Catalytic Friedel–Crafts Acylation of Aniline Derivatives

Shū Kobayashi,* Ichiro Komoto, Jun-ichi Matsuo

Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113–0033 Japan
Fax: +81 3 5684 0634; e-mail: skobayas@mol.f.u-tokyo.ac.jp

Received August 8, 2000; Accepted October 16, 2000

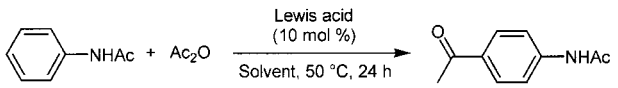
Keywords: aryl ketones; Friedel-Crafts acylation; gallium; homogeneous catalysis; Lewis acids; solvent systems

Friedel–Crafts acylation provides a fundamental and useful method for the preparation of aromatic ketones. While catalytic amounts of Lewis acids are used in Friedel–Crafts alkylation, more than stoichiometric amounts of Lewis acids such as $AlCl_3$ are required for the acylation.[1] There is considerable concern that large amounts of aluminum residues as well as the use of harmful organic solvents will induce some environmental problems, especially in industrial-scale processes. To address this issue, several excellent catalysts were developed, and catalytic acylation of activated benzenes such as anisole, xylenes, and toluene was achieved.[2] However, catalytic Friedel–Crafts acylation of benzene and deactivated benzenes such as chlorobenzene was still difficult to realize. Recently, Dubac et al. and our group independently reported that $Bi(OTf)_3$[3] and $Hf(OTf)_4$[4] were effective catalysts for the Friedel–Crafts acylation of benzene and deactivated benzenes. Quite recently, we have further demonstrated that a gallium catalyst, especially gallium tris(perfluoroalkanesulfonate), showed the highest activity in Friedel–Crafts acylation.[5]

On the other hand, *p*-ketoaniline structures are often observed in biologically active compounds as well as in fine chemicals, and the controlled and efficient synthesis of these structures is an important task. Although Friedel–Crafts acylation of aniline derivatives is a simple and straightforward method for the synthesis of *p*-ketoanilines, no example of a catalytic reaction has been reported, to the best of our knowledge.[6,7] In this paper, we describe the first example of the catalytic Friedel–Crafts acylation of aniline derivatives using a gallium compound.

The difficulty of Friedel–Crafts acylation of aniline derivatives could be ascribed to the low activity of Lewis acid catalysts caused by basic nitrogen atoms of the aniline derivatives. In literature, it was reported that Friedel–Crafts acylation of acylanilides using more than stoichiometric amounts of $AlCl_3$ gave the corresponding acylated products in low yields.[8,9] Based on our findings that gallium tris(perfluoroalkanesulfonate) showed high catalytic activities in Friedel–Crafts acylations of benzene and deactivated benzenes,[5] we envisioned that these highly active gallium catalysts would promote Friedel–Crafts acylation of aniline derivatives. First, we tested the reaction of acetanilide (**1a**) with acetic anhydride using 10 mol % of $Ga(OTf)_3$.[10] Although $Ga(OTf)_3$ itself gave the desired adduct in a low yield in nitromethane ($MeNO_2$), the addition of lithium perchlorate ($LiClO_4$) to the reaction mixture improved the yield dramatically (Table 1).[2j,o,4a,b] As the amounts

Table 1. Effect of Lewis acids



1a **2a**

Entry	Lewis acid	Solvent (Media)	Yield (%)
1	$Ga(OTf)_3$	CH_3NO_2	3
2	$Ga(OTf)_3$	$MeNO_2$-$LiClO_4$ (3 M)	62
3	$Ga(OTf)_3$	$MeNO_2$-$LiClO_4$ (4.8 M)	82
4	$Ga(OTf)_3$	$MeNO_2$-$LiClO_4$ (6 M)	93
5	$Ga(ONf)_3$	$MeNO_2$-$LiClO_4$ (6 M)	90
6	$GaCl_3$	$MeNO_2$-$LiClO_4$ (6 M)	33
7	$Sc(OTf)_3$	$MeNO_2$-$LiClO_4$ (6 M)	10
8	$Sc(ONf)_3$	$MeNO_2$-$LiClO_4$ (6 M)	48
9	$Hf(OTf)_4$	$MeNO_2$-$LiClO_4$ (6 M)	44
10	$Sb(OTf)_3$	$MeNO_2$-$LiClO_4$ (6 M)	59
11	$Bi(OTf)_3$	$MeNO_2$-$LiClO_4$ (6 M)	59
12	$AlCl_3$[a]	$MeNO_2$-$LiClO_4$ (6 M)	<1
13	none	$MeNO_2$-$LiClO_4$ (6 M)	<1
14	$AlCl_3$[b]	$ClCH_2CH_2Cl$	9

[a] $AlCl_3$ (5.1 equiv) was used. [b] $AlCl_3$ (3.2 equiv) was used. The reaction time was 12 h.

Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/asc/ or from the author.

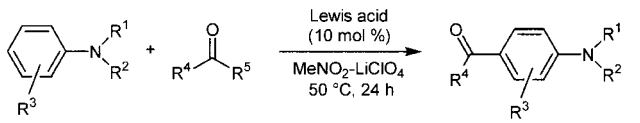
  1615-4150/01/34301-71–74 $ 17.50-.50/0

of $LiClO_4$ were increased, the yields of the desired adducts improved, and 93% yield of the acetylated adduct was obtained in a 6.0 M $MeNO_2$–$LiClO_4$ solution. While gallium tris(nonafluorobutanesulfonate) ($Ga(ONf)_3$) also catalyzed the reaction efficiently, the catalytic activity of $GaCl_3$ was low. We examined other catalysts such as $Sc(OTf)_3$, $Sc(ONf)_3$, $Hf(OTf)_4$, $Sb(OTf)_3$,[11] $Bi(OTf)_3$, etc., and it was found that $Ga(OTf)_3$ gave the best result. It is noted that $AlCl_3$, a representative Lewis acid for Friedel–Crafts acylation, was not effective in this reaction. In a $MeNO_2$–$LiClO_4$ solution, even more than stoichiometric amounts of $AlCl_3$ gave the desired adduct in a very low yield. Independently, **1a** reacted with acetic anhydride in the presence of 3.2 equivalents of $AlCl_3$ in 1,2-dichloroethane at 50 °C for 12 h to afford the acetylated adduct in 9% yield.

Several examples of $Ga(OTf)_3$- or $Ga(ONf)_3$-catalyzed Friedel–Crafts acylation of aniline derivatives are shown in Table 2. In all cases, the reactions proceeded smoothly in the presence of a catalytic amount of the gallium compound in $MeNO_2$–$LiClO_4$ in good to excellent yields. Not only acetanilide (**1a**) but also benzanilide (**1b**) reacted with several acetic anhydrides to afford the corresponding acylated adducts in high yields. Although *N*-methanesulfonyl(Ms)-aniline reacted with acetic anhydride in the presence of 10 mol % of $Ga(OTf)_3$ to give the *N*-acetylated adduct in a high yield, *N*-methanesulfonyl(Ms)-*N*-methylaniline (**1c**) reacted with acetic anhydride under the same reaction conditions to afford **2e** in 97% yield. Several *o*- and *m*-substituted aniline derivatives also worked well in the presence of a catalytic amount of $Ga(OTf)_3$ or $Ga(ONf)_3$. It is noted that single regioisomers shown in Table 2 were obtained in all these acylation reactions except for entry 7. For benzoylation, **1c** and **1k** smoothly reacted with benzoyl chloride in 1,2-dichloroethane under reflux for 24 h to afford the desired adducts (**2m** and **2n**) in high yields. A carboxylic acid was directly employed in this reaction in combination with trifluoroacetic anhydride, and the desired acetylated adduct (**2b**) was obtained in an excellent yield without formation of trifluoroacetylated adducts.

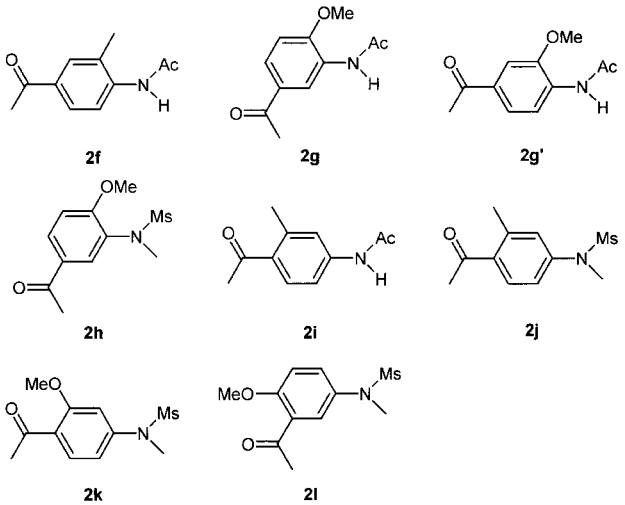
During our investigation of the Friedel–Crafts acylation of aniline derivatives, we found that the *N*-substituents of the aniline derivatives influenced the reaction rate to a large extent (Table 3). While $Ga(OTf)_3$-catalyzed acetylation of **1a** and **1b** proceeded smoothly, *N*-methylacetanilide (**1l**) and *N*-methylbenzanilide (**1m**) reacted with acetic anhydride sluggishly under the same reaction conditions. To understand the difference in reactivities, we measured the ^{13}C NMR spectra of the anilides and compared the chemical shifts of the reaction sites (the C4 position). It was interesting to find that ^{13}C NMR signals at the C4 position of *N*-methylated acylanilides

Table 2. Friedel-Crafts acylation of aniline derivatives



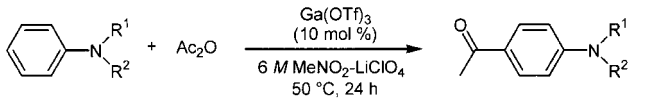
Entry	Lewis acid	R^1	R^2	R^3		R^4	R^5	Product	Yield (%)
1	$Ga(OTf)_3$	Ac	H	H	(**1a**)	Me	OAc	**2a**	93
2	$Ga(OTf)_3$	Bz	H	H	(**1b**)	Me	OAc	**2b**	quant
3	$Ga(OTf)_3$	Bz	H	H	(**1b**)	Et	OCOEt	**2c**	95
4	$Ga(OTf)_3$	Bz	H	H	(**1b**)	*i*-Pr	OCO*i*-Pr	**2d**	74 (83)[a]
5	$Ga(OTf)_3$	Ms	Me	H	(**1c**)	Me	OAc	**2e**	97
6	$Ga(OTf)_3$	Ac	H	*o*-Me	(**1d**)	Me	OAc	**2f**	61[a]
7	$Ga(OTf)_3$	Ac	H	*o*-OMe	(**1e**)	Me	OAc	**2g**	75[a,b]
8	$Ga(ONf)_3$	Ms	Me	*o*-OMe	(**1f**)	Me	OAc	**2h**	79
9	$Ga(OTf)_3$	Ac	H	*m*-Me	(**1g**)	Me	OAc	**2i**	62
10	$Ga(ONf)_3$	Ms	Me	*m*-Me	(**1h**)	Me	OAc	**2j**	62
11	$Ga(ONf)_3$	Ms	Me	*m*-OMe	(**1i**)	Me	OAc	**2k**	76
12	$Ga(OTf)_3$	Ms	Me	*p*-OMe	(**1j**)	Me	OAc	**2l**	54[a]
13	$Ga(OTf)_3$	Ms	Me	H	(**1c**)	Ph	Cl	**2m**	quant[c,d]
14	$Ga(ONf)_3$	*i*-BuOCO	H	H	(**1k**)	Ph	Cl	**2n**	80[c]
15	$Ga(OTf)_3$	Bz	H	H	(**1b**)	Me	OH	**2b**	90[e]

[a]Twenty mol % of the catalyst was used. [b]Regioisomer **2g'** was obtained in 5% yield. [c]The reaction was carried out in 1,2-dichloromethane under reflux for 24 h. [d]After the acylation, the crude product was treated with 25%HBr/AcOH. [e]Trifluoroacetic anhydride was added.



(**1l** and **1m**) were observed at lower field than those of acylanilides (**1a** and **1b**) in both cases. This means that the electron density at the C4 position of *N*-methylated acylanilides is lower than that of acylanilides.[12] This electronic factor can explain the observed lower yields of *N*-methylated acylanilides in the above-mentioned Friedel–Crafts acylation. This lower electron density at the C4 positions of *N*-methylated acylanilides is explained in terms of their conformations. The dihedral angles of N–Ph of **1l** and **1m** are 87.1° and 60.0°, respectively, in their crystal structures, and it has been proved that these conformations are maintained in their solution states.[13] In these conformations, the conjugation between amido

Table 3. Effect of *N*-substitution of aniline derivatives (1)

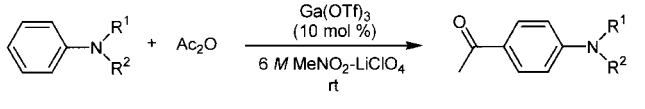


Entry	R^1	R^2		Yield (%)	^{13}C NMR at C4 (ppm)
1	Ac	H	(**1a**)	93	122.9
2	Ac	Me	(**1l**)	0	127.5
3	Bz	H	(**1b**)	quant	124.6
4	Bz	Me	(**1m**)	14	126.4
5	$COCF_3$	H	(**1n**)	37	126.5

nitrogens and aniline's phenyl rings is lost. On the other hand, **1a**[13c] and **1b**[13a] have almost coplanar structures in their crystals, and the conjugation between amido nitrogens and aniline's phenyl rings exists. This conjugation enables donation of electrons from the nitrogens to the aniline's aromatic rings, and causes higher reactivity in the electrophilic aromatic substitution reactions. According to the chemical shift value of the C4 position, the reactivity of trifluoroacetylanilide (**1n**) could be predicted.

On the other hand, *N*-Ms-*N*-methylaniline (**1c**) was acetylated more easily than **1a** (Table 4). In terms of the electronic factor, **1c** has some disadvantages because the Ms group is a stronger electron-withdrawing group than the acetyl group.[14] Actually, the lower electron density of the aromatic ring of **1c** was supported by ^{13}C NMR chemical shifts at the C4 position of **1c** and **1a** (127.4 and 122.9 ppm, respectively). We thought that the higher reactivity of **1c** could be explained by assuming that coordination of $Ga(OTf)_3$ with the oxygen of the sulfonamide structure of **1c** was weaker than that of $Ga(OTf)_3$ with the oxygen of the amide group of **1a**, and that this caused increased population of free $Ga(OTf)_3$ in the Friedel-Crafts acylation of **1c**. To confirm this hypothesis, we conducted NMR experiments. Equimolar amounts of **1a**, **1c**, and $Ga(OTf)_3$ were combined in $MeNO_2$-d_3 at 50 °C, and ^{1}H NMR spectrum was measured. While the chemical shifts of **1c** did not change, the ^{1}H NMR signal of the methyl group of **1a** became broad and moved by 0.5 ppm downfield. These results support the preferential coordination of $Ga(OTf)_3$ to **1a** rather than **1c**.

Table 4. Effect of *N*-substitution of aniline derivatives (2)



Entry	R^1	R^2		Time (h)	Yield (%)	^{13}C NMR at C4 (ppm)
1	Ac	H	(**1a**)	1	trace	122.9
2				12	70	
3	Ms	Me	(**1c**)	1	44	127.4
4				12	97	

In conclusion, we have discovered that the Friedel–Crafts acylations of aniline derivatives proceeded in good to excellent yields using a catalytic amount of $Ga(OTf)_3$ or $Ga(ONf)_3$ in $LiClO_4$–$MeNO_2$. While acylanilides reacted smoothly, acylation of *N*-methylated acylanilides was difficult because of electronic factors. On the other hand, *N*-alkylsulfonyl-*N*-alkylanilines were more easily acylated than acylanilides, presumably due to weak coordination of the gallium compound with the sulfonyl groups. It should be noted that this is the first example of the catalytic Friedel–Crafts acylation of aniline derivatives. Further investigations to clarify the precise mechanism of this acylation including the catalytic cycle as well as to apply this reaction to the synthesis of biologically important compounds are now in progress.

Experimental Section

Typical Procedure for the Catalytic Friedel–Crafts Acylation

To a stirred solution of acetanilide (108 mg, 0.80 mmol), $LiClO_4$ (1.28 g, 12.0 mmol), acetic anhydride (168 mg, 1.65 mmol), and nitromethane (2.0 mL) was added $Ga(OTf)_3$ (41.5 mg, 0.08 mmol) in one portion. After the mixture had been stirred at 50 °C for 24 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to a residue that was subjected to column chromatography (50:1 $CHCl_3$/MeOH) on silica gel to give **2a** as a colorless solid; yield: 131 mg (93%); mp 169–171 °C (lit. [15] mp 167–168 °C); ^{1}H NMR ($CDCl_3$): δ = 2.22 (s, 3H), 2.58 (s, 3H), 7.63 (d, J = 8.8 Hz, 2H), 7.75 (brs, 1H), 7.94 (d, J = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ = 24.81 26.48, 118.85, 129.76, 132.80, 142.35, 168.68, 197.11.

Similarly, 10 mmol-scale experiments were successfully performed and the same levels of yields were obtained.[16]

Acknowledgments

This work was partially supported by CREST, Japan Science and Technology Corporation (JST), and a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan.

References

[1] (a) *Friedel-Crafts and Related Reactions* (Ed.: G. A. Olah), Wiley, New York, 1963–64, Vol. I–IV; (b) G. A. Olah, *Friedel-Crafts Chemistry, Wiley-Interscience*, New York, **1973**; (c) H. Heaney in *Comprehensive Organic Synthesis* (Eds: B. M. Trost, I. Fleming), Pergamon Press, Oxford, **1991**, Vol. 2, pp. 733–752.

[2] (a) D. E. Pearson, C. A. Buehler, *Synthesis* **1972**, 533; (b) F. Effenberger, G. Epple, *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 300; (c) R. M. G. Roberts, A. R. Sadri, *Tetrahedron* **1983**, *39*, 137; (d) F. Effenberger, E. Sohn, G. Epple, *Chem. Ber.* **1983**, *116*, 1195; (e) T. Mukaiyama, H. Nagaoka, M. Ohshima, M. Murakami, *Chem. Lett.* **1986**, 165; (f) F. Effenberger, D. Steegmuller, *Chem. Ber.* **1988**, *121*, 117; (g) F. Effenberger, D. Steegmuller, V. Null, T. Ziegler, *Chem. Ber.* **1988**, *121*, 125; (h) T. Mukaiyama, T. Ohno, T. Nishimura, S. Suda, S. Kobayashi, *Chem. Lett.* **1991**, 1059; (i) T. Harada, T. Ohno, S. Kobayashi, T. Mukaiyama, *Synthesis* **1991**, 1216; (j) T. Mukaiyama, K. Suzuki, J. S. Han, S. Kobayashi, *Chem. Lett.* **1992**, 435–438; (k) A. Kawada, S. Mitamura, S. Kobayashi, *J. Chem. Soc. Chem. Commun.* **1993**, 1157; (l) K. Suzuki, H. Kitagawa, T. Mukaiyama, *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3729; (m) A. Kawada, S. Mitamura, S. Kobayashi, *Synlett* **1994**, 545; (n) S. Pivsa-Art, K. Okuro, M. Miura, S. Murata, M. Nomura, *J. Chem. Soc. Perkin Trans. 1* **1994**, 1703; (o) A. Kawada, S. Mitamura, S. Kobayashi, *J. Chem. Soc. Chem. Commun.* **1996**, 183; (p) K. Mikami, O. Kotera, Y. Motoyama, H. Sakaguchi, M. Maruta, *Synlett* **1996**, 171; (q) J. Izumi, T. Mukaiyama, *Chem. Lett.* **1996**, 739; (r) F. Effenberger, J. K. Eberhard, A. H. Maier, *J. Am. Chem. Soc.* **1996**, *118*, 12572; (s) J. Nishikido, H. Nakajima, T. Saeki, A. Ishii, K. Mikami, *Synlett* **1998**, 1347.

[3] (a) J. R. Desmurs, M. Labrouillère, C. L. Roux, H. Gaspard, A. Laporterie, J. Dubac, *Tetrahedron Lett.* **1997**, *38*, 8871; (b) S. Répichet, C. L. Roux, J. Dubac, J.-R. Desmurs, *Eur. J. Org. Chem.* **1998**, 2743.

[4] (a) I. Hachiya, M. Moriwaki, S. Kobayashi, *Tetrahedron Lett.* **1995**, *36*, 409; (b) I. Hachiya, M. Moriwaki, S. Kobayashi, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 2053; (c) S. Kobayashi, S. Iwamoto, *Tetrahedron Lett.* **1998**, *39*, 4697.

[5] J. Matsuo, K. Odashima, S. Kobayashi, *Synlett* **2000**, 403.

[6] For the synthesis of *o*-ketoanilines, Houben–Hoesch type reactions using BCl_3–$AlCl_3$ were reported, see: T. Sugasawa, T. Toyada, M. Adachi, K. Sakakura, *J. Am. Chem. Soc.* **1978**, *100*, 4842 and references cited therein.

[7] Acylation of *N,N*-dialkylaniline can be done by the Vilsmeier reaction, but it is hard to deprotect the *N,N*-dialkyl groups of the products, see: C. D. Hurd, C. N. Webb, Org. Synth. 1941, *Coll. Vol. I*, 217 and references cited therein.

[8] (a) F. Kunchell, Ber. dttsch. chem. Ges. **1900**, *33*, 2641; 2644; (b) M. J. Sacha, S. R. Patel, *J. Indian Chem. Soc.* **1956**, *33*, 129; (c) V. K. Mehta, M. J. Sacha, S. R. Patel, *J. Indian Chem. Soc.* **1956**, *33*, 867; (d) Using special acylating agents, such as chloroacetyl chloride, $AlCl_3$-catalyzed reaction proceeds in good yields, see: J. L. Leiserson, A. Weissberger, *Org. Synth*. **1955**, *Coll. Vol. III*, 183.

[9] Although acylation using excess polyphosphoric acid (PPA) was reported, substrates were limited; (a) D. A. Denton, H. Suschitzky, *J. Chem. Soc.* **1963**, 4741; (b) B. Staskun, *J. Org. Chem*. **1964**, *29*, 2856.

[10] Olah et al. reported that the reaction of toluene with acetyl chloride proceeded in the presence of 50 mol % $Ga(OTf)_3$ to afford the corresponding aromatic ketone in 72% yield; (a) G. A. Olah, O. Farooq, S. M. F. Farnia, J. A. Olah, *J. Am. Chem. Soc.* **1988**, *110*, 2560; (b) G. A. Olah, *US Patent* 5,110,778, **1992** [*Chem Abstr.* **1998**, *109*, 57031.

[11] S. Kobayashi, I. Komoto, *Tetrahedron*, **2000**, *56*, 6463.

[12] Semi-empirical calculations of the electron density also supported these results.

[13] (a) A. Itai, Y. Toriumi, N. Tomioka, H. Kagechika, I. Azumaya, K. Shudo, *Tetraherdron Lett.* **1989**, *30*, 6177; (b) A. Itai, Y. Toriumi, S. Saito, H. Kagechika, K. Shudo, *J. Am. Chem. Soc.* **1992**, *114*, 10649; (c) S. Saito, Y. Toriumi, N. Tomioka, A. Itai, *J. Org. Chem.* **1995**, *60*, 4715.

[14] Cf. The pK_a value: MsOH (–1.9); AcOH (4.76).

[15] Y. Sakata, T. Hashimoto, *Yakugaku Zasshi* **1959**, *79*, 881.

[16] Physical data of other acylation adducts are shown in Supporting Information.