and entry 15 (50 °C). b) Ortho/para = 3/97. c) 1-Acetylnaphthalene/2-Acetylnaphthalene = 52/48.

The effects of Lewis acids in 4M LiClO<sub>4</sub>-MeNO<sub>2</sub> in the model reaction of acetic anhydride with *m*-xylene are shown in Table 1. Among the Lewis acids screened, Hf(OTf)<sub>4</sub><sup>6</sup> was found to be the most effective, and 2,4-dimethylacetophenone was obtained in a high yield. It is noted that the turnover of all the catalysts tested was 10-20 times improved in 4M MeNO<sub>2</sub>-LiClO<sub>4</sub>. We also examined the effects of solvents in this reaction. While the reaction proceeded smoothly in LiClO<sub>4</sub>-MeNO<sub>2</sub>, <sup>i</sup>PrNO<sub>2</sub>, or CH<sub>2</sub>Cl<sub>2</sub>, only a trace amount of the product was detected in Et<sub>2</sub>O or CS<sub>2</sub>. Several examples of the Friedel-Crafts acylation reactions of substituted benzenes with acid anhydrides using a catalytic amount of Hf(OTf)<sub>4</sub> in LiClO<sub>4</sub>-MeNO<sub>2</sub> are shown in Table 2. The features of the present Friedel-Crafts acylation reactions are as follows. In every case (except

for entry 8), the reactions proceeded smoothly using a catalytic amount of  $\text{Hf}(\text{OTf})_4$  in  $\text{LiClO}_4\text{-MeNO}_2$  to give the corresponding aromatic ketones in high yields. Various substituted benzenes could be employed, and not only acetic anhydride but also propionic anhydride and benzoic anhydride reacted with substituted benzenes to give the corresponding aromatic ketones in high yields. Even sterically hindered acid anhydrides such as isopropionic anhydride and pivalic anhydride worked well. The yield in the Friedel-Crafts reaction of mesitylene with acetic anhydride was up to 250,000% (based on the catalyst).

A typical experimental procedure is described for the reaction of *m*-xylene with acetic anhydride: To  $\text{Hf}(\text{OTf})_4$  (0.1 mmol, 5 mol%) and  $\text{LiClO}_4$  (12 mmol) was added a mixture of *m*-xylene (2 mmol) and acetic anhydride (4 mmol) in nitromethane (1 ml) at room temperature. The mixture was stirred for 6 h at this temperature and then aqueous saturated sodium hydrogen carbonate was added. After separation of the organic layer, the aqueous layer was extracted with dichloromethane and the organic solvents were dried ( $\text{Na}_2\text{SO}_4$ ). The solvents were removed under reduced pressure, and the crude product was chromatographed on silica gel to afford 2,4-dimethylacetophenone (91%).

It is assumed that in the present Friedel-Crafts acylations an active species is generated from acetic anhydride and  $\text{LiClO}_4$  in the presence of a catalytic amount of  $\text{Hf}(\text{OTf})_4$ . Although precise structure is not yet clear, IR data supported the existence of this species. The absorption of the carbonyl groups of acetic anhydride in nitromethane was measured at 1826 and 1757  $\text{cm}^{-1}$ , while absorptions were observed in lower wave numbers in the presence of  $\text{Hf}(\text{OTf})_4$  in accordance with the amount of  $\text{LiClO}_4$  (Table 3).

In summary, the catalytic Friedel-Crafts acylation reactions of substituted benzenes with acid anhydrides were successfully carried out by using  $\text{Hf}(\text{OTf})_4$  as a catalyst. We also found that the turnover of Lewis acid catalysts in the Friedel-Crafts acylation is 10-20 times improved in lithium perchlorate-nitromethane ( $\text{LiClO}_4\text{-MeNO}_2$ ).

Further investigations to develop other synthetic reactions using a catalytic amount of  $\text{Hf}(\text{OTf})_4$  as well as to clarify the origin of the high efficiency in  $\text{LiClO}_4\text{-MeNO}_2$  are now in progress.

**Table 3.** Wave Numbers of the Key Intermediate

$\text{LiClO}_4$	$\text{Hf}(\text{OTf})_4$	wave number ( $\text{cm}^{-1}$ )
—	—	1826, 1757
1 eq	—	1824, 1801, 1726
1 eq	0.025 eq	1807, 1724
2 eq	0.025 eq	1803, 1724

**Acknowledgment.** I. H. thanks the JSPS fellowship for Japanese Junior Scientists.

## References and Notes

- 1) Schinzer, D., Ed. *Selectivities in Lewis Acid Promoted Reactions*, Kluwer Academic Publishers: Dordrecht, 1989.

- 2) a) Olah, G. A. *Friedel-Crafts and Related Reaction*; Interscience: New York, 1964; Vol. III, Part 1. b) Heaney, H. "Comprehensive Organic Synthesis," Vol. 2; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; p. 733.
- 3) For catalytic Friedel-Crafts acylations, a) Hino, M.; Arata, K. *Chem. Lett.* **1978**, 325. b) Nomita, K.; Sugaya, Y.; Sasa, S.; Miwa, M. *Bull. Chem. Soc. Jpn.* **1980**, 53, 2089. c) Yamaguchi, T.; Mitoh, A.; Tanabe, K. *Chem. Lett.* **1982**, 1229. d) Effenberger, F.; Epple, G. *Angew. Chem., Int. Ed. Engl.* **1972**, 11, 300. e) Mukaiyama, T.; Nagaoka, H.; Ohshima, M.; Murakami, M. *Chem. Lett.* **1986**, 165. f) Effenberger, F.; Steegmüller, D. *Chem. Ber.* **1988**, 121, 117. g) Mukaiyama, T.; Ohno, T.; Nishimura, T.; Han, S. J.; Kobayashi, S. *Chem. Lett.* **1991**, 1059. h) Mukaiyama, T.; Suzuki, K.; Han, S. J.; Kobayashi, S. *Chem. Lett.* **1992**, 435. i) Suzuki, K.; Kitagawa, H.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1993**, 66, 3729, and references cited therein.
- 4) Quite recently, we reported that lanthanide triflates ( $\text{Ln}(\text{OTf})_3$ ) and scandium triflate ( $\text{Sc}(\text{OTf})_3$ ) are effective catalysts in Friedel-Crafts acylation reactions. a) Kawada, A.; Mitamura, S.; Kobayashi, S. *J. Chem. Soc., Chem. Commun.* **1993**, 1157. b) Kawada, A.; Mitamura, S.; Kobayashi, S. *Synlett* **1994**, 545.
- 5) Grieco et al. reported that Diels-Alder and some other reactions proceeded smoothly in highly concentrated  $\text{LiClO}_4\text{-Et}_2\text{O}$  solution. a) Grieco, P. A.; Nunes, R. J.; Gaul, M. D. *J. Am. Chem. Soc.* **1990**, 112, 4595. b) Grieco, P. A.; Clark, J. D.; Jagoe, C. T. *ibid.* **1991**, 113, 5488. c) Grieco, P. A.; Cooke, R. J.; Henry, K. J.; VanderRoest, J. M. *Tetrahedron Lett.* **1991**, 32, 4665. See also, d) Palani, N.; Balasubramanian, K. K. *ibid.* **1993**, 34, 5001. We have already reported that  $\text{LiClO}_4$  is an effective additive in some glycosylation reactions. e) Mukaiyama, T.; Kobayashi, S.; Shoda, S. *Chem. Lett.* **1984**, 953. f) Mukaiyama, T.; Shimpuku, T.; Takashima, T.; Kobayashi, S. *ibid.* **1989**, 145. See also, g) Winstein, S.; Smith, S.; Darwish, D. *J. Am. Chem. Soc.* **1959**, 81, 5511. h) Pocker, Y.; Buchholz, R. F. *ibid.* **1970**, 92, 2075.
- 6) Trifluoromethanesulfonic acid 22.1 ml (250 mmol) was added to hafnium tetrachloride 8.61 g (26.9 mmol) and the mixture was heated at 50 °C for 68 h under argon. The excess trifluoromethanesulfonic acid was removed and then the residue was washed with petroleum ether. White powder was dried for 8 h (100 °C/0.5 mmHg) to give  $\text{Hf}(\text{OTf})_4$  20.9 g (100%). Mp. >300 °C. IR (KBr) 1637, 1350, 1311, 1267, 1209, 1161, 1030, 985, 715, 675, 638, 573, 534, 513, 463, 426  $\text{cm}^{-1}$ ;  $^{13}\text{C}$  NMR  $\delta$  ( $\text{CD}_3\text{CN}$ ) 120.1 (q,  $J = 316.6$  Hz). Anal. Calcd for  $\text{C}_4\text{F}_{12}\text{HfO}_{12}\text{S}_4$ : C, 6.19; S, 16.55. Found: C, 6.23; S, 16.02.

(Received in Japan 6 August 1994; revised 22 October 1994; accepted 4 November 1994)