

# Remarkable Effect of Lithium Salts in Friedel–Crafts Acylation of 2-Methoxynaphthalene Catalyzed by Metal Triflates

Shū Kobayashi\* and Ichiro Komoto

Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

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**Abstract**—In the presence of a catalytic amount of a metal triflate such as  $\text{Sb}(\text{OTf})_3$  or  $\text{Ga}(\text{OTf})_3$ , 2-methoxynaphthalene reacted with acetic anhydride in nitromethane–lithium perchlorate to afford 2-acetyl-6-methoxynaphthalene, a well-known intermediate for the synthesis of naproxen, in a high yield. © 2000 Elsevier Science Ltd. All rights reserved.

Regioselective Friedel–Crafts acylation of naphthalene derivatives provides efficient methods for the preparation of pharmaceuticals, polymers, liquid crystals, etc.<sup>1</sup> For example, the reaction of 2-methoxynaphthalene with acetyl chloride or acetic anhydride provides the shortest route to 2-acetyl-6-methoxynaphthalene, which has been used for the synthesis of naproxen, a potent anti-inflammatory agent.<sup>1a,2</sup> However, conventional Friedel–Crafts acylation of 2-methoxynaphthalene requires more than 1 equiv. of aluminum chloride ( $\text{AlCl}_3$ ) in carbon disulfide or nitrobenzene, and moderate regioselectivity was obtained.<sup>3</sup> More recently, the use of boron trifluoride in  $\text{HF}$ ,<sup>4</sup> indium chloride in nitrobenzene or 1,2-dichloroethane,<sup>5</sup> or mesoporous molecular sieves<sup>6</sup> has been reported. In these reactions, however, regioselectivities are moderate in some cases, and more than stoichiometric amounts of the Lewis acids and/or hazardous solvents are needed. In the course of our investigations to develop efficient catalytic Friedel–Crafts acylation, we have found that a small amount of a metal triflate such as antimony (III) triflate ( $\text{Sb}(\text{OTf})_3$ ) or galium (III) triflate ( $\text{Ga}(\text{OTf})_3$ ) catalyzed the reaction of 2-methoxynaphthalene with acetic anhydride in nitromethane ( $\text{MeNO}_2$ )–lithium perchlorate ( $\text{LiClO}_4$ ), to afford the desired 2-acetyl-6-methoxynaphthalene in a high yield with high regioselectivity. In this paper, we report these results in details.

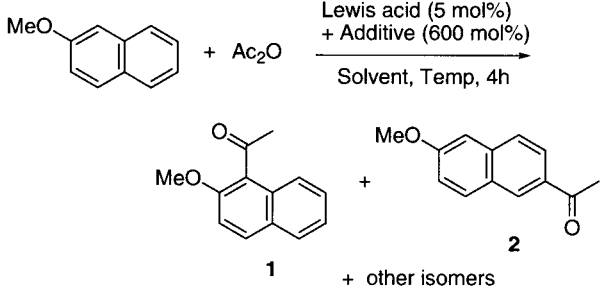
Recently, we have developed several catalytic Friedel–Crafts acylation reactions using metal triflates such as  $\text{Yb}(\text{OTf})_3$ ,<sup>7</sup>  $\text{Sc}(\text{OTf})_3$ ,<sup>8</sup> and  $\text{Hf}(\text{OTf})_4$ <sup>9</sup> as catalysts. Moreover, it was demonstrated that turnover of the metal triflates in the Friedel–Crafts acylation dramatically improved when combined with  $\text{LiClO}_4$ .<sup>9a,b,10,11</sup> Bearing these results in mind, we examined the reaction of 2-methoxynaphthalene

with acetic anhydride using metal triflates as catalysts. The effect of metal triflates is shown in Table 1. When 5 mol% of  $\text{Sb}(\text{OTf})_3$ <sup>12</sup> was used in  $\text{MeNO}_2$ , 1-acetylated adduct **1** was obtained preferentially (entry 1). Adduct **1** was also obtained when other solvents such as acetonitrile, nitrobenzene, and dichloromethane were used (entries 2–4). On the other hand, a dramatic change of the regioselectivity was observed when  $\text{Sb}(\text{OTf})_3$  was used in  $\text{MeNO}_2$ – $\text{LiClO}_4$ . Namely, 2-methoxynaphthalene reacted with acetic anhydride in the presence of 5 mol% of  $\text{Sb}(\text{OTf})_3$  in  $\text{MeNO}_2$ – $\text{LiClO}_4$  to afford 6-acetylated adduct **2** in 93% yield (determined by GC), and no 1-acetylated adduct **1** was detected (entry 5). While other metal triflates were effective for the preparation of **2** (entries 6–12), the highest yields and selectivities were obtained when  $\text{Sb}(\text{OTf})_3$  or  $\text{Ga}(\text{OTf})_3$ <sup>13</sup> was combined with  $\text{LiClO}_4$ . For other lithium salts, *N*-lithiotrifluoromethanesulfonimide ( $\text{LiNTf}_2$ ) was effective, while lower yields and selectivities were obtained using other lithium salts (entries 13–16). It is interesting to note that the use of  $\text{NaClO}_4$  instead of  $\text{LiClO}_4$  gave much lower yield and selectivity of the desired adduct (**2**) (entry 17), and that the catalytic use of  $\text{AlCl}_3$  was not effective even when combined with  $\text{LiClO}_4$  (entry 19).

A preliminary kinetic study was performed in the reaction of 2-methoxynaphthalene with acetic anhydride using 5 mol% of  $\text{Sb}(\text{OTf})_3$  in  $\text{MeNO}_2$ – $\text{LiClO}_4$  (Fig. 1). It was found that 1-acetylated adduct **1** was formed in the initial stage of the reaction, and that migration from **1** to 6-acetylated adduct **2** occurred during the reaction course. These results indicate that adducts **1** and **2** are kinetic and thermodynamic products, respectively.<sup>3,14</sup>

In summary, we have observed a remarkable effect of lithium salts in Friedel–Crafts acylation of 2-methoxynaphthalene. Regioselective reactions proceeded smoothly in the presence of a catalytic amount of a metal triflate such

\* Corresponding author. Tel.: +81-3-5841-4790; fax: +81-3-5684-0634; e-mail: skobayas@mol.f.u-tokyo.ac.jp

**Table 1.** Effect of Lewis acids and additives


Entry	Lewis acid	Additive	Solvent	Temperature (°C)	Yield (%) <sup>a</sup>	
					1	2
1	Sb(OTf) <sub>3</sub>	–	MeNO <sub>2</sub>	rt	77	4
2	Sb(OTf) <sub>3</sub>	–	MeCN	50	83	2
3	Sb(OTf) <sub>3</sub>	–	PhNO <sub>2</sub>	50	46	5
4	Sb(OTf) <sub>3</sub>	–	CH <sub>2</sub> Cl <sub>2</sub>	40	66	4
5	Sb(OTf) <sub>3</sub>	LiClO <sub>4</sub>	MeNO <sub>2</sub>	50	ND <sup>b</sup>	93
6	Sc(OTf) <sub>3</sub>	LiClO <sub>4</sub>	MeNO <sub>2</sub>	50	14	62
7	Fe(OTf) <sub>3</sub>	LiClO <sub>4</sub>	MeNO <sub>2</sub>	50	2	72
8	Ga(OTf) <sub>3</sub>	LiClO <sub>4</sub>	MeNO <sub>2</sub>	50	ND <sup>b</sup>	92
9	Sn(OTf) <sub>2</sub>	LiClO <sub>4</sub>	MeNO <sub>2</sub>	50	2	73
10	Yb(OTf) <sub>3</sub>	LiClO <sub>4</sub>	MeNO <sub>2</sub>	50	26	45
11	Hf(OTf) <sub>4</sub>	LiClO <sub>4</sub>	MeNO <sub>2</sub>	50	ND <sup>b</sup>	67
12	Bi(OTf) <sub>3</sub>	LiClO <sub>4</sub>	MeNO <sub>2</sub>	50	ND <sup>b</sup>	69
13	Sb(OTf) <sub>3</sub>	LiNTf <sub>2</sub>	MeNO <sub>2</sub>	50	ND <sup>b</sup>	76
14	Sb(OTf) <sub>3</sub>	LiOTf	MeNO <sub>2</sub>	50	0	39
15	Sb(OTf) <sub>3</sub>	LiNO <sub>3</sub>	MeNO <sub>2</sub>	50	36	1
16	Sb(OTf) <sub>3</sub>	LiAc	MeNO <sub>2</sub>	50	19	7
17	Sb(OTf) <sub>3</sub>	NaClO <sub>4</sub>	MeNO <sub>2</sub>	50	7	17
18	Al(OTf) <sub>3</sub>	LiClO <sub>4</sub>	MeNO <sub>2</sub>	50	ND <sup>b</sup>	83
19	AlCl <sub>3</sub>	LiClO <sub>4</sub>	MeNO <sub>2</sub>	50	35	27

<sup>a</sup> Determined by GC analysis.<sup>b</sup> Not detected.

as Sb(OTf)<sub>3</sub> or Ga(OTf)<sub>3</sub> in MeNO<sub>2</sub>–LiClO<sub>4</sub>. 2-Acetyl-6-methoxynaphthalene, a well-known intermediate for the synthesis of naproxen, has been prepared based on this reaction. Further investigations to clarify the mechanism of these reactions and the role of the lithium salts are in progress.

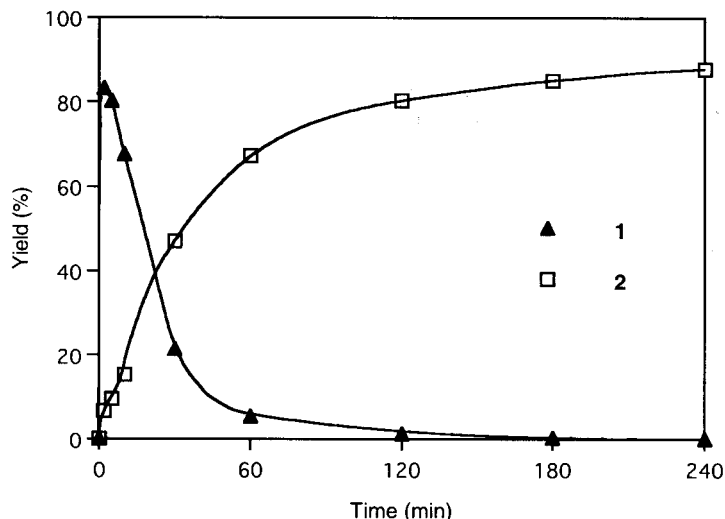
## Experimental

### General

Melting points were uncorrected. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a JEOL JNM-LA300, JNM-LA400, or JNM-LA500 spectrometer. Tetramethylsilane (TMS) served as internal standard ( $\delta=0$ ) for <sup>1</sup>H NMR, and CDCl<sub>3</sub> was used as internal standard ( $\delta=77.0$ ) for <sup>13</sup>C NMR. Column chromatography was conducted on Silica gel 60 (Merck) and preparative thin-layer chromatography was carried out using Wakogel B-5F.

**Antimony (III) triflate (Sb(OTf)<sub>3</sub>).** Sb(OTf)<sub>3</sub> was prepared from SbPh<sub>3</sub> and TfOH according to the preparation method of Bi(OTf)<sub>3</sub>.<sup>15</sup> Under an argon atmosphere, TfOH (3 equiv.) was added to a mixture of SbPh<sub>3</sub> (1 equiv.) and dichloromethane at  $-78^{\circ}\text{C}$ . After stirred at room temperature for 4 h, the mixture was filtered and the residue was washed with dichloromethane for several times. The pale yellow powder was dried in vacuo at room temperature for 2 h and  $50^{\circ}\text{C}$  for 3 h to afford Sb(OTf)<sub>3</sub>. Anal. Calcd for C<sub>3</sub>F<sub>9</sub>O<sub>9</sub>S<sub>3</sub> 1.6H<sub>2</sub>O: C, 6.02; H, 0.55. Found: C, 6.28; H, 0.55. The water observed in the elemental analysis was supposed to be contaminated during the measurement.

**A typical procedure for the reaction of 2-methoxynaphthalene with acetic anhydride.** A mixture of 2-methoxynaphthalene (158 mg, 1.0 mmol), acetic anhydride (102 mg, 1.0 mmol), Sb(OTf)<sub>3</sub> (29 mg, 0.05 mmol, 5 mol%), and LiClO<sub>4</sub> (639 mg, 6.0 mmol) in MeNO<sub>2</sub> (1.0 mL) was stirred at  $50^{\circ}\text{C}$  for 4 h. After adding saturated aqueous NaHCO<sub>3</sub> (10 mL), the mixture was extracted with Et<sub>2</sub>O (20 mL $\times$ 2). The combined organic extract was dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated to give a crude oil. This crude product was purified by preparative TLC (hexane/ethyl acetate=10/1) to afford 2-acetyl-6-methoxynaphthalene (159 mg, 0.80 mmol, 80%). 1-acetyl-6-methoxynaphthalene could also be purified by preparative TLC.



**Figure 1.** Formation of 1 and 2 in the reaction of 2-methoxynaphthalene with acetic anhydride using Sb(OTf)<sub>3</sub> in MeNO<sub>2</sub>–LiClO<sub>4</sub>.

**A gram-scale synthesis of 2-acetyl-6-methoxynaphthalene.** To a mixture of 2-methoxynaphthalene (1.634 g, 10.3 mmol) and LiClO<sub>4</sub> (6.593 g, 62.0 mmol) in MeNO<sub>2</sub> (10 mL), Sb(OTf)<sub>3</sub> (0.294 g, 0.5 mmol, 5 mol%) was added. Acetic anhydride (1.266 g, 12.4 mmol) was slowly added at 50°C for 5 min, and the reaction mixture was stirred at 50°C for 5 h. After the mixture was poured into saturated aqueous NaHCO<sub>3</sub> (50 mL), the mixture was extracted with Et<sub>2</sub>O (100 mL×2) and the combined organic phase was washed with H<sub>2</sub>O (50 mL×2). The organic extract was dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated to give a crude oil. This crude product was treated with activated charcoal in AcOEt, and then filtered. The solvent was removed and the residue was recrystallized from heptane to afford 2-acetyl-6-methoxynaphthalene (1.542 g, 7.70 mmol, 75%).

**2-Acetyl-6-methoxynaphthalene.** A pale yellow crystal. Mp 104.5–106°C (lit.<sup>3b</sup> 106.5°C). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 2.71 (s, 3H), 3.96 (s, 3H) 7.16 (d, *J*=2.6 Hz, 1H), 7.21 (dd, *J*=8.8, 2.6 Hz, 1H), 7.77 (d, *J*=8.6 Hz, 1H), 7.86 (d, *J*=8.8 Hz, 1H), 8.01 (dd, *J*=8.6, 1.8 Hz, 1H), 8.40 (d, *J*=1.8 Hz, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 26.6, 55.4, 105.7, 119.7, 124.7, 127.1, 127.8, 130.1, 131.1, 132.6, 137.3, 159.7, 197.9.

**1-Acetyl-2-methoxynaphthalene.** A pale yellow crystal. Mp 54.5–56.5°C (lit.<sup>16</sup> 57–58°C). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.65 (s, 3H), 3.98 (s, 3H), 7.29 (d, *J*=9.2 Hz, 1H), 7.37 (ddd, *J*=8.1, 6.9, 1.2 Hz, 1H), 7.48 (ddd, *J*=8.1, 6.9, 1.5 Hz, 1H), 7.76 (d, *J*=8.1 Hz, 1H), 7.80 (d, *J*=8.1 Hz, 1H), 7.89 (d, *J*=9.2 Hz, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 32.7, 56.4, 112.8, 123.6, 124.1, 125.1, 127.7, 128.1, 128.8, 130.3, 131.4, 153.9, 205.2.

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