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2-(Trifluoromethylsulfonyloxy)pyridine as a Reagent for the Ketone Synthesis from Carboxylic Acids and Aromatic Hydrocarbons

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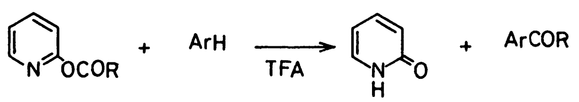
A new reagent 2-(trifluoromethylsulfonyloxy)pyridine (**TFOP**) was prepared by the reaction of sodium salt of 2-pyridinol with trifluoromethylsulfonyl chloride in dioxane. The compound **TFOP** in trifluoroacetic acid has been found to intermolecularly dehydrate from benzoic acid and aromatic hydrocarbons to give the corresponding benzophenones in high yield. It was further elucidated, in the reaction of fluorene, that a variety of carboxylic acids can be used as the acyl precursor for the aromatic ketone synthesis in conjunction with the **TFOP/TFA** system. This acylation procedure has been applied to the synthesis of 2-acylthiophenes, which are hard to prepare in a satisfactory yield by the classical Friedel-Crafts reaction using aluminum chloride as the catalyst.

Acylation is one of the most important reaction in organic synthesis. Although various procedures for the acylation of hetero atoms of amines or alcohols, and for that of aliphatic carbons are available, only a few routes of acylation of aromatic carbons are known.[1] Among them, the Friedel-Crafts reaction using aluminum chloride as a catalyst is the most useful means.[2] However, we have encountered some inconveniences in the use of aluminum chloride as the catalyst. The acylation generally requires molar amounts of a catalyst which is a hygroscopic solid and forms complexes with the products. A consequent work-up is needed to decompose these complexes, and the catalyst is usually non-recoverable. A large amount of hydrochloric acid evolves during the reaction and during the hydrolysis of the complexes. In addition, the catalyst sometimes induces undesirable side reactions. For example, an acylation of thiophene with acid chloride and aluminum chloride is accompanied by a polymerization of the substrate.[3]

Recently, some procedures capable of acylating aromatic hydrocarbons without the use of the classical catalyst have been developed.[4–13] Above all the report by Effenberger that a carboxylic trifluoromethylsulfonic anhydride (I) has an ability to acylate aromatic hydrocarbons is very interesting.[4]

We have previously reported that an acyl group of 2-acyloxypyridines undergoes transacylation catalyzed by trifluoroacetic acid (**TFA**) to aromatic hydrocarbons existing in the solution to give aromatic ketones (Eq. 1).[8]

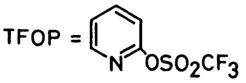


(1)

Analogously, the "transsulfonylation" could be expected to occur from 2-(trifluoromethylsulfonyloxy)pyridine (**TFOP**) to carboxylic acid in a **TFA** solution to give the mixed anhydride **I**, which is a good acylating agent of aromatic hydrocarbons.

In the present paper, we will report on the synthesis of **TFOP** and its application to a condensation reaction between carboxylic acids and aromatic hydrocarbons to give aromatic ketones.[14]

$$\mathrm{ArH} \quad + \quad \mathrm{RCOOH} \xrightarrow[\mathrm{TFA}]{\mathrm{TFOP}} \mathrm{ArCOR}$$

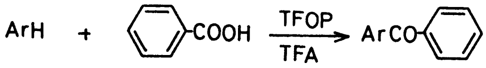


(2)

Results and Discussion

A new reagent, **TFOP**, was prepared by a reaction of the sodium salt of 2-pyridinol with trifluoromethylsulfonyl chloride in dioxane. The compound is a relatively stable and colorless liquid. Its physical data are shown in the experimental section.

The utility of **TFOP** as a dehydrating reagent between carboxylic acid and aromatic hydrocarbon to give aromatic ketones was investigated. First, a reaction involving some kinds of aromatic hydrocarbons with benzoic acid in the presence of **TFOP** has been carried out in **TFA** solution (Eq. 3). For example, durene was heated with benzoic acid and **TFOP** in a molar ratio of 1 : 1.1 : 1.1, respectively, in **TFA** under reflux for 5 h to give 2,3,5,6-tetramethylbenzophenone in a quantitative yield. In a similar procedure, reactions of some other aromatic hydrocarbons with benzoic acid were carried out. The results are summarized in Table 1. Dimethoxybenzenes, tri- and tetramethylbenzenes, anisoles, dibenzofuran, and diphenyl ether reacted with benzoic acid in the presence of **TFOP** in **TFA** to give the corresponding benzophenone derivatives in satisfactory yields. Alternatively, benzene, biphenyl, and *p*-xylene were not benzoylated by this method.



(3)

The validity of the **TFOP/TFA** system as a reagent leading carboxylic acids and aromatic hydrocarbons to

Table 1. The Results of Benzoylation of Aromatic Hydrocarbons with **TFOP** and Benzoic Acid[a]

Aromatic substrate	Product	Isolated yield	Mp or Bp/°C/mmHg		IR $\nu_{C=O}$/cm^{-1}
		%	Found	Reported	(KBr or neat)
o-Dimethoxybenzene	3,4-Dimethoxy-BZ[b]	97	99—100	103—104[15]	1640
m-Dimethoxybenzene	2,4-Dimethoxy-BZ	97	86—88	87—88[15]	1660
p-Dimethoxybenzene	2,5-Dimethoxy-BZ	93	49—50	51[16]	1665
Dibenzofuran	2-Benzoyldibenzofuran	75	136—137	136—137[17]	1655
Durene	2,3,5,6-Tetramethyl-BZ	99	119—120	119[15]	1670
1,2,3,5-Tetramethylbenzene	2,3,4,6-Tetramethyl-BZ	99	60—61	62—63[15]	1665
o-Methylanisole	3-Methyl-4-methoxy-BZ	99	80—81	80[18]	1643
Anisole	4-Methoxy-BZ	97	61—63	61—62[15]	1650
Diphenyl ether	4-Phenoxy-BZ	99	66—67	71[19]	1650
Mesitylene	2,4,6-Trimethyl-BZ	96	156—157/6	189/17[15]	1670
m-Xylene	2,4-Dimethyl-BZ	95	186/12	186—190/15[15]	1660
p-Xylene	2,5-Dimethyl-BZ	19[c]	36	36[15]	1668
Biphenyl	4-Phenyl-BZ	31[c]	102—103	103[15]	1642
Benzene	BZ	17[c]	48	49[15]	1655

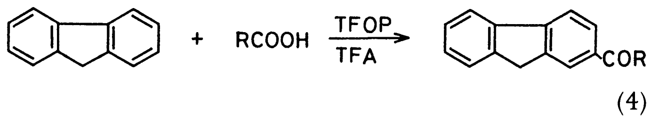
a) All the reactions were carried out under reflux of a solution of ArH (6 mmol), benzoic acid (7 mmol), and **TFOP** (7 mmol) in **TFA** (5 mL) for 5 h. b) BZ=Benzophenone. c) Determined by GLC.

Table 2. The Reaction of Acylation of Fluorene with a Carboxylic Acid and **TFOP**[a]

Entry	Carboxylic acid	2-Acylfluorene isolated yield/%	Mp[b]/°C	IR $\nu_{C=O}$/cm^{-1} (KBr)
1	CH_3COOH	81	130—131	1678
2	CH_3CH_2COOH	82	118—119	1675
3	C_6H_5COOH	93	122—123	1645
4	*p*-$CH_3OC_6H_4COOH$	82	155—156	1640
5	*m*-$CH_3OC_6H_4COOH$	67	99—100	1645
6	*p*-$CH_3C_6H_4COOH$	96	118—119	1645
7	*m*-$CH_3C_6H_4COOH$	80	115—116	1655
8	*o*-$CH_3C_6H_4COOH$	71	138—139	1660
9	*p*-ClC_6H_4COOH	81	177—179	1648
10	*m*-ClC_6H_4COOH	56	149—151	1650
11	*o*-ClC_6H_4COOH	75	133—134	1650
12[c]	*p*-$NO_2C_6H_4COOH$	34	184—185	1644

a) All the reactions were carried out under reflux of a solution of fluorene (6 mmol), carboxylic acid (7 mmol), and TFOP (7 mmol) in TFA (5 mL) for 5 h. b) The products were identified by the mixed melting point test with authentic samples previously reported in Ref. 9. c) Heterogeneous reaction due to the low solubility of *p*-nitrobenzoic acid in boiling TFA.

ketones was further investigated in a reaction of fluorene with a variety of carboxylic acids (Eq. 4). Reactions were also carried out in a manner similar to that described for the benzoylation of durene. The results are summarized in Table 2. Except for *p*-nitrobenzoic acid, aliphatic and aromatic carboxylic acids gave the corresponding 2-acylfluorenes in good isolated yields. Particularly, aliphatic carboxylic acids and benzoic acids, having an electron-donating group, resulted in a high yield of 2-acylfluorenes.



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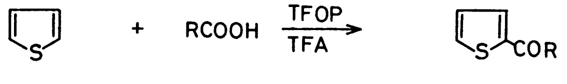
The combination of carboxylic acid with the **TFOP/TFA** system was applied to the acylation of thiophene (Eq. 5). A mixture of thiophene, *p*-chlorobenzoic acid, and **TFOP** was heated in **TFA** under reflux for 4 h to yield 2-(*p*-chlorobenzoyl)thiophene in a quantitative yield. Other acylthiophenes were also obtained by the reaction of thiophene with **TFOP** and carboxylic acids in satisfactory yields. The results are given in Table 3.



(5)

Thus, **TFOP** has been shown to serve as a condensation reagent between a variety of carboxylic acids and aromatic hydrocarbons to give aromatic ketones.

The classical catalyst aluminum chloride is not so suitable for an acylation of thiophene by Friedel-Crafts method since the catalyst partly induces a polymerization of thiophene. Although some improved procedures using less weak acids such as BF_3/MeOH complex,[24] $SnCl_4$,[3] 85% H_3PO_4,[21] or solid super acid Nafion-H,[12] and so on, have been used, the yields of acylthiophenes are still not very satisfactory. The

Table 3. The Results of Acylation of Thiophene with a Carboxylic Acid and **TFOP**[a)]

Carboxylic acid	2-Acylthiophene Isolated yield/%	Mp or Bp/°C/mmHg Found	Mp or Bp/°C/mmHg Reported	IR $\nu_{C=O}$/cm^{-1} (KBr or neat)
CH_3COOH	99	107—110/30	89—91/9[3)]	1662
CH_3CH_2COOH	95	115—116/33	116/20[20)]	1662
C_6H_5COOH	99	55—56	56—57[21)]	1630
p-$CH_3OC_6H_4COOH$	93	72—74	76—77[22)]	1630
m-$CH_3OC_6H_4COOH$	92	146—148/3		1635
p-$CH_3C_6H_4COOH$	89	70—71	75—76[23)]	1630
m-$CH_3C_6H_4COOH$	93	219—220/25		1632
o-$CH_3C_6H_4COOH$	95	145—147/5		1637
p-ClC_6H_4COOH	99	94—95	99—100[22)]	1632
m-ClC_6H_4COOH	93	62—64		1635
p-FC_6H_4COOH	99	95—96		1630

a) All the reactions were carried out under reflux of a solution of thiophene (6 mmol), carboxylic acid (7 mmol), and **TFOP** (7 mmol) in **TFA** (5 mL) for 4 h.

Table 4. Effects of **TFA** and Solvent on the Benzoylation of Thiophene with Benzoic Acid and **TFOP**[a)]

Entry	Solvent	Molar ratio of **TFA**/ thiophene	Yield of 2-benzoyl-thiophene/%[b)]
1	1,2-Dichloroethane	10	99
2	1,2-Dichloroethane	5	99
3	1,2-Dichloroethane	2	86
4	1,2-Dichloroethane	1	29
5	1,2-Dichloroethane	0	0
6	Acetonitrile	5	62
7	Chloroform	5	11
8	Dichloromethane	5	2

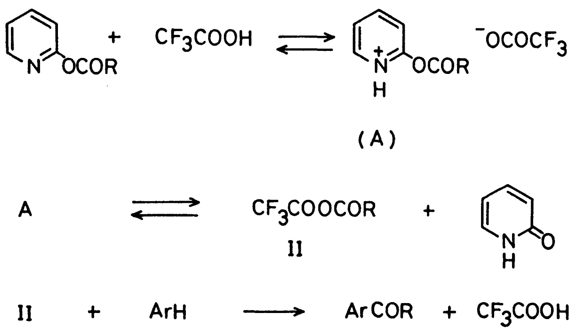
a) All the reactions were carried out under reflux of a solution of thiophene (6 mmol), benzoic acid (7 mmol), and **TFOP** (7 mmol) in a given solvent (5 mL) for 4 h. b) Determined by GLC.

method described here directly gives the 2-acylthiophenes from carboxylic acid and thiophene in a quite high yield.

In light of the reaction mechanism, the effect of **TFA** on the ketone yields was investigated in the benzoylation of thiophene with benzoic acid and **TFOP** in a solvent. The results are shown in Table 4. As can be seen, the acylation reaction dose not occur without the addition of **TFA**. The reaction requires at least two equivalents of **TFA** to **TFOP** to result in a satisfactory yield of the ketone. An inert solvent with a relatively high boiling point, 1,2-dichloroethane, seems to be recommendable as a co-solvent for a ketone synthesis by the carboxylic acid/**TFOP**/**TFA** system.

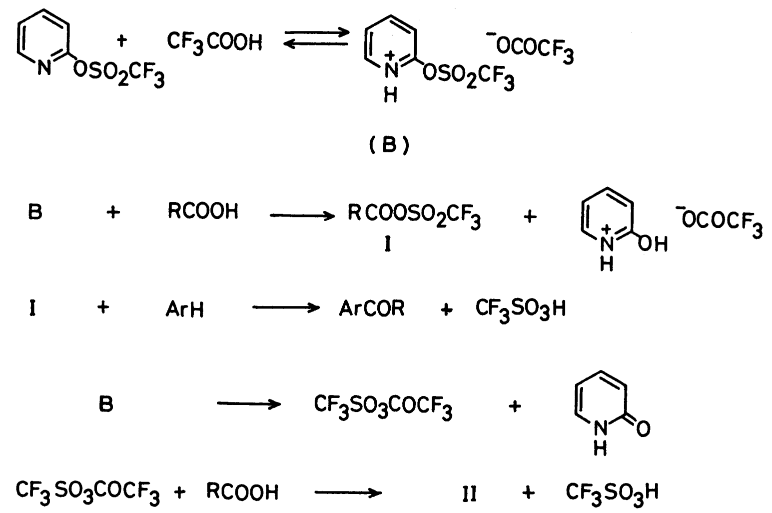
If the acylation reaction proceeds via a cationic acyl species which attacks an aromatic nucleus in the rate-determining step, as in a usual Friedel-Crafts reaction, the ketone yields should increase with an electron-withdrawing group in the acylating species.[25)] On the contrary the yields of 2-acylfluorenes by the substituted benzoic acid/**TFOP**/**TFA** system have resulted in a decrease with an electron-withdrawing group in the benzoic acid (entries 5 and 10 in Table 2). Hence, a direct electrophilic attack on the aromatic nucleus by the cationic acyl carbon dose not seem to be involved in the rate-determining step.

We have previously reported that the 2-acyloxypyridine/**TFA** system acylates fluorene to give 2-acylfluorene, in which a mechanism proceeding via the formation of pyridinium salt **A** followed by acyl trifluoroacetate (**II**) playing a role as the real acylating entities was assumed (shown in Scheme 1).[8)] The substituent effects on acylation of fluorene by the substituted benzoic acids/**TFOP**/**TFA** system is similar to the trend observed in the acylation by the 2-acyloxypyridine/**TFA** system.



Scheme 1.

Effenberger had reported that the mixed anhydride **I** prepared from carboxylic acid chloride and silver trifluoromethylsulfonate can acylate an aromatic hydrocarbon. Here also, it can be considered that these kinds of mixed anhydrides could be formed via the activated pyridinium salt **B** in the course of the reaction. Thus, the transsulfonylation of the salt **B** to carboxylic acid would take place to give the anhydride **I**, and/or the salt **B** would generate the very reactive trifluoroacetic trifluoromethylsulfonic anhydride which reacts with carboxylic acid to give the mixed anhydride **II**. Either **I** or **II**, or both of them, seem to work as an acylating agent of aromatic compounds, as shown in Scheme 2. The formation of mixed anhydrides **I** and **II** might be involved in the rate-controlling step regarding the reaction. A significant substituent effect in the substi-



Scheme 2.

tuted benzoic acids, however, has not been observed in the acylation of thiophene which is more reactive than fluorene. Consequently, a cleavage of the carbon-oxygen bond between the acyl group and trifluoromethylsulfonate or trifluoroacetate, respectively, in **I** or **II** would be involved in the transition state, so that the yield of 2-acylfluorenes would be lower in the reaction with the benzoic acids containing an electron-withdrawing group, since the bond in such anhydrides is difficult to break.

In conclusion, we have now established that **TFOP** is useful as a reagent for a condensation between carboxylic acid and aromatic hydrocarbon to give aromatic ketones. Our method seems to have the following superior points. The ketones can be directly obtained by a reaction of aromatic compound with an equivalent mole of carboxylic acid in quite high yield. This system can acylate thiophene to give 2-acylthiophenes free from contamination by polymerization products. Trifluoroacetic acid is now popular and it has a moderate boiling point to make it easy to recover from the reaction mixture by distillation. If necessary, we can use 1,2-dichloroethane as the co-solvent to reduce a quantity of **TFA**. The reaction products can be easily separated by washing the mixture with water after distilling off **TFA**. Trifluoromethylsulfonic acid dissolved in the washing aqueous solution can be recoverd quantitatively as the barium salt.

Experimental

Materials and Measurements. All the acylated products were identified by comparing their physical data with those of authentic samples synthesized by classical Friedel-Crafts reactions, or by IR, ^{1}H NMR, and elemental analysis. Melting points are uncorrected. The IR spectra were recorded on a Hitachi EPI-S2 model infrared spectrophotometer. ^{1}H NMR spectra were recorded on a JEOL-FX 270 FT-NMR spectrometer in chloroform-*d* solution with tetramethylsilane internal standard. GLC analysis was carried out on a Hitachi GC Model 163 gas chromatograph equipped with a hydrogen flame ionization detector and a stainless steel column (length 3 m, i.d. 3 mm) packed with 3% Dexil 300 GC on Chromosorb W.

Preparation of TFOP. To a solution of 2-hydroxypyridine (14.07 g, 0.148 mol) in dry dioxane (100 mL), a suspension of sodium hydride (3.55 g, 0.148 mol) in dioxane (20 mL) was added with stirring at 40 °C over 15 min. Then, a solution of trifluoromethylsulfonyl chloride (25.0 g, 0.148 mol) in dry tetrahydrofuran (20 mL) was added slowly to the mixture with stirring over 1 h. After stirring at room temperature for 2 h, the reaction mixture was filtered, and the solvent of filtrate was evaporated under reduced pressure. The residue was distilled under reduced pressure to give **TFOP** (22 g, 65% yield); bp 108 °C/25 mmHg,[†] 105 °C/22 mmHg, 95 °C/19 mmHg; IR (neat) 1600, 1430, 1260, 1175, and 890 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=8.41 (dd, 1H, J=0.5 and 2 Hz), 7.92 (dt, 1H, J=0.72 and 3Hz), 7.38—7.43 (m, 1H), and 7.24 (d, 1H, J=7 Hz); MS m/z (rel intensity, %) 227 (M^+, 70), 163 (10), 135 (100), and 113 (20). Found: C, 31.65; H, 2.00; N, 6.18%. Calcd for $C_6H_4NO_3SF_3$: C, 31.72; H, 1.77; N, 5.17%.

Benzoylation of Durene. To a mixture of benzoic acid (7 mmol) and **TFOP** (7 mmol) in **TFA** (5 mL), durene (6 mmol) was added. After the mixture was heated under reflux for 5 h, it was poured into ice-water, and the resulting precipitate was filtered and washed with water and a dilute alkali solution to give the crude product of 2,3,5,6-tetramethylbenzophenone (mp 119 °C, 99% yield). Recrystallization of the crude product from methanol gave a product of mp 119—120 °C (85% yield).

***p*-Chlorobenzoylation of Fluorene.** To a mixture of fluorene (6 mmol), *p*-chlorobenzoic acid (7 mmol), and **TFOP** (7 mmol), **TFA** (5 mL) was added and the mixture was heated under reflux for 5 h. Then, after evaporating **TFA** under reduced pressure, unreacted fluorene was distilled off with steam to give 2-(*p*-chlorobenzoyl)fluorene as the residue (mp 172—176 °C, 81% yield). Recrystallization of the product from ethanol gave a product of mp 177—179 °C.

***o*-Methylbenzoylation of Thiophene.** To a mixture of thiophene (6 mmol), *o*-methylbenzoic acid (7 mmol), and

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[†] 1 mmHg=133.322 Pa.

TFOP (7 mmol), **TFA** (5 mL) was added and the mixture was heated under reflux for 4 h. Then, the reaction mixture was poured into ice-water and was extracted by ether. The organic layer was washed with water, alkali, and water, and was dried over anhydrous sodium sulfate. After evaporation of the solvent, crude 2-(*o*-methylbenzoyl)thiophene was obtained as the oily product (95% yield). The distillation of the oil under reduced pressure gave a product of bp 145—147 °C/5 mmHg (85% yield); IR (Neat) 1637, 1410, 1305, 1276, 850, and 735 cm^{-1}; ^1H NMR ($CDCl_3$) δ=7.70 (d, 1H, *J*=2 Hz), 7.36—7.66 (m, 5H), 7.13—7.16 (m, 1H), and 2.42 (s, 3H, Me). Found: C, 71.21; H, 4.94%. Calcd for $C_{12}H_{10}OS$: C, 71.26; H, 4.98%.

By a similar procedure, the following 2-acylthiophenes were prepared.

2-(*m*-Methylbenzoyl)thiophene: 93% yield; bp 219—220 °C/25 mmHg; IR (neat) 1632, 1410, 1290, 1210, 775, and 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ=7.70—7.72 (m, 4H), 7.29—7.42 (m, 2H), 7.08—7.25 (m, 1H), and 2.38 (s, 3H, Me). Found: C, 71.42; H, 4.99%. Calcd for $C_{12}H_{10}OS$: C, 71.26; H, 4.98%.

2-(*m*-Methoxybenzoyl)thiophene: 92% yield; bp 146—148 °C/3 mmHg; IR (neat) 1635, 1410, 1285, 890, and 730 cm^{-1}; ^1H NMR($CDCl_3$) δ=7.65—7.71 (m, 2H), 7.38—7.45 (m, 3H), 7.10—7.16 (m, 2H), and 3.85 (s, 3H, OMe). Found: C, 66.09; H, 4.58%. Calcd for $C_{12}H_{10}O_2S$: C, 66.03; H, 4.62%.

2-(*m*-Chlorobenzoyl)thiophene: 93% yield; Mp 62—64 °C (from hexane); IR (KBr) 1635, 1400. 1290, 890, and 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ=7.41—7.83 (m, 6H) and 7.16—7.20 (m, 1H). Found: C, 9.49; H, 3.22%. Calcd for $C_{11}H_7OSCl$: C, 59.33; H, 3.17%.

2-(*p*-Fluorobenzoyl)thiophene: 99% yield; Mp 95—96 °C (from 60% EtOH); IR (KBr) 1630, 1412, 1295, 850, and 720 cm^{-1}; ^1H NMR ($CDCl_3$) δ=7.89—7.94 (m, 2H), 7.63—7.75 (m, 2H), and 7.15—7.25 (m, 3H). Found: C, 63.89; H, 3.21%. Calcd for $C_{11}H_7OSF$: C, 64.06; H, 3.42%.

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