N-Acylimidazoles-Trifluoroacetic Acid System as the Acylating Agent for Aromatic Hydrocarbons

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(Received September 20, 1979)

N-Benzoylimidazole in trifluoroacetic acid could benzoylate electron-rich aromatic compounds, such as durene, *p*-dimethoxybenzene, mesitylene, anisole, thiophene, and fluorene, to give the corresponding benzophenone derivatives in good yields. It was further elucidated, in the reaction of fluorene, that *N*-acylimidazoles composed of a variety of acyl groups also could be used for the ketone synthesis. Therein, the imidazolides of aliphatic carboxylic acids or substituted benzoic acids with an electron-donating group gave ketones in high yields. The above-mentioned aromatic compounds were also acylated with *N*-trifluoroacetylimidazole and free carboxylic acids in trifluoroacetic acid. The mechanism for these reactions was assumed to proceed *via* a mixed anhydride between trifluoroacetic acid and carboxylic acid.

Acylation is one of the most important reactions in organic chemistry. Many kinds of procedures for the acylation of hetero atoms of amines or alcohols, and for that of aliphatic carbons are available[1] but only a few routes for aromatic carbons are known. Of them, the Friedel-Crafts reaction using aluminum chloride as the catalyst is the most famous and the most useful.[2] However, the Friedel-Crafts acylation generally requires molar amounts of a catalyst which is a hygroscopic solid and which forms complexes with the product. A work-up, consequently, is needed to decompose these complexes, and the catalyst is usually non-recoverable. In addition, a large amount of hydrochloric acid evolves during the reaction and at the hydrolysis of the complexes. Therefore, the use of aluminum chloride as the catalyst for ketone synthesis is sometimes inconvenient, particularly when carrying out a large-scale reaction.

Recently, some methods capable of acylating aromatic hydrocarbons with a small amount of a catalyst or none at all have been developed.[3-5] Above all, it is very interesting, in the reports by Bourne[4] and Effenberger,[5] that a mixed anhydride of carboxylic acid with trifluoroacetic acid or trifluoromethanesulfonic acid can be used for the acylation of aromatic hydrocarbons without the use of aluminum chloride. We ourselves have previously reported that trifluoromethylsulfonyloxypyridine can be used for the condensation of carboxylic acid and aromatic hydrocarbon to give the ketone.[6] In the present paper, we will report that *N*-acylimidazoles are useful as acylating agents for some aromatic compounds in trifluoroacetic acid.

Results and Discussion

The chemistry of imidazolides has been well established and reviewed precisely by Staab.[8] *N*-Acylimidazoles generally are very powerful acylating agents for hetero atoms of alcohols or amines, but they can not be used with aromatic carbons. Ried and Shubert[9] attempted the application of *N*-acylimidazoles as the acylating agents in the Friedel-Crafts ketone synthesis, and they observed that the imidazolides were not more suitable than acyl chlorides or acid anhydrides for the reactions. We also attempted the benzoylation of fluorene with *N*-benzoylimidazole, using aluminum chloride as the catalyst in dichloromethane at room temperature, but little benzoylfluorene was obtained.

The enhanced reactivities of *N*-acylimidazoles to the hetero atoms can be explained as being due to the delocalization of the lone-pair electron of the amide-nitrogen to make up the aromatic sextet and the electron-withdrawing effects of the other one, behaving like pyridine-nitrogen.[8] If the imidazolide is used together with a strong Brönsted acid, the pyridine-like nitrogen is protonated to form an imidazolium ion, so the electrophilicity of the acyl group might be increased. Thus, we found that *N*-acylimidazoles could acylate aromatic hydrocarbons in conjunction with trifluoroacetic acid to give ketones in good yields. For example, 2-benzoylfluorene was isolated in a yield of 80% by heating under reflux for 5 h a mixture of fluorene, *N*-benzoylimidazole, and trifluoroacetic acid in a molar ratio of 1: 1.2: 10 respectively. Under the same conditions, other aromatic compounds, such as durene, *p*-dimethoxybenzene, anisole, mesitylene, and thiophene, were benzoylated to give the corresponding ketones in good yields. However, benzophenone could not be obtained by this procedure. The results are summarized in Table 1 (Method A).

The validity of *N*-acylimidazoles as the acylating agent for aromatic substrates was further investigated by an examination of the reaction of fluorene with a wide variety of *N*-acylimidazoles. The results are summarized in Table 2 (Method A). The reactions were carried out under the same conditions, that is, by heating, under reflux for 10 h, a mixture of fluorene, *N*-acylimidazole, and trifluoroacetic acid in a molar ratio of 1: 1.2: 10 respectively.

All the imidazolides, except for *N*-(*p*-nitrobenzoyl)-imidazole, gave the corresponding 2-acylfluorenes in satisfactory yields. The imidazolides of aliphatic carboxylic acids or aromatic carboxylic acids containing an electron-donating group gave 2-acylfluorenes in especially high yields. Although we can not discuss the results in detail, for this work is not a quantitative one, the Hammett plots for the logarithm of ketone yields indicated a correlation with the reaction constant of -1.62 ($r=0.872$, $n=8$). If the *N*-acylimidazole generates an acyl cation which attacks the aromatic nucleus, as in usual Friedel-Crafts reactions, or if the acyl group of the imidazolide attacks directly through a cooperative activation by trifluoroacetic acid (Eq. 1

Table 1. Benzoylation of aromatic hydrocarbons with *N*-benzoylimidazole or *N*-trifluoroacetylimidazole and benzoic acid in trifluoroacetic acid

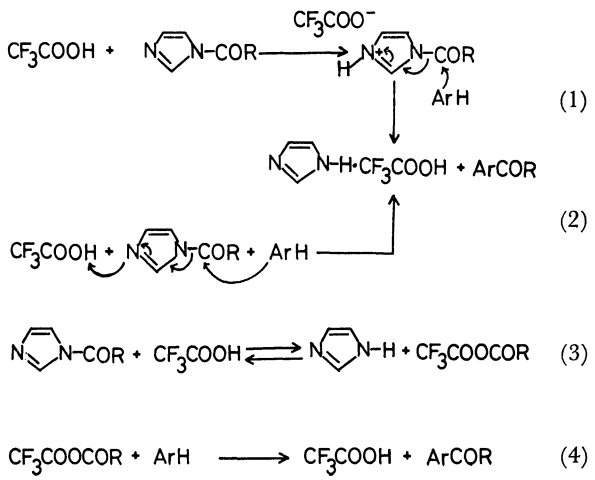
Aromatic substrate	Ketone yield/%		Isolated product			IR $\nu_{C=O}$ (cm^{-1}) (KBr or Neat)
	Method A[a]	Method B[b]	Mp or Bp/°C/Torr		Compound	
			Found	Reported		
Durene(D)	77	99	119—120	119[14]	3-Benzoyl-D	1670
p-Dimethoxybenzene(DMB)	73	95	50—52	51[15]	2-Benzoyl-DMB	1665
Mesitylene(M)	78	98	156—157/6	189/17[16]	2-Benzoyl-M	1670
Thiophene(TH)	80	100	55—56	56—57[17]	2-Benzoyl-TH	1625
Anisole(A)	86	98	61—63	61—63[18]	4-Benzoyl-A	1650
Fluorene(F)	80	91	122—123	122[19]	2-Benzoyl-F	1645
Anthracene(AT)	—	82	145—146	148[20]	9-Benzoyl-AT	1660
m-Xylene(MX)	—	66	140/5	321/744[21]	4-Benzoyl-MX	1660
p-Xylene(PX)	—	8[c]	36	36[22]	2-Benzoyl-PX	1668
Toluene(T)	—	5[c]	oil	55[23]	4-Benzoyl-T	1645
Benzene	0	—				

a) Purified ketone yield. b) Crude ketone yield. c) Determined by GLC.

Table 2. Acylation of fluorene with *N*-acylimidazoles or *N*-trifluoroacetylimidazole and carboxylic acids in trifluoroacetic acid

Acyl group in the product	Isolated 2-acylfluorene							
	Yield/%[a]		Mp/°C (Reported)	IR $\nu_{C=O}$(cm^{-1}) (KBr)	Elemental analysis			
					Found (%)		Calcd (%)	
	Method A	Method B			C	H	C	H
CH_3CO	89	82	130—131 (128—129)[24]	1678	86.66	5.93	86.51	5.81
CH_3CH_2CO	86	82	118—119 (120—121)[25]	1675	86.53	6.30	86.45	6.35
$CH_3CH_2CH_2CO$	96	92	118—119	1670	86.48	6.64	86.40	6.82
m-$CH_3OC_6H_4CO$	80	88	99—100	1645	83.94	5.30	83.98	5.37
p-$CH_3OC_6H_4CO$	93	95	155—156	1640	83.87	5.35	83.98	5.37
o-$CH_3C_6H_4CO$	84	92	138—139 (138)[26]	1660	88.77	5.76	88.70	5.67
m-$CH_3C_6H_4CO$	90	88	115—116	1655	88.64	5.54	88.70	5.67
p-$CH_3C_6H_4CO$	95	93	118—119	1645	88.82	5.55	88.70	5.67
C_6H_5CO	80	91	122—123 (122)[27]	1645	88.85	5.19	88.86	5.22
m-ClC_6H_4CO	65	72	149—151	1650	78.85	4.33	78.82	4.30
p-ClC_6H_4CO	76	79	177—179	1648	78.86	4.40	78.82	4.30
p-$NO_2C_6H_4CO$	16	15	184—186	1644	76.15	4.09	76.18	4.16

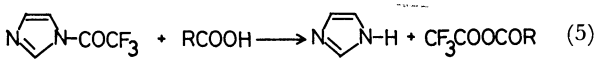
a) The remainder was the unreacted fluorene.



or 2), the reaction constant should be a positive value, because the reaction constants for the aluminum chloride-catalyzed Friedel-Crafts benzoylation[10] and the hydrolysis of the *N*-benzoylimidazoles[11] have been reported to be +1.858 and +1.85 respectively. Hence, this reaction mechanism does not to be a direct electrophilic attack on the aromatic nucleus by either the acyl cation or the *N*-acylimidazole.

It is well known that imidazolides generally react with carboxylic acids to give acid anhydrides.[12] Furthermore, according to Bourne,[4] a mixed anhydride between trifluoroacetic acid and carboxylic acid can work as the acylating agent for some aromatic hydrocarbons in the presence of trifluoroacetic acid. Therefore, it can be considered that this kind of mixed anhydride, *i.e.*, carboxylic trifluoroacetic anhydride, could be yielded

at the first of the reaction and that it then attacks the aromatic carbon to give ketone (Eqs. 3 and 4). A cleavage of the carbon–oxygen bond between the trifluoroacetate and the acyl group would be involved in the transition state, so that the yield of the ketone would be lower in the reaction with mixed anhydrides containing a strong electron-withdrawing group, because the bond in such anhydrides is difficult to break down. If this assumption is correct, results similar to those observed above should be obtained in the reaction of an aromatic substrate with carboxylic acid and *N*-trifluoroacetylimidazole which affords the carboxylic trifluoroacetic anhydride according to Eq. 5:



(5)

Thus, the acylation reactions of aromatic compounds with *N*-trifluoroacetylimidazole and carboxylic acids were examined. The reactions were carried out by heating, under reflux for 10 h, a mixture of an aromatic substrate, carboxylic acid, and *N*-trifluoroacetylimidazole, in a molar ratio of 1: 1.2: 1.2 respectively, in trifluoroacetic acid. The results are summarized in Tables 1 and 2 (Method B).

As expected, the aromatic compounds shown in Table 1, except for toluene and *p*-xylene, were benzoylated in good yields with free benzoic acid and *N*-trifluoroacetylimidazole in trifluoroacetic acid. This method was also established to be useful in reactions with a variety of carboxylic acids. The substituent effects of substituted benzoic acids on the ketone yield were similar to those which were obtained in the reaction with the *N*-acylimidazole–trifluoroacetic acid system. Consequently, the acylation with the *N*-acylimidazole–trifluoroacetic acid system is considered to proceed *via* the carboxylic trifluoroacetic anhydride. It has already been shown by Bourne[4] that the mixed anhydride can be used as the acylating agent for some aromatic compounds. However, the use of the mixed anhydride as the starting material is, in general, troublesome because these compounds are sensitive to moisture and tend to be disproportionate.[13] In addition, excess trifluoroacetic anhydride must be used to prepare them. We have now established that we can acylate aromatic hydrocarbons with *N*-acylimidazoles in trifluoroacetic acid without the use of this kind of mixed anhydride nor trifluoroacetic anhydride. Trifluoroacetic acid, which is now very popular, has a moderate boiling point, making it easy to recover from the reaction mixture by distillation. *N*-Acylimidazoles can also be easily prepared and are relatively stable.

In conclusion, the *N*-acylimidazole–trifluoroacetic acid system seems to offer one method capable of acylating aromatic hydrocarbons without the use of the classical Friedel-Crafts catalyst. Above all, the *N*-trifluoroacetylimidazole–trifluoroacetic acid system is superior as a reagent for a condensation between aromatic compounds and free carboxylic acids to give aromatic ketones.

Experimental

Materials and Measurements. All the *N*-acylimidazoles used for the acylation were synthesized according to the procedure described in the literature.[7] All the other materials were commercially available and were purified, when necessary, by distillation or recrystallization. All the acylated products were identified by comparing their physical data with those of authentic samples synthesized by Classical Friedel-Crafts reactions. All the melting points are uncorrected. The infrared spectra were obtained on a Hitachi EPI-S2 model infrared spectrophotometer.

Method A; *Benzoylation of Anisole by* N-*Benzoylimidazole in Trifluoroacetic Acid.* To a mixture of 8.9 mmol of *N*-benzoylimidazole and 7.5 mmol of anisole, 5 ml of trifluoroacetic acid were added, after which the new mixture was heated under reflux for 5 h. After cooling, water was added. The resulting precipitates were collected by filtration, washed with water and aqueous sodium carbonate, and dried to obtain 1.54 g of crude benzoylanisole (mp 52—57 °C; 96% yield). Crystallization from ethanol gave pure *p*-methoxybenzophenone (1.38 g; mp 61—63 °C; 86% yield).

Butyrylation of Fluorene by N-*Butyrylimidazole in Trifluoroacetic Acid.* To a mixture of 6 mmol of fluorene and 7.2 mmol of *N*-butyrylimidazole, 5 ml of trifluoroacetic acid were added, after which the new mixture was heated under reflux for 5 h. After cooling, water was added to the mixture, the unreacted fluorene was distilled off with steam, and the residue was separated by filtration to obtain butyrylfluorene (1.37 g; mp 112—115 °C; 96% yield). Crystallization from ethanol gave 2-butyrylfluorene (mp 118—119 °C). Unreacted fluorene was recovered (3%) from the distillate.

Method B; *Benzoylation of Durene by* N-*Trifluoroacetylimidazole and Benzoic Acid in Trifluoroacetic Acid.* To a mixture of 7.5 mmol of durene, 9 mmol of benzoic acid, and 5.5 ml of trifluoroacetic acid, 9 mmol of *N*-trifluoroacetylimidazole were added, after which the new mixture was heated under reflux for 10 h. Then water was added, and the resulting precipitates were collected by filtration, washed with water, and dried to obtain benzoyldurene (1.76 g; mp 118—120 °C; 99% yield). Crystallization from ethanol gave 3-benzoyldurene (mp 119—120 °C).

Butyrylation of Fluorene by N-*Trifluoroacetylimidazole and Butyric Acid in Trifluoroacetic Acid.* To a mixture of 6 mmol of fluorene, 7.2 mmol of butyric acid, and 5 ml of trifluoroacetic acid, *N*-trifluoroacetylimidazole (7.2 mmol) was added, after which the new mixture was heated under reflux for 5 h. After cooling, water was added to the mixture, then, after the unreacted fluorene had beed distilled off with steam, the residue was collected by filtration, washed with water, and dried to obtain butyrylfluorene (1.30 g; mp 112—114 °C; 92% yield). Crystallization from ethanol gave 2-butyrylfluorene (mp 118—119 °C). Unreacted fluorene was recovered in a 7% yield from the distillate.

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