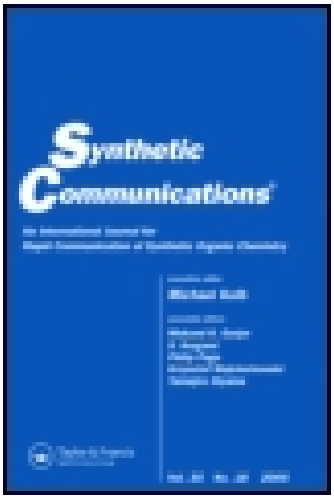

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Electrophilic Aromatic Aroylation with CF_3-Bearing Arenecarboxylic Acid Derivatives: Reaction Behavior and Acidic Mediator Dependence

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Electrophilic Aromatic Aroylation with CF_3-Bearing Arenecarboxylic Acid Derivatives: Reaction Behavior and Acidic Mediator Dependence

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Abstract: Triflic acid (TfOH) has been proven to be effective as a tolerant acidic mediator in electrophilic aromatic aroylation with CF_3-bearing aroyl chlorides. The TfOH-mediated aroylation of fluorobenzene proceeds with high selectivity to give CF_3-bearing aryl fluorophenyl ketones in good yields, which are hardly obtained with the aid of $AlCl_3$ or direct condensation reagents.

Keywords: acidic mediator, CF_3-bearing aroyl chloride, CF_3-bearing diaryl ketone, regioselective electrophilic aromatic aroylation, triflic acid

INTRODUCTION

A great number of synthetic studies on organic compounds that have perfluoroalkyl groups have been reported by polymer chemists,[1–4] medicinal chemists,[5] and organic synthetic chemists.[6–10] For example, aromatic ring systems having CF_3 groups and different electronically polarizable groups have been of interest as potential functional compounds for

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optoelectronic devices such as liquid-crystalline molecules[11–13] and nonlinear optical materials.[14] As a natural consequence of this, diaryl ketone skeletons having these substituents show unique chemical and physical behaviors. For example, 4-fluoro-4′-trifluoromethylbenzophenone (**5**) possesses characteristic electronic structure.[15–18] It has been utilized as an effective initiator for nucleophilic aromatic substitution polymerization giving monodispersed poly(aromatic ether ketone)s,[19–21] a coating agent for the toner-supplying part in one-component electrophotographic developing apparatus,[22–24] and a synthetic precursor for antimalarial radiopharmaceutical guanylhydrazones.[25,26]

For construction of such diaryl ketone structures, Friedel–Crafts acylation would be the primary candidate. However, contrary to the Friedel–Crafts alkylation, the corresponding acylation reaction often suffers from intrinsic low reactivity and low selectivity, especially against the acyl-acceptant arene substrates with low electron density. It is because acylium cation intermediate is too inert to undergo smooth formation of the ketonic carbonyl group–aromatic ring linkages with such arenes. Because of this disadvantage, the use of this well-known bond-formation reaction has been rather restrictedly applied to diaryl ketone synthesis compared to transition-metal-catalyzed coupling reaction.[27,28]

Furthermore, electrophilic aromatic acylation of the arenes bearing CF_3 groups is known to be troublesome. Such reactions often afford complex mixtures. In addition, electrophilic aromatic aroylation with CF_3-bearing arenecarboxylic acid also demonstrates low selectivity. In the course of the investigation of the synthesis of wholly aromatic polyketones,[29–34] the authors have confirmed that electrophilic aromatic aroylation with 3-trifluoromethylbenzoic acid or the aroyl chloride proceeds only with low conversion and poor selectivity unless the highly activated arene is employed as an acyl-acceptant substrate in the presence of phosphorus(V) oxide–methanesulfonic acid (P_2O_5–MsOH)[35] as acidic mediator.[31] Actually, electrophilic aromatic aroylation syntheses of trifluoromethylated benzophenone homologues bearing other electron-withdrawing groups with CF_3-bearing arenecarboxylic acid derivatives have been scarcely reported except for TfOH-mediated aroylation synthesis of 4-fluoro-4′-trifluoromethylbenzophenone (**5**) by Ridd and Yousaf.[36]

Under such a circumstance, the authors have aimed to develop the general synthetic protocol for CF_3-bearing diaryl ketones via electrophilic aromatic aroylation. Especially the synthesis of diaryl ketones having CF_3 groups and a fluorine group has been focused on because aryl–F bonds are valuable in preparating of various organic compounds having a CF_3-bearing aroylaryl moiety via nucleophilic aromatic substitution. To estimate the influence of CF_3 groups of the aroyl moieties in electrophilic aromatic aroylation more accurately and make the guideline of choice of the reagent for this transformation, the authors have undertaken the reaction of arenecarboxylic acids/aroyl chlorides with the aid of three different types of acidic mediators: typical

Friedel–Crafts catalyst, direct condensation mediator, and superacidic mediator (TfOH).

In this article, the authors discuss the acidic mediator dependence and the influence of the CF_3 groups in the reaction of CF_3-bearing arenecarboxylic acid derivatives in electrophilic aromatic aroylation.

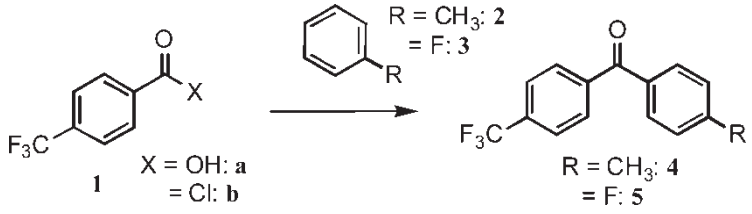
RESULTS AND DISCUSSION

Electrophilic Aromatic Aroylation of Toluene (2)/Fluorobenzene (3) with 4-Trifluoromethylbenzoic Acid/4-Trifluoromethybenzoyl Chloride (1)

To grasp the outline of the reaction feature, 4-trifluoromethylbenzoic acid (**1a**)/4-trifluoromethylbenzoyl chloride (**1b**) were allowed to react with toluene (**2**)/fluorobenzene (**3**) by the aid of three different types of acidic mediators: $AlCl_3$, P_2O_5–MsOH, and TfOH (Table 1). $AlCl_3$ is one of the most conventional Lewis acids for Friedel–Crafts reaction. P_2O_5–MsOH is known as an acidic mediator for direct condensation, which has high solubilizing ability against various organic compounds and sufficiently low viscosity as a reaction solvent in comparison to the related phosphoric anhydride-based mediators such as polyphosphoric acid (PPA). TfOH is a Brønsted superacid having moderate superacidity (Hammett's function: H_0 −14.1). The acidity of TfOH is situated between those of 100% H_2SO_4 (H_0 −11.9) and magic acid (H_0 −24.3).

In the reaction of toluene (**2**) or fluorobenzene (**3**) with 4-trifluoromethylbenzoyl chloride (**1b**) by $AlCl_3$, a complex mixture was obtained (entries 1, 7–9). Although the constituents of the complex mixture were unsatisfactorily identified, the conversion of CF_3 group in 4-trifluoromethylbenzoyl chloride (**1b**) probably proceeded. In the reaction with 4-trifluoromethylbenzoic acid (**1a**) by P_2O_5–MsOH, the aimed phenones were obtained in moderate yields with a large amount of mesylated products and the starting material (entries 4, 5, and 10). The aroylation by P_2O_5–MsOH needed a long reaction interval to achieve satisfactory conversion when fluorobenzene (**3**) was employed as the acyl-acceptant arene (entry 10 vs. 11). On the other hand, in the reaction by TfOH, the aimed phenones were obtained quantitatively against both toluene (**2**) and fluorobenzene (**3**) without formation of by-products, although the aroylation required a rather long interval against fluorobenzene (**3**) (entry 6 vs. 16). Furthermore, the difference of the reaction behavior between the combinations of the acidic mediator and arenecarboxylic acid/aroyl chloride (**1**) is also demonstrated. When P_2O_5–MsOH and arenecarboxylic acid **1a** were treated with fluorobenzene (**3**), the yield and the chemoselectivity were higher than those against aroyl chloride **1b** (entry 11 vs. 13). On the other hand, the reverse behavior was observed in the reaction mediated by TfOH: arenecarboxylic acid **1a** showed lower chemoselectivity than the corresponding aroyl chloride (**1b**) (entry 14 vs. 15).

Table 1. Electrophilic aromatic aroylation of arene **2**/**3** with 4-trifluoromethylbenzoic acid/4-trifluoromethylbenzoyl chloride (1)[a]



Entry	Substrate		Acidic mediator	Temp.	Time (h)	Product distribution[b](%)	
						1	**4**/**5**
1	**1b**	**2**	$AlCl_3$	rt	24	0	—[c]
2	**1b**	**2**	P_2O_5–MsOH	rt	48	0	Trace
3	**1a**	**2**	P_2O_5–MsOH	rt	48	0	Trace
4	**1a**	**2**	P_2O_5–MsOH	80°C	24	11	79 (10[d])
5	**1a**	**2**	P_2O_5–MsOH	Reflux	1.5	15	58 (27[d])
6[e]	**1b**	**2**	TfOH (0.25 eq)	Reflux	1.5	0	100
7	**1b**	**3**	$AlCl_3$	rt	24	0	—[c]
8[f]	**1b**	**3**	$AlCl_3$	rt	24	0	—[c]
9	**1b**	**3**	$AlCl_3$	Reflux	24	0	—[c]
10	**1a**	**3**	P_2O_5–MsOH	Reflux	24	32	36 (32[d])
11	**1a**	**3**	P_2O_5–MsOH	Reflux	192	0	83 (17[d])
12	**1b**	**3**	P_2O_5–MsOH	Reflux	24	45	24 (31[d])
13	**1b**	**3**	P_2O_5–MsOH	Reflux	192	0	66 (34[d])
14[g]	**1a**	**3**	TfOH (0.10 eq)	Reflux	144	0	Trace
15	**1b**	**3**	TfOH (0.10 eq)	Reflux	144	60	40
16[h]	**1b**	**3**	TfOH (0.50 eq)	Reflux	144	2	98

[a]Reaction conditions: arene (acidic mediator) against 1.0 mmol of 4-trifluoromethylbenzoic acid/aroyl chloride (**1**); 15 mmol: $AlCl_3$ (3.0 mmol); 12 mmol: P_2O_5–MsOH (2.0 mL); 12 mmol: TfOH (0.10 mmol); N_2 atmosphere.

[b]Calculated on the basis of ^{1}HNMR spectrum.

[c]A complex mixture was obtained.

[d]Mesylated product was obtained.

[e]TfOH (0.25 mmol) was employed against 1.0 mmol of aroyl chloride **1b**.

[f]1,2-Dichloroethane was employed as cosolvent.

[g]Complex mixtures were obtained.

[h]TfOH (0.50 mmol) was employed against 1.0 mmol of aroyl chloride **1b**.

These results suggest that with the aid of TfOH, effective electrophilic aromatic aroylation by CF_3-bearing aroyl chloride might be performed as general protocols. Hence, the generality of TfOH was evaluated by investigating the reaction behavior of several homologous acid derivatives in detail.

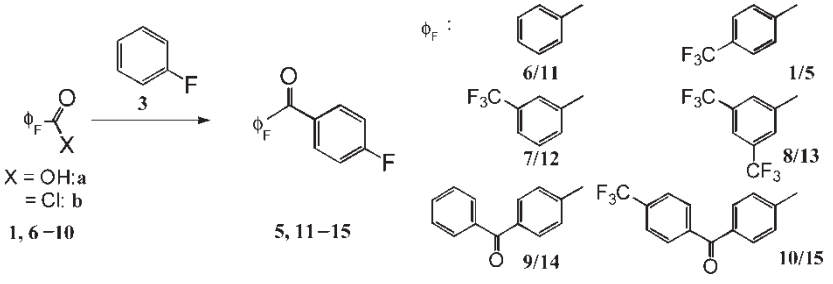
Electrophilic Aromatic Aroylation of Fluorobenzene (3) with Arenecarboxylic Acids/Aroyl Chlorides Bearing Trifluoromethyl Groups

To estimate the influence of the number and the position of CF_3 substituents on aroyl-donor species in electrophilic aromatic aroylation, the reaction of several arenecarboxylic acids/aroyl chlorides was undertaken with the aid of three acidic mediators (Table 2).

The reaction by $AlCl_3$ gave complex mixtures against the CF_3-bearing aroyl chlorides (**1b**, **7b**, **8b**, **10b**), whereas the aimed phenones were obtained in high conversion in the reaction with the CF_3-free aroyl chlorides (**6b**, **9b**) (entries 2–4, 6 vs. 1, 5). In the reaction of the CF_3-bearing aroyl chlorides (**1b**, **7b**, **8b**, **10b**) by $AlCl_3$, side reactions were not suppressed even at low temperature. When P_2O_5–MsOH was employed, the arenecarboxylic acids (except for acid **8a**) gave the aimed phenones in low conversions with a rather large amount of mesylated compounds (entries 7–12). The amount of the mesylated products increased with the number of CF_3 groups (entry 7 vs. 9 vs. 10). On the other hand, TfOH showed high regioselectivity and high chemoselectivity whether the aroyl chlorides have CF_3 groups or not (entries 13–18). Especially when the CF_3-bearing aroyl chlorides (**1b**, **7b**, **8b**, **10b**) were employed, the aimed phenones were obtained in high yields (entries 14–16, 18). In addition, the substitution position of the CF_3 groups against the carbonyl group is shown to affect the conversion. 4-Trifluoromethylbenzoyl chloride (**1b**) gave the aimed phenone (**5**) quantitatively. On the other hand, the reaction of 3-trifluoromethylbenzoyl chloride (**7b**) proceeded with a high but somewhat lower conversion (entry 14 vs. 15). Therefore, one CF_3 group substituted at the *p*-position against the carbonyl group is more effective to obtain the aimed phenones in a high yield than one or two *m*-positioned CF_3 groups (entry 14 vs. 15, 16). As well as 4-trifluoromethylbenzoyl chloride (**1b**), 4-(4-trifluoromethylbenzoyl)benzoyl chloride (**10b**) gave the aimed phenone (**15**) with a high conversion (entry 18). This indicates that the electron-withdrawing effect of the CF_3 group is transmitted through the *p*-positioned ketonic carbonyl group of benzophenone unit.

The relationships among acidic mediators, number and substituted position of CF_3-groups, and yield in electrophilic aroylation of fluorobenzene (**3**) are also summarized in Fig. 1. This chart shows the characteristics, scope, and limitations of acidic mediators in the reaction. The reaction by P_2O_5–MsOH yielded the aimed phenones with low conversion and low selectivity against the arenecarboxylic acids (**1, 6–10a**), and the conversion descended with number of CF_3 groups of arenecarboxylic acids. In our previous study, P_2O_5–MsOH has been proven an effective aroylation reagent for *o*-terphenyl[30] and 2,2′-dimethoxy-1,1′-binaphthyl[37] as acyl-acceptant arenes. In contrast, P_2O_5–MsOH was shown to be unsuitable against

Table 2. Electrophilic aromatic aroylation of fluorobenzene (**3**) with arenecarboxylic acids/aroyl chlorides **1**, **6**–**10**[a]



Entry	Acidic mediator	Substrate	Temp.	Time (h)	Product distribution[b](%) Ketone		Recovery[c]	By-product
1	$AlCl_3$	**6b**	Reflux	12	**11**	91	9	0
2	$AlCl_3$	**1b**	rt	24	**5**	0	0	—[d]
3	$AlCl_3$	**7b**	rt	24	**12**	0	0	—[d]
4	$AlCl_3$	**8b**	rt	24	**13**	0	0	—[d]
5	$AlCl_3$	**9b**	Reflux	12	**14**	86	14	0
6	$AlCl_3$	**10b**	rt	24	**15**	0	0	—[d]
7	P_2O_5–MsOH	**6a**	Reflux	24	**11**	53	19	28[e]
8	P_2O_5–MsOH	**1a**	Reflux	24	**5**	36	32	32[e]
9	P_2O_5–MsOH	**7a**	Reflux	24	**12**	28	30	42
10	P_2O_5–MsOH	**8a**	Reflux	24	**13**	0	43	57
11	P_2O_5–MsOH	**9a**	Reflux	24	**14**	32	29	39[e]
12	P_2O_5–MsOH	**10a**	Reflux	24	**15**	37	45	18[e]
13	TfOH	**6b**	Reflux	144	**11**	79	21	0
14	TfOH	**1b**	Reflux	144	**5**	98	2	0
15	TfOH	**7b**	Reflux	144	**12**	80	20	0
16	TfOH	**8b**	Reflux	144	**13**	85	15	0
17	TfOH	**9b**	Reflux	144	**14**	47	53	0
18	TfOH	**10b**	Reflux	144	**15**	92	8	0

[a]Reaction conditions: arene **3** (acidic mediator) against 1.0 mmol of arenecarboxylic acid/aroyl chloride; 15 mmol: $AlCl_3$ (3.0 mmol); 12 mmol: P_2O_5–MsOH (2.0 mL); 12 mmol: TfOH (0.50 mmol); N_2 atmosphere.

[b]Calculated on the basis of ^1H NMR spectrum.

[c]Starting material (arenecarboxylic acid/aroyl chloride).

[d]A complex mixture was obtained.

[e]Mesylated compound was obtained.

fluorobenzene (**3**). The reaction by TfOH yielded the aimed phenone with high conversion against each aroyl chloride. Especially in the case of the CF_3-bearing aroyl chlorides (**1b**, **7b**, **8b**, **10b**), TfOH gave excellent results, which are in remarkable contrast with $AlCl_3$.

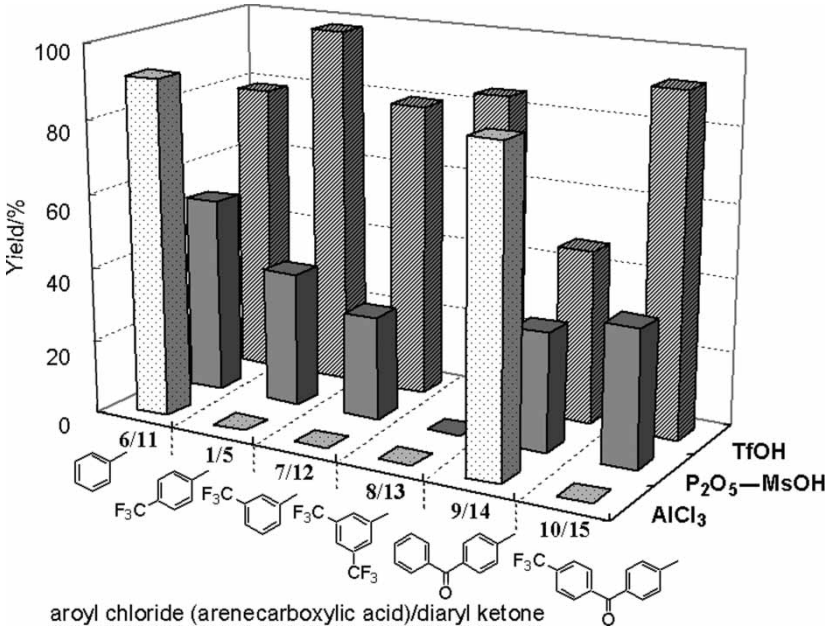
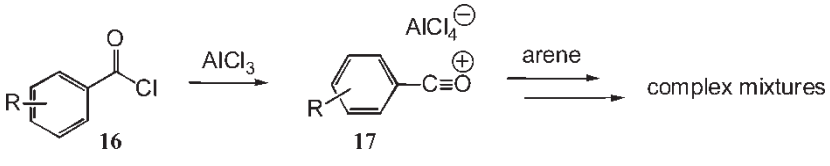


Figure 1. Relationships among acidic mediators, structural factors of arenecarboxylic acids/aroyl chlorides and yields in electrophilic aromatic aroylation of fluorobenzene (**3**).

Postulated Reaction Mechanism

The susceptibility, the selectivity, and the structural dependence of the reaction are interpreted on the basis of the speculated reaction mechanisms described next (Schemes 1–3).

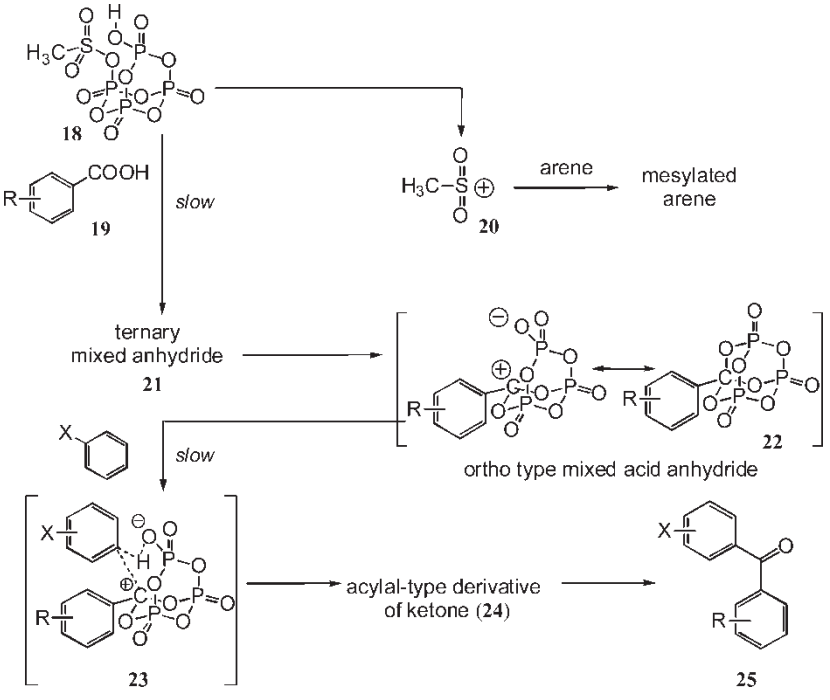
As shown in Table 2 (entries 1–6), the CF_3-free aroyl chlorides (**6b**, **9b**) gave the corresponding phenones (**11**, **14**) with excellent yields in the $AlCl_3$-mediated reaction, whereas the CF_3-bearing aroyl chlorides (**1b**, **7b**, **8b**, **10b**) resulted in only complex mixtures. The distinct difference clearly manifests because intermediates **17**, formed from CF_3-bearing aroyl chlorides **16**, are too reactive to give diaryl ketones selectively (Scheme 1). Furthermore, the C—F bonds in the CF_3 group have enough reactivity to cleave the connection and form new bonds instead.[38]



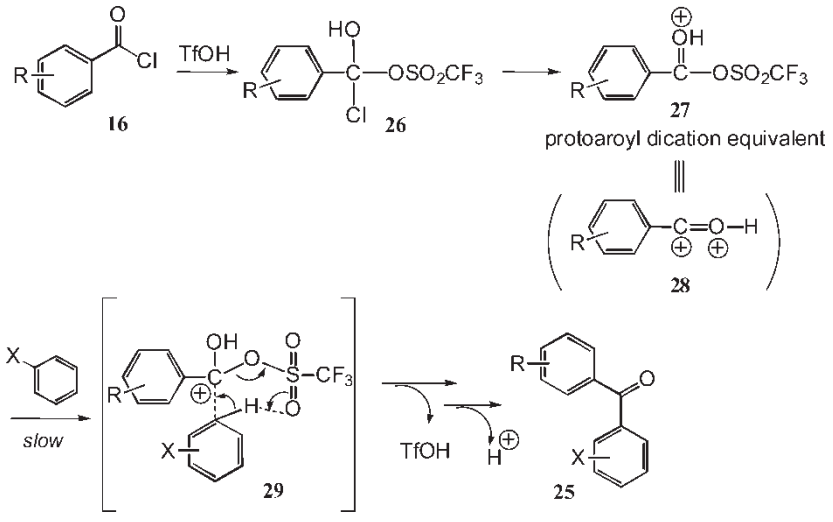
Scheme 1.

On the other hand, the active intermediate in P_2O_5–MsOH-mediated aroylation is plausibly the mildest chemical species among those in three types of aroylation reaction systems. In P_2O_5–MsOH-mediated system, the rather stable intermediate (**22**), formed from arenecarboxylic acid **19** and P_2O_5–MsOH complex, for example, structure **18**, should gradually react with arenes, probably via a possible concerted process (**23**) to give the acylal-like derivatives (**24**) of diaryl ketones **25** (Scheme 2). In this system, CF_3-bearing arenecarboxylic acids **19** form ternary mixed anhydrides **21** so slowly that the unimolecular decomposition of the primarily formed complex (**18**) should precede to yield a methanesulfonium ion (**20**; mesyl cation) equivalent, resulting in partial formation of mesylated products. Furthermore, nonactivated arene reacts with complex **22** slowly. It is also presumed to stimulate the mesylation of the arene. As a natural consequence, P_2O_5–MsOH shows the best efficiency only against the electron-rich acyl-acceptant compound. In other words, with nonactivated arenes, the P_2O_5–MsOH-mediated aroylation system should lack the balance between the reactivities of the acyl-acceptants and the acyl-donors.

In the TfOH-mediated aroylation system (Scheme 3), the active species is anticipated to have a ortho-type acid anhydride/aroyl chloride structure or



Scheme 2.



Scheme 3.

acylal-like one (**26**). This species might have an intramolecular hydrogen-bonded cyclic structure, which gradually eliminates the chloride ion to yield another cationic species (**27**). This cation is considered to be an equivalent of protoaroyl dication **28**.[39] In the TfOH-mediated system, the intermediates are presumably stable enough but more labile than those in the P_2O_5–MsOH-mediated system. The intermediates in the P_2O_5–MsOH-mediated system occasionally cleave by unimolecular mode to form mesyl cation (**20**), resulting in formation of a substantial amount of mesylated by-products. However, the intermediates in the TfOH-mediated system are essentially free from scission, giving active species to yield by-products. In addition, the participation of this highly cationic TfOH adduct probably promotes withdrawal of the electron from the aromatic ring moiety, resulting in depression of the cleavage of C—F bond in the CF_3 group attached, which is unavoidable in an $AlCl_3$-mediated system. In consequence, cation **27** should undertake concerted electrophilic attack (**29**) sufficiently slowly to achieve high selectivity.

CONCLUSION

TfOH has been ascertained to be a tolerant acidic mediator against several CF_3-bearing aroyl chlorides for their aroylating function in electrophilic aromatic aroylation. The electrophilic aroylation of fluorobenzene with CF_3-bearing aroyl chlorides has been demonstrated to proceed with high selectivity by suppressing the side reactions that are unpreventable in $AlCl_3$- and P_2O_5-MsOH–mediated reactions, though the sufficient conversion needs a rather

long reaction interval. According to this method, CF_3-bearing aryl fluorophenyl ketones are efficiently prepared.

EXPERIMENTAL

General

^{1}H NMR spectra were recorded on a JEOL JNM-AL300 spectrometer (300 MHz) and a JEOL JNM-A500 spectrometer (500 MHz). Chemical shifts are expressed in parts per million (ppm) relative to internal standard of Me_4Si (δ, 0.00). ^{13}C NMR spectra were recorded on a JEOL JNM-AL300 spectrometer (75 MHz) and a JEOL JNM-A500 spectrometer (125 MHz). Chemical shifts are expressed in ppm relative to the internal standard of $CDCl_3$ (δ, 77.0). IR spectra were recorded on a JASCO FR/IR-5300 spectrometer.

P_2O_5–MsOH was prepared according to literature.[35]

4-(4-Trifluoromethylbenzoyl)benzoic Acid (**10a**)

4-Methyl-4′-trifluoromethylbenzophenone (**4**, 10.0 mmol, 2.64 g) and glacial acetic acid (24 mL) were placed into a two-necked flask and refluxed for 30 min. Then a mixture of CrO_3(IV) (5.00 g, 50.0 mmol), glacial acetic acid (12 mL), and conc. H_2SO_4 (2.64 mL) was dropped into the reaction solution for 30 min. After 12 h, it was poured into ice water (60 mL), and the resulting mixture was extracted with diethyl ether (3 × 30 mL). The combined extracts were washed with aqueous saturated NaCl solution (sat. NaCl aq.) and dried over anhydrous sodium sulfate overnight. After removal of diethyl ether, the residue was purified by recrystallization from AcOEt (74% isolated yield).

Colorless plates; mp 238.5–239°C (lit. mp 82–83°C[40]; though the melting point differs from that reported in the literature, the formation of the compound described is ascertained by the consistent spectroscopic data and elemental analytical data after the derivation to aroyl chloride. IR ν (KBr): 1691, 1651, 1575, 1502 cm^{-1}; ^{1}H NMR δ (300 MHz, DMSO-d_6): 7.85 (2H, d, J = 8.4 Hz), 7.92–7.95 (4H, m), 8.09 (2H, d, J = 8.1 Hz) ppm; ^{13}C NMR δ (75 MHz, DMSO-d_6): 125.58, 125.63, 129.49, 129.85, 129.88, 130.34, 132.49, 134.50, 139.57, 139.59, 140.14, 166.56, 194.53 ppm.

4-(4-Trifluoromethylbenzoyl)benzoyl Chloride (**10b**)

Thionyl chloride (250 mmol, 29.5 g) and 4-(4-trifluoromethylbenzoyl)benzoic acid (**10a**, 5.00 mmol, 1.47 g) were placed into a two-necked flask, and the reaction mixture was refluxed for 2 h. After removal of thionyl chloride, the residue was purified by recrystallization from hexane (95% isolated yield).

Colorless needles; mp 84–85°C; IR ν (KBr): 1777, 1661, 1510 cm^{-1}; ^1H NMR δ (300 MHz, $CDCl_3$): 7.80 (2H, d, $J = 8.1$ Hz), 7.91 (2H, d, $J = 8.4$ Hz), 7.92 (2H, $J = 8.1$ Hz), 8.27 (2H, d, $J = 8.1$ Hz) ppm; ^{13}C NMR δ (75 MHz, $CDCl_3$): 121.64, 125.25, 125.59, 125.64, 125.69, 125.74, 130.11, 130.24, 131.31, 134.31, 134.75, 136.33, 139.37, 142.13, 167.80, 194.20 ppm. Anal. calcd. for $C_{15}H_8ClF_3O_2$: C, 57.62; H, 2.58. Found: C, 57.92; H, 2.68.

Electrophilic Aromatic Aroylation of Fluorobenzene (3) with 4-Trifluoromethylbenzoic Acid/4-Trifluoromethylbenzoyl Chloride (1)

Typical Procedure of Friedel–Crafts Aroylation Mediated by $AlCl_3$

Fluorobenzene (**3**, 15.0 mmol, 1.44 g) and 4-trifluoromethylbenzoyl chloride (**1b**, 1.00 mmol, 208 mg) were placed into a two-necked flask. To the solution thus obtained, $AlCl_3$ (3.00 mmol, 400 mg) was added by portions at rt under a nitrogen atmosphere. After the reaction mixture was stirred at rt for 24 h, it was poured into ice water (20 mL), and the mixture was extracted with $CHCl_3$ (3 × 15 mL). The combined extracts were washed with sat. NaCl aq. and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to give a viscous oil.

Typical Procedure of Direct Condensation Mediated by P_2O_5–MsOH

Fluorobenzene (**3**, 12.0 mmol, 1.15 g) and 4-trifluoromethylbenzoic acid (**1a**, 1.00 mmol, 190 mg) were placed into a two-necked flask. To the solution thus obtained, P_2O_5–MsOH (2 mL) was added by portions at rt. After the reaction mixture was stirred at 100°C for 24 h, it was poured into ice water (20 mL), and the mixture was extracted with $CHCl_3$ (3 × 15 mL). The combined extracts were washed with sat. NaCl aq. and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to give a powdery product.

Typical Procedure of Modified Friedel–Crafts Aroylation Mediated by TfOH[36]

Fluorobenzene (36.0 mmol, 3.46 g) and 4-trifluoromethylbenzoyl chloride (**1b**, 3.00 mmol, 624 mg) were placed into a two-necked flask. To the solution thus obtained, TfOH (1.50 mmol, 225 mg) was added by portions at rt under nitrogen atmosphere. After the reaction mixture was stirred at 100°C for 144 h, it was poured into ice water (40 mL), and the mixture was extracted with $CHCl_3$ (3 × 30 mL). The combined extracts were washed with sat. NaCl aq. and dried over anhydrous sodium sulfate. After removal

of $CHCl_3$, the residue was purified by recrystallization from EtOH to give colorless needles (98% isolated yield).

Other reactions were undertaken by essentially the same procedure.

Spectral Data and Elemental Analyses

4-Methyl-4′-trifluoromethylbenzophenone (**4**)[41]

Colorless plates (EtOH; 97% isolated yield.); mp 144–145°C (lit. mp 144.5–150°C[41]); IR ν (KBr): 1649, 1599, 1501 cm^{-1}; ^1H NMR δ (300 MHz, $CDCl_3$): 2.46 (3H, s), 7.31 (2H, d, $J = 8.1$ Hz), 7.71 (2H, d, $J = 7.8$ Hz), 7.75 (2H, d, $J = 8.1$ Hz), 7.87 (2H, d, $J = 8.1$ Hz) ppm; ^{13}C NMR δ (75 MHz, $CDCl_3$): 21.715, 121.88, 125.19, 125.23, 125.29, 129.21, 129.99, 130.33, 134.02, 141.08, 144.09, 195.28 ppm.

4-Fluoro-4′-trifluoromethylbenzophenone (**5**)[15,19]

Colorless needles (EtOH; 98% isolated yield); mp 100–101°C (lit. mp 100–100.5°C[15]); IR ν (KBr): 1651, 1599, 1506 cm^{-1}; ^1H NMR δ (300 MHz, $CDCl_3$): 7.19 (2H, dd, $J = 8.7$, 8.7 Hz), 7.76 (2H, d, $J = 8.1$ Hz), 7.81–7.88 (4H, m) ppm; ^{13}C NMR δ (75 MHz, $CDCl_3$): 115.61, 115.90, 121.89, 125.39, 125.44, 125.49, 129.93, 132.68, 132.80, 132.98, 133.02, 134.02, 140.63, 164.06, 167.44, 193.98 ppm.

4-Fluoro-3′-trifluoromethylbenzophenone (**12**)[15]

Yellow needles (EtOH; 76% isolated yield.); mp 44–45°C (lit. mp 45–46°C[15]); IR ν (KBr): 1652, 1598, 1507 cm^{-1}; ^1H NMR δ (300 MHz, $CDCl_3$): 7.19 (2H, dd, $J = 8.7$, 8.4 Hz), 7.64 (1H, t, $J = 7.5$ Hz), 7.82–7.87 (3H, m), 7.95 (1H, d, $J = 7.8$ Hz), 8.03 (1H, s); ^{13}C NMR δ (75 MHz, $CDCl_3$): 115.63, 115.92, 121.81, 125.42, 126.46, 126.51, 128.78, 128.83, 128.88, 128.92, 129.00, 130.83, 131.27, 132.58, 132.71, 132.88, 132.95, 132.99, 138.15, 163.99, 167.37, 193.68 ppm.

4-Fluoro-3′,5′-bis(trifluoromethyl)benzophenone (**13**)

Colorless oil; bp 110–136°C/4 mmHg (85% isolated yield.); IR ν (KBr): 1672, 1601, 1508 cm^{-1}; ^1H NMR δ (300 MHz, $CDCl_3$): 7.24 (2H, dd, $J = 8.4$, 8.4 Hz), 7.82–7.87 (2H, m), 8.10 (1H, s), 8.19 (2H, s) ppm; ^{13}C NMR δ (75 MHz, $CDCl_3$): 116.06, 116.35, 120.98, 124.65, 125.70, 129.61, 131.93, 132.15, 132.19, 132.38, 132.65, 132.77, 139.29, 164.34, 167.73, 192.11 ppm. Anal. calcd for $C_{15}H_7F_7O$: C, 53.59; H, 2.10. Found: C, 53.90; H, 1.99.

4-(4-Fluorobenzoyl)-4′-trifluoromethylbenzophenone (**15**)

Yellow needles (acetone; 88% isolated yield); mp 200–201°C; IR ν (KBr): 1651, 1601, 1508 cm^{-1}; ^1H NMR δ (300 MHz, $CDCl_3$): 7.21 (2H, dd, $J = 8.4$, 8.4 Hz), 7.79 (2H, d, $J = 8.1$ Hz), 7.88–7.95 (8H, m) ppm; ^{13}C NMR δ (75 MHz, $CDCl_3$): 115.63, 115.93, 125.59, 129.70, 129.86, 130.22, 132.72, 132.85, 139.67, 139.97, 141.16, 167.45, 194.30, 194.74 ppm. Anal. calcd. for $C_{21}H_{12}F_4O_2$: C, 67.75; H, 3.25. Found: C, 67.87; H, 3.09.

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