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Efficient Friedel–Crafts benzoylation of aniline derivatives with 4-fluorobenzoyl chloride using copper triflate in the synthesis of aminobenzophenones

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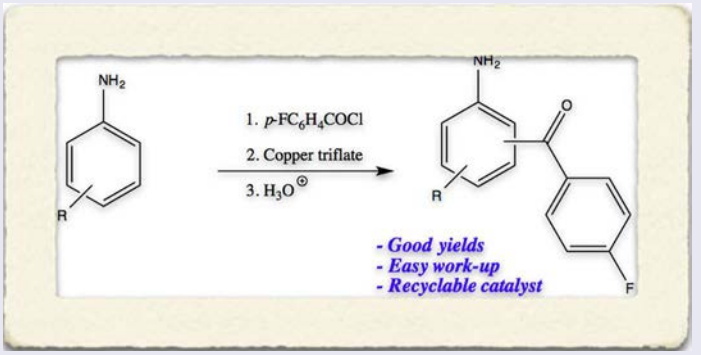
ABSTRACT

An efficient pathway for the synthesis of the aminobenzophenone derivatives via Friedel–Crafts benzoylation using copper triflate as catalyst is proposed. New derivatives are synthesized. The copper triflate could be easily recovered and reused without loss of catalytic activity. Both the use of ionic liquids and microwave heating turned out to be fruitful.

GRAPHICAL ABSTRACT



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Aminobenzophenone; Friedel–Crafts acylation; ionic liquid; metal triflate; microwave heating

Introduction

Aminobenzophenone derivatives play a crucial role in organic synthesis and are known as important groups for anticancer therapy.[1–9] Among these, 4-aminobenzophenones are known as the precursors for the synthesis of a wide range of benzothiazole and triazole derivatives.[10,11] In addition, 2-aminobenzophenone derivatives have been prepared by Fries rearrangement,[12–16] from benzoisoxazole,[17,18] by *ortho*-acylation of anilides with toluene derivatives,[19] by addition of arylboronic acids,[20] or by cross-coupling of *N*-nitrosoanilines and toluene derivatives.[21] 4-Aminobenzophenone derivatives have

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normally been prepared via Friedel–Crafts acylation.[22–24] However, the well-known traditional catalysts such as $AlCl_3$, $FeCl_3$, and $TiCl_4$ are usually required in more than stoichiometric amounts and cannot be recycled after aqueous workup.[25–27] Besides, the use of volatile organic solvents in this process may be dangerous to the environment, especially on an industrial scale.[26] The direct Friedel–Crafts acylation of aniline derivatives is unsuccessful because *N*-acylation is much more rapid than Friedel–Crafts acylation.[28,29] Consequently, *N*-protection of the amino group is necessary for the Friedel–Crafts acylation process, and 4-aminobenzophenone derivatives are obtained after an acidic hydrolysis step. Moreover, the Friedel–Crafts acylation of acylanilides using excess of $AlCl_3$ afforded the corresponding ketones in poor yields due to the loss of the catalytic activity of the Lewis acid in the presence of the basic nitrogen.[25] Recently, Kobayashi and coworkers reported the use of gallium triflate in nitromethane and lithium perchlorate in the Friedel–Crafts acylation of acylanilides. The yields of ketones were good to excellent after testing a range of aliphatic acid anhydrides and a couple of acid chlorides. In the latter case *N*-methyl-*N*-methylsulfonylaniline was the substrate using methylene chloride as solvent giving a yield of 90% or better for the acylation step.[30] We report here an efficient procedure to synthesize 4-aminobenzophenone derivatives via Friedel–Crafts benzoylation with 4-fluorobenzoyl chloride using copper triflate under solvent-free condition. Aniline derivatives with electron-rich and electron-poor substituents are also reactive with substituent selectively in the *para*-position.

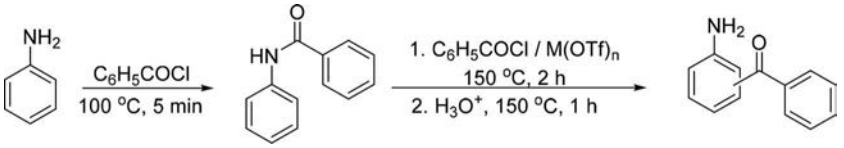
Results and discussion

The proposed Friedel–Crafts benzoylation of 4-aminobenzophenone derivatives using copper triflate is a procedure including three steps with moderate yields (overall yield 55–75%): (i) the first step is to synthesize the amide derivatives, (ii) the second step involves the Friedel–Crafts benzoylation reaction, (iii) and the third step is the hydrolysis of the amide derivatives in acidic solution. Three new compounds were prepared from dichloroanilines and 4-fluorobenzoyl chloride: 4-amino-2,5-dichloro-4′-fluorobenzophenone, 4-amino-2,6-dichloro-4′-fluorobenzophenone, and 2-amino-4,5-dichloro-4′-fluorobenzophenone.

Initially, the effect of metal triflates in the process using aniline as substrate with benzoyl chloride was investigated. The Friedel–Crafts acylation of aniline derivatives catalyzed by traditional Lewis acids is usually reported in poor yield due to the formation of the Lewis acid–base adduct between the catalyst and the amine group of the aniline derivatives. Metal triflates, a new type of Lewis acid, could avoid this problem. The most characteristic feature of metal triflates can be used as catalyst without loss of activity in the presence of many types of Lewis bases.[31] Initially, we examined the reaction and the activity of metal triflates with aniline as the starting material and benzoyl chloride as the acylating agent to find the best catalyst. Five rare-earth metal triflates (La, Pr, Nd, Ho, and Er) and four well-known metal triflates (Cu, In, Y, Bi) were chosen to test the catalytic activity in the process. The Friedel–Crafts benzoylation was carried out at 150 °C for 2 h in a thermostat-controlled oil bath, and copper triflate showed the greatest catalytic activity (Table 1, entry 1). 4-Aminobenzophenone was the major product. The yield of product was overall 68% (in three steps) with 80% selectivity for the *para*-position using copper triflate.

A Fries-type rearrangement with copper triflate under the same condition was also tested. Benzamide (1 mmol) isolated from step 1 with 100% purity (checked by gas

Table 1. Effect of metal triflates in the synthesis of aminobenzophenone from aniline with benzoyl chloride.[a]



Entry	Metal triflate	Total yield (%)	*o*-/*p*- selectivity
1	$Cu(OTf)_2$	68	20/80
2	$Y(OTf)_3$	34	17/83
3	$In(OTf)_3$	64	28/72
4	$La(OTf)_3$	40	16/84
5	$Pr(OTf)_3$	50	19/81
6	$Nd(OTf)_3$	41	20/80
7	$Ho(OTf)_3$	44	21/79
8	$Er(OTf)_3$	34	22/78
9	$Bi(OTf)_3$	57	20/80

[a]The benzamide product was purified before using for the next steps. The Friedel–Crafts benzoylation of benzamide was monitored by GC-MS. The benzoylated product was used for the hydrolysis step without purification.

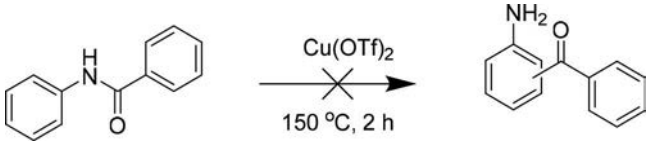
chromatography–mass spectrometry, GC-MS) was allowed to react with $Cu(OTf)_2$ (0.1 mmol). The reaction mixture was kept at 150 °C for 2 h but aminobenzophenones were not formed and the benzamides still remained (checked by GC-MS) (Scheme 1). Consequently, copper triflate catalyzes the Friedel–Crafts benzoylation of benzamide but not the Fries-type rearrangement.

After having optimized the reaction conditions, we also examined the reaction between aniline derivatives containing methyl- or dichloro-substituents with 4-fluorobenzoyl chloride catalyzed by copper triflate (Scheme 2). As reported by Cortez-Maya and coworkers,[32] these aminobenzophenone derivatives have potential anticancer activity.

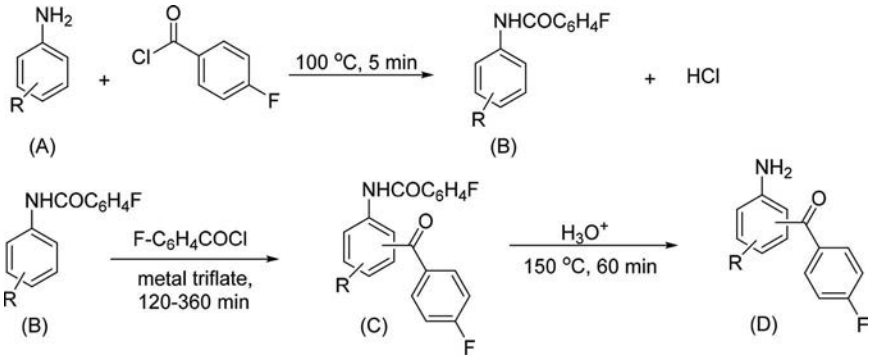
The general synthesis to prepare aminobenzophenone derivatives in a mild and efficient way is shown in Scheme 2. *N*-Acylation of several aniline derivatives (A) with 4-fluorobenzoyl chloride easily produced amide derivative (B) in 100% conversion (GC) at 100 °C for 5 min without the use of catalyst (Table 2). All products of this step are easily isolated and used for the next step. The structures and purity were determined by ^{1}H NMR spectroscopy and GC-MS.

The benzoylated products (C) were obtained by Friedel–Crafts benzoylation of the acylanilides using copper triflate. In this method, acylanilides (B) were used without further purification. The following step was the deprotection of the amides to give the -NH_2 compounds under acidic condition (H_2SO_4:CH_3COOH:H_2O) at 150 °C for 60 min. The yields of products (D) (steps ii, iii) are given in Table 3.

Most of the anilines with the methyl- or chloro- substituents gave good yields with high selectivity toward the *para*-position (Table 3, entries 2–6). Although the use of copper

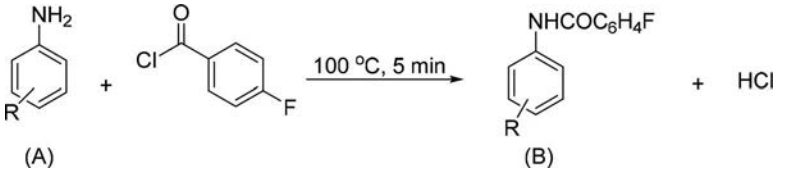


Scheme 1. Testing for Fries rearrangement.



Scheme 2. Synthesis of aminobenzophenone derivatives via Friedel–Crafts benzoylation.

Table 2. Protection of amine group.



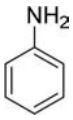
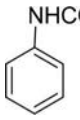
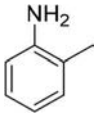
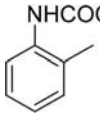
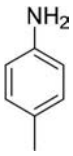
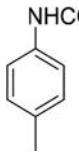
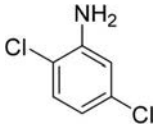
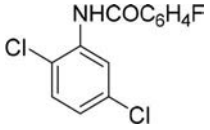
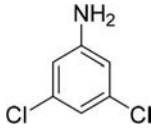
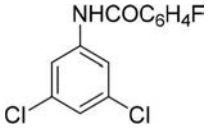
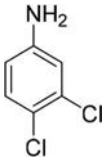
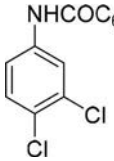
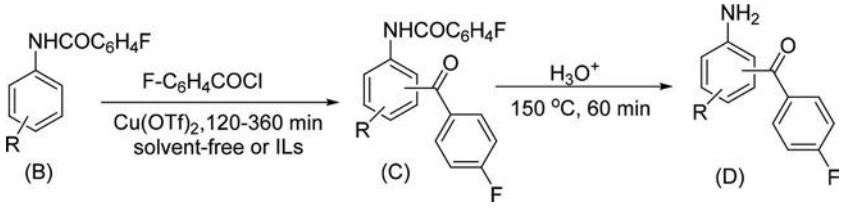
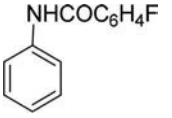
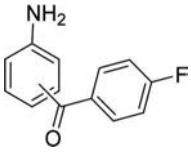
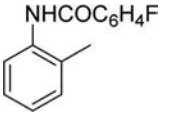
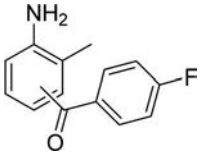
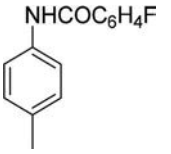
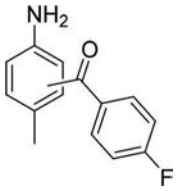
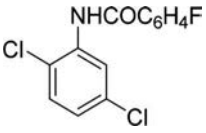
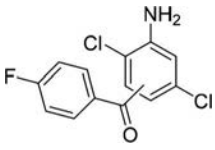
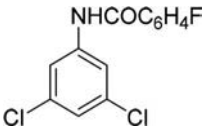
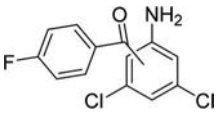
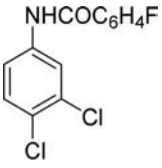
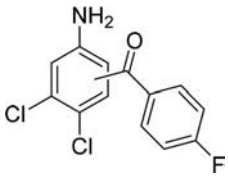
Entry	Substrate (A)	Product (B)	Conversion (%)	Yield (%)
1			100	90
2			100	92
3			100	92
4			100	89
5			100	91
6			100	92

Table 3. Friedel–Crafts benzoylation of anilides and hydrolysis of amide groups.



Entry	(B)	Condition (B–C)	Product (D)	Yield of D (%)	Isomeric ratio
1		150 °C, 2 h [BMIM]PF_6[a], 150 °C, 1 h [BMIM]BF_4[a], 150 °C, 1 h MW, 150 °C, 0.5 h		79 78 80 77	*o*-/*p*- = 21/79 *o*-/*p*- = 22/79 *o*-/*p*- = 20/80 *o*-/*p*- = 19/81
2		150 °C, 2 h		81	15/85[b]
3		150 °C, 2 h		70	25/75[c]
4		200 °C, 6 h		78	16/84[d]
5		200 °C, 6 h		71	30/70[e]
6		200 °C, 6 h		63	10/90[f]

[a][BMIM]PF_6, 1-butyl-3-methylimidazolium hexafluorophosphate; [BMIM]BF_4, 1-butyl-3-methylimidazolium tetrafluoroborate.
[b]Isomeric ratio of (2-amino-3-methylphenyl)(4-fluorophenyl)methanone/(4-amino-3-methylphenyl)(4-fluorophenyl) methanone.
[c]Isomeric ratio of (5-amino-2-methylphenyl)(4-fluorophenyl)methanone/(2-amino-5-methylphenyl)(4-fluorophenyl) methanone.
[d]Isomeric ratio of (2-amino-3,6-dichlorophenyl)(4-fluorophenyl)methanone/4-amino-2,5-dichlorophenyl)(4-fluorophenyl) methanone.
[e]Isomeric ratio of (2-amino-4,6-dichlorophenyl)(4-fluorophenyl)methanone/(4-amino-2,6-dichlorophenyl)(4-fluorophenyl) methanone.
[f]Isomeric ratio of (6-amino-2,3-dichlorophenyl)(4-fluorophenyl)methanone/(2-amino-4,5-dichlorophenyl)(4-fluorophenyl) methanone.

triflate required harsh reaction temperature of more than 150 °C, the reaction time is much shorter than comparing with the previous report usually using 24 h of reaction time.[30] Moreover, the present method is solvent free and consequently is an environmentally friendly method for synthesis of aminobenzophenone derivatives.[30] The presence of electron-withdrawing groups such as chlorine required higher temperatures and longer reaction times (Table 3, entries 4–6). In general, the Friedel–Crafts benzoylation in position *para* to -$NHCOC_6H_4$ group gave better yields while the products in *ortho*-substitution to the -$NHCOC_6H_4$ group were obtained in moderate yields, presumably due to steric hindrance (Table 3, entries 2–6). However, *p*-nitroaniline containing strong electron-withdrawing substituent (-NO_2) was not suitable in this method. The Friedel–Crafts benzoylation of 4-fluoro-*N*-phenylbenzamide was also investigated in ionic liquid media under conventional heating. The Friedel–Crafts benzoylation of 4-fluoro-*N*-phenylbenzamide gave good yield using commercial imidazolium ionic liquids such as [BMIM]BF_4 or [BMIM]PF_6 (Table 3, entry 1) and a shorter reaction time was achieved under solvent-free microwave irradiation (Table 3, entry 1). The copper triflate was recovered and reused in three consecutive cycles in the Friedel–Crafts benzoylation of 4-fluoro-*N*-phenylbenzamide with 4-fluorobenzoyl chloride at 150 °C for 2 h under conventional heating. The yields of product were only slightly decreased after each cycle (78, 75, and 74%).

Conclusions

This article describes an efficient method to prepare 4-aminobenzophenone derivatives via Friedel–Crafts acylation using copper triflate. The copper triflate catalyst was easily recovered and reused without significant loss of its catalytic activity. The protection–deprotection of the amino group was carried out in good yields with easy workup. Three new fluorine-containing compounds with dichloro-substituents in the aminobenzophenone ring are obtained. These may have potential anticancer activity. Biological activity tests are now in progress.

Experimental

Chemicals and supplies

Aniline derivatives, 4-fluorobenzoyl chloride, ionic liquids, and metal triflates were purchased from Sigma-Aldrich and used without further purification. Solvents were obtained from Labscan and Chemsol (Vietnam) and also used without purification. Silica gel 60 (0.040–0.063 mm) was from Merck.

Instruments

GC-MS analyses were performed on an Agilent GC System 7890 equipped with a mass selective detector Agilent 5973 N and a capillary DB-5MS column (30 m × 250 µm × 0.25 µm). The ^1H and ^{13}C NMR spectra were recorded on a Bruker Advance 500 using $CDCl_3$ as solvent and solvent peaks or tetramethylsilane (TMS) as internal standards. HRMS (ESI) data were recorded on a Bruker micro-TOF-QII MS at 80 eV. Conventional heating was performed on an IKA-RET thermostat-controlled oil bath. Microwave irradiation was performed on a CEM Discover BenchMate apparatus, which offers microwave synthesis with

safe pressure regulation using a 10-mL pressurized glass tube with Teflon-coated septum and vertically focused IR temperature sensor controlling the reaction temperature. Flash column chromatography (length 60 cm, internal diameter 1.5 cm) was performed on silica gel.

General procedure

First step: Protection of the amine group

4-Fluoro-*N*-phenylbenzamide derivatives were prepared from aniline derivatives (1 mmol) and 4-fluorobenzoyl chloride (1.2 mmol) under solvent-free conditions at 100 °C for 5 min. The reaction mixture was cooled to room temperature and extracted with ethyl acetate (3 × 15 mL) and quenched with sodium bicarbonate (2 × 20 ml) and water (2 × 20 mL). The combined organic layers were dried over magnesium sulfate and concentrated under vacuum. The crude product was purified by flash column chromatography on silica gel (hexane/ethyl acetate = 9:1) to obtain the desired product.

The second step: Friedel–Crafts benzoylation

4-Fluoro-*N*-phenylbenzamide derivative (1 mmol), 4-fluorobenzoyl chloride (2 mmol), and metal triflate (0.1 mmol) were heated at appropriate temperature and time. The reaction mixture was extracted with ethyl acetate / H_2O. The ethyl acetate layer was dried and concentrated under vacuum. The crude product was used for the next step without further purification. Attempts were made to recover and reuse the copper triflate. After extraction the reaction mixture with ethyl acetate the aqueous layer was evaporated under reduced pressure at 80 °C. Mass of pure copper triflate (white powder) obtained: 0.0317 g (86% yield of recovery).

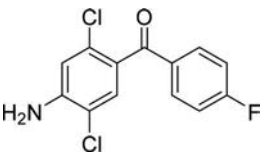
Third step

The benzoylated product was added to a mixture of H_2SO_4, CH_3COOH, and H_2O (5:3.5:1 mL) and heated at 150 °C for 60 min. The reaction mixture was extracted with ethyl acetate (3 × 15 mL), neutralized with sodium carbonate (2 × 100 mL), and washed with water (2 × 50 mL). The organic layer was dried over magnesium sulfate and concentrated under vacuum. The pure regioisomer was obtained after column chromatography on silica gel (eluent, hexane followed by an appropriate volume of ethyl acetate).

Compounds

The following new compounds were synthesized.

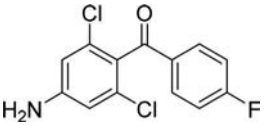
4-Amino-2,5-dichloro-4′-fluorobenzophenone



Yellow solid, mp 144–146 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.81 (dd, J = 8.8 Hz, 5.5 Hz, 2H), 7.35 (s, 1H), 7.13 (t, J = 8.6 Hz, 2H), 6.81 (s, 1H), 4.44 (br s, 2H). ^{13}C NMR (125 MHz,

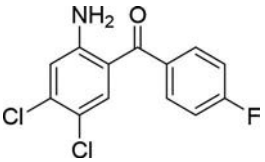
$CDCl_3$): δ = 191.2 (CO), 164.9 (d, J = 253.8 Hz), 144.9, 132.8 (d, J = 2.8 Hz), 131.6 (d, J = 9.3 Hz), 130.8, 130.3, 126.7, 115.9, 115.1, 114.7 (d, J = 21.9 Hz). MS (EI) *m/z* 283 (M^+), 248, 188, 160, 133, 123, 95, 75. HRMS (ESI) calcd for $C_{13}H_8Cl_2FNONa$ 305.9859 $[M+Na]^+$, found 305.9863.

4-Amino-2,6-dichloro-4′-fluorobenzophenone



Brown liquid; bp not determined, decomposed at 400 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.86 (dd, J = 8.8 Hz, 5.4 Hz, 2H), 7.13 (t, J = 8.6 Hz), 6.63 (s, 2H), 3.88 (br s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 191.1, 166.3 (d, J = 254.8 Hz), 148.8, 133.0 (d, J = 2.6 Hz), 132.5 (s, 2C), 132.4 (d, J = 9.6 Hz), 126.4, 116.1 (d, J = 22.0 Hz), 113.9. MS (EI) *m/z* 283 (M^+), 247, 213, 188, 157, 133, 123, 109, 95,75, 63, 50. HRMS (ESI) calcd for $C_{13}H_8Cl_2FNONa$ $[M+Na]^+$ 305.9859, found 305.9876.

2-Amino-4,5-dicloro-4′-fluorobenzophenon



Yellow solid; mp 139–141 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.66 (dd, J = 8.8 Hz, 5.4 Hz, 2H), δ = 7.47 (s, 1H), 7.17 (t, J = 8.6 Hz, 2H), 6.87 (s, 1H), 6.02 (br s). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 194.7, 163.9 (d, J = 251.9 Hz), 148.8, 137.4, 134.1 (d, J = 3.1 Hz), 133.7, 130.6 (d, J = 8.9 Hz), 117.5, 117.2, 116.6, 114.6 (d, J = 21.8 Hz). MS (EI) *m/z* 283 $(M)^+$, 266, 247, 219, 188, 160, 133, 123,109, 95, 75, 63, 50. HRMS (ESI) calcd. for $C_{13}H_8Cl_2FNO$ $[M+H]^+$ 284.0039, found 284.0031.

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