In(OTf)$_3$-Catalyzed Friedel–Crafts Reaction of Aromatic Compounds with Methyl Trifluoropyruvate in Water

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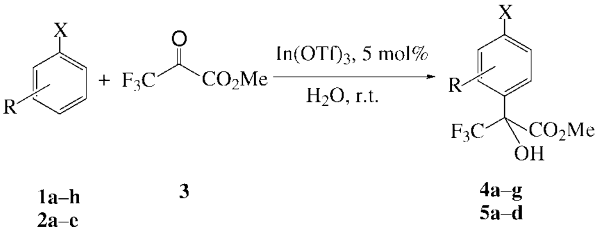
Abstract: In the presence of In(OTf)$_3$ as a catalyst, aniline derivatives **1a**–**c**, **1e**–**h** and anisole derivatives **2a**–**c**, **2e** reacted with methyl trifluoropyruvate **3** in water at room temperature to give the corresponding Friedel–Crafts reaction products **4a**–**g** and **5a**–**d** in good yields, respectively.

Key words: In(OTf)$_3$ catalyst, Friedel–Crafts reaction, methyl trifluoropyruvate, water, CF$_3$-substituted compound

Recently, aqueous organic reactions have received considerable attention in view of their synthetic efficiency and environmental friendliness.[1] Accordingly, Lewis acid catalyzed carbon-carbon bond forming reactions in aqueous media becomes one of the most challenging topics in organic synthesis.[2] Among the C-C bond forming reactions, Friedel–Crafts alkylation is an important reaction, which provides an effectively synthetic route to numerous functionalized aromatic compounds with special properties.[3] The development of aqueous Friedel–Crafts reactions should be very interesating to organic chemists. It was found that lanthanide triflates effectively catalyzed the reaction of indole with imines using aqueous ethanol (ethanol–water: 4:1) as solvent.[4] Recently, Kobayashi[5] reported that in the presence of Lewis acid-surfactant-combined catalyst (LASC), Friedel–Crafts type conjugate addition of indoles with α,β-unsaturated carbonyl compounds can be carried out in water. Jørgensen[6] developed reactions of indoles and pyrroles with ethyl glyoxylate in aqueous NaHCO$_3$ solution without the use of the traditional Lewis acid catalyst to give Friedel–Crafts addition adducts in good yields. It was noteworthy that all three examples on aqueous Friedel–Crafts reaction have to involve the use of more activated heteroaromatic compounds, indole and pyrrole derivatives. There has been no example of aqueous Friedel–Crafts reaction of other type of aromatic compounds reported, probably due to the lower reactivity of aromatic compounds in water than that of activated heteroaromatic compounds under the reaction conditions mentioned above. On the other hand, organofluorine compounds are important in both organic synthesis and the development of novel drugs. In particular, the synthesis of biologically active CF$_3$-substituted compounds have attracted considerable attention.[7]



Scheme 1

A chiral Cu-Lewis acid-catalyzed asymmetric addition reaction of heteroaromatics to trifluoropyruvate was carried out in organic solvent,[8] which provided a new synthetic route to Mosher's acid analogs.[9] More recently, Olah[10] reported a superacid-catalyzed reaction of highly activated heteroaromatic or substituted benzene with trifluoropyruvate in suitable organic solvent and under inert atmosphere. Herein, we wish to report an In(OTf)$_3$-catalyzed Friedel–Crafts reaction of amino- and methoxy-substituted aromatic compounds with methyl trifluoropyruvate in water for the synthesis of methyl α-CF$_3$-α-hydroxy phenyl acetate with amino and methoxy substituents on the phenyl ring.

To start the investigation, *N*,*N*-dimethylaniline (**1a**) was reacted with methyl 3,3,3-trifluoropyruvate (**3**) in the presence of various Lewis acids (5 mol%) in water at room temperature (Scheme 1). For screening purposes, Sc(OTf)$_3$, Ce(OTf)$_3$, Nd(OTf)$_3$, Gd(OTf)$_3$, Yb(OTf)$_3$ and Y(OTf)$_3$ were selected as catalysts; however, in all cases no reaction product was detected by TLC. The addition of a surfactant (SDS) is not efficient to catalyze the reaction in water either (Table 1, entry 6). In the presence of triflic acid (TfOH) as catalyst, the reaction of **1a** with **3** in water gave the product *N*,*N*-dimethyl-4-(hydroxy trifluoromethyl ester)aniline (**4a**) in only 18% yield (entry 7). Moreover, the reaction of **1a** with **3** in saturated NaHCO$_3$ aqueous solution without the use of Lewis acid catalyst only gave a trace of **4a** (entry 8). Cu(OTf)$_2$ and Ga(OTf)$_3$ showed a catalytic ability for the reaction of **1a** with **3** in water, giving the product **4a** in 55% and 58% yields with 5 mol% catalyst loading, and 88% and 78% yields with 20 mol% catalyst loading, respectively (entries 1–4). However, Cu(OTf)$_2$ could not catalyze the reaction of anisole **2a** with **3** in water (entry 9). The lower yields in the case of Ga(OTf)$_3$ (entries 3 and 10) would be attributed to slight decomposition of the catalyst in water. Fortunately,

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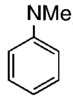
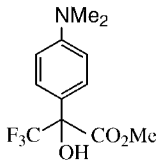
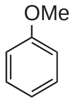
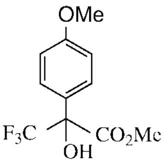
Table 1 Lewis Acid-Catalyzed Friedel–Crafts Reaction of **1a** or **2a** with **3** in Water

Entry	Substrate	Catalyst (mol%)	Time (h)[a]	Product	Yield (%)[b]
1	 **1a**	Cu(OTf)$_2$, (5)	24	 **4a**	55
2	**1a**	Cu(OTf)$_2$, (20)	12	**4a**	88
3	**1a**	Ga(OTf)$_3$, (5)	12	**4a**	58
4	**1a**	Ga(OTf)$_3$, (20)	12	**4a**	78
5	**1a**	In(OTf)$_3$, (5)	6	**4a**	89
6	**1a**	Sc(OTf)$_3$/SDS, (20)	12	NR	
7	**1a**	TfOH (5)	12	**4a**	18
8	**1a**	NaHCO$_3$[c]	12	**4a**	<5
9	 **2a**	Cu(OTf)$_2$, (20)	12	NR	
10	**2a**	Ga(OTf)$_2$, (5)	12	 **5a**	52
11	**2a**	Ga(OTf)$_3$, (20)	12	**5a**	72
12	**2a**	In(OTf)$_3$, (5)	6	**5a**	88

[a] Reaction temperature: r.t.
[b] Isolated yield.
[c] Sat. aq solution of NaHCO$_3$.

by using 5 mol% In(OTf)$_3$ as catalyst, the reaction of **1a** with **3** in water proceeded smoothly to give the product **4a** in 89% yield (entry 5). For the reaction of **2a** with **3** in water, In(OTf)$_3$ also showed the same catalytic ability, giving the product 4-(hydroxy trifluoromethyl ester)anisole (**5a**) in 88% yield (entry 12). The 4-substituted products **4a** and **5a** were the only isomer formed in the reaction of **1a** and **2a** with **3**, which demonstrates that the Friedel–Crafts reaction in water has excellent *para*-regioselectivity. Subsequently, In(OTf)$_3$ was selected as a Lewis acid catalyst for the following Friedel–Crafts reactions in water.

Based on these experimental results, various aniline derivatives **1a**–**h** and anisole derivatives **2a**–**e** were used in the In(OTf)$_3$-catalyzed Friedel–Crafts reactions with **3** in water and air at room temperature. The reactions proceeded smoothly to give addition products **4a**–**g** and **5a**–**d** in good yields (Table 2). The reaction provides a synthetic route to the derivatives of Mosher's acid with substitutions on the phenyl ring, which are not easily accessible by the conventional method employing phenyl trifluoromethyl ketones. Since the reaction is the nucleophilic attack of electron-rich aromatic moiety to a carbonyl group, the introduction of electron-withdrawing group into the phenyl ring would retard the reaction. The good regioselectivities are consistent with Jørgenson's observation[8a] for the reaction in organic solvent. Although aniline **1d** and phenol **2d** could not react with **3** in water in the presence of In(OTf)$_3$ (entries 4 and 13), it is found that their derivatives **1e** and **2e** have enough activity to react with **3** in water by using 5 mol% In(OTf)$_3$ as a catalyst to afford the products **4d** and **5d** in good yields (entries 5 and 14). The aqueous Friedel–Crafts reaction provides a convenient method for the synthesis of the products with mono-N-substituent and free amino groups, for example, **4e** and **4d**, which are usually prepared by the deprotection of *N*,*N*-dialkyl compounds, such as **4f**.[11] It can be noted from the investigations that the Lewis acid-catalyzed Friedel–Crafts addition of aromatic moiety with carbonyl group in water is an atom-economic reaction, according with the principle of green chemistry.

Table 2 In(OTf)$_3$-catalyzed Friedel–Craft Reactions of Aromatic Compounds with **3** in Water[a]

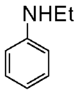
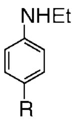
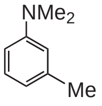
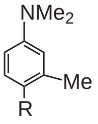
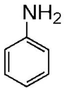
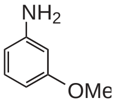
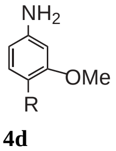
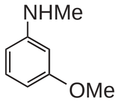
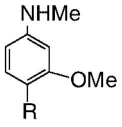
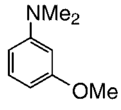
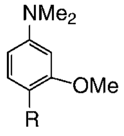
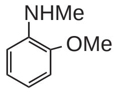
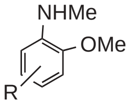
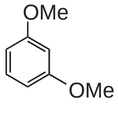
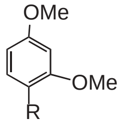
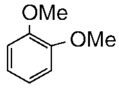
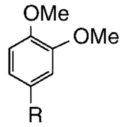
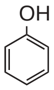
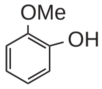
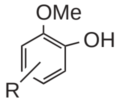
Entry	Substrate	Time (h)[b]	Product[c]	Yield (%)[d]
1	**1a**	6	**4a**	89
2	 **1b**	6	 **4b**	91
3	 **1c**	6	 **4c**	87
4	 **1d**	6	NR	
5	 **1e**	12	 **4d**	65
6	**1e**	12	**4d**	75[e]
7	 **1f**	12	 **4e**	75

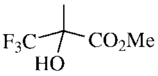
Table 2 In(OTf)$_3$-catalyzed Friedel–Craft Reactions of Aromatic Compounds with **3** in Water[a] (continued)

Entry	Substrate	Time (h)[b]	Product[c]	Yield (%)[d]
8	 **1g**	12	 **4f**	76
9	 **1h**	12	 **4g**	71
10	**2a**	6	**5a**	88
11	 **2b**	12	 **5b**	84
12	 **2c**	24	 **5c**	76
13	 **2d**	6	NR	
14	 **2e**	72	 **5d**	63[e]

[a] Catalyst loading: 5 mol%.

[b] Reaction temperature: r.t.

[c] R:



[d] Isolated yield.

[e] Catalyst 10 mol%

A Typical Experimental Procedure is as follow:

A mixture of **1a** (84 mg, 0.7 mmol), **3** (108 mg, 0.7 mmol) and In(OTf)$_3$ (20 mg, 0.035 mmol) in water (4 mL) was stirred at r.t. After the reaction was completed (monitored by TLC), diethyl ether (15 mL) was added. The organic phase was separated and aqueous phase was extracted with diethyl ether (3 × 10 mL). The combined organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The crude material was purified by a flash chromatography on silica gel (eluent: petroleum ether–EtOAc = 15:1) to give the product **4a** (171 mg, 89%).

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