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AlCl$_3$-mediated Defluorinative Diarylhydroxylation Transformation of CF$_3$: Chemoselective Arylation of CF$_3$ and Chlorocarbonyl Groups Attached to Aromatic Rings

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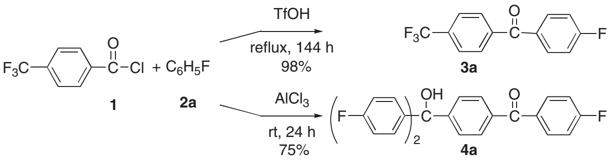
The CF$_3$ group in 4-trifluoromethylbenzoyl chloride is efficiently diarylated and converted into a diarylhydroxymethyl group by treatment with AlCl$_3$ in the presence of an excess amount of halobenzene (C$_6$H$_5$X; X = F, Cl, and Br). The diarylation is followed by arylation of the chlorocarbonyl group to afford triarylated products, diarylhydroxymethylated benzophenones. The employment of TfOH in place of AlCl$_3$ promotes the exclusive arylation of the chlorocarbonyl group leaving the CF$_3$ group unchanged to afford selectively 4-trifluoromethylbenzophenones, which then undergo diarylhydroxymethylation with the aid of AlCl$_3$.

Fluorinated organic molecules are of great interest due to their biological, optical, electrical, and mechanical properties. Along with such aspects of practical uses, controlled activation of C–F bonds has received much attention in organic chemistry.[1–7] For example, regioselective defluorination by organometallic complexes successfully yields difluorinated organic molecules.[2] Furthermore, Ozerov's group and Kambe's group have recently reported ready conversion of CF$_3$ to CR$_3$ by treatment with AlR$_3$.[3] On the other hand, in acid-mediated reactions such as Friedel–Crafts reactions, perfluoroalkyl (R$_F$)-bearing aromatic compounds show rather troublesome behavior. Not only do R$_F$-bearing aromatic carboxylic acid derivatives act as labile highly electrophilic acyl-donor species, R$_F$-bearing aromatic compounds behave as poor acyl-acceptors. So electrophilic aromatic substitution where an R$_F$ group is involved as a substituent in either substrate generally suffers from low yield and/or poor selectivity.[8] As a natural consequence, a smart solution for acid-mediated transformation of R$_F$ groups implies further possibilities for R$_F$-bearing compounds in a wide range of organic chemistry.[6,7]

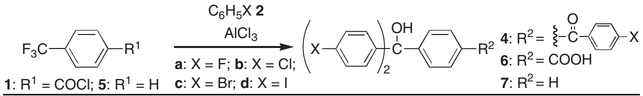
Recently, we have reported a versatile synthetic protocol for CF$_3$-bearing aromatic ketones by electrophilic aromatic aroylation with 4-trifluoromethylbenzoyl chloride (**1**).[9] In this transformation, trifluoromethanesulfonic acid (TfOH) has been proven to promote excellent selectivity and high conversion in the formation of CF$_3$-bearing benzophenone **3**. On the other hand, employment of AlCl$_3$ in place of TfOH for reaction of **1** and fluorobenzene (**2a**) resulted in formation of an unexpected product, carbinol-ketone **4a**,[10] in a high conversion instead of the expected aromatic ketone (**3a**; Scheme 1).

In this paper, we introduce and discuss the reaction behavior and scope of this anomalous transformation of a CF$_3$ group into a diarylhydroxymethyl unit.



Scheme 1.

Table 1. AlCl$_3$-mediated reaction of substrate **1**/**5** with halobenzene **2**[a]

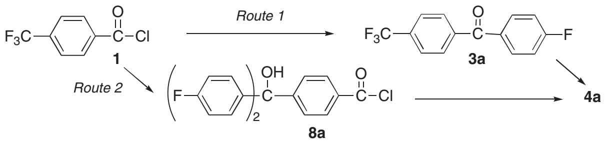


Run	1/5	Halobenzene (X)	AlCl$_3$[b]	Temp	Time	Product (X)	Yield /%[c]
1	**1**	**2a** (F)	3 equiv	rt	24 h	**4a** (F)	75
2	**1**	**2a** (F)	3 equiv	reflux	24 h	**4a** (F)	82
3	**1**	**2a** (F)	1 equiv	reflux	24 h	**4a** (F)	0
4	**1**	**2a** (F)	6 equiv	reflux	24 h	**4a** (F)	86
5	**1**	**2b** (Cl)	3 equiv	rt	24 h	**4b** (Cl)	52
6	**1**	**2b** (Cl)	3 equiv	100 °C	24 h	**4b** (Cl)	32
7[d]	**1**	**2c** (Br)	3 equiv	rt	24 h	**4c** (Br)	52
8	**1**	**2c** (Br)	3 equiv	100 °C	24 h	**4c** (Br)	21
9	**1**	**2d** (I)	3 equiv	rt	24 h	**4d** (I)	0
10	**1**	**2d** (I)	3 equiv	100 °C	24 h	**4d** (I)	0
11	**1**	**2d** (I)	6 equiv	rt	24 h	**4d** (I)	0
12	**1**	**2a** (F)	3 equiv	rt	5 min	**6a** (F)	trace
13	**5**	**2a** (F)	3 equiv	rt	24 h	**7a** (F)	87

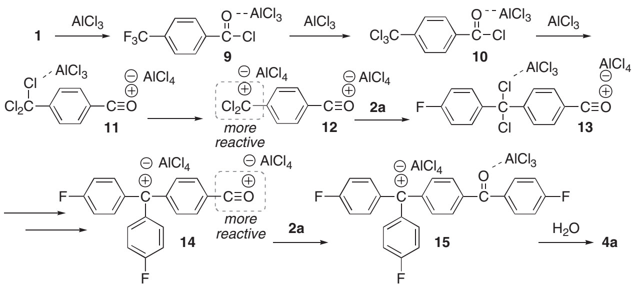
[a]All of the reactions were carried out under N$_2$ atmosphere using 15 equiv of halobenzene **2** against substrate **1**/**5**. [b]Against 4-trifluoromethylbenzoyl chloride (**1**). [c]Isolated yield. [d]**6c** was isolated (12%).

The results of the AlCl$_3$-mediated reaction of **1** and a related compound with halobenzene **2** are summarized in Table 1. The reaction of **1** with **2a** in the presence of AlCl$_3$ to give **4a** proceeded at room temperature with a good conversion (Run 1). At elevated temperature, the yield became slightly higher and at the same time, however, coloration was also observed (Run 2). About 3 equimolar amounts of AlCl$_3$ were required against **1** for smooth arylations (Runs 2 vs. 3). An excess amount of AlCl$_3$ provided a small acceleration of the reaction (Runs 4 vs. 2). Furthermore, reaction of **2b** and **2c** as halobenzenes giving the corresponding ketones also proceeded in moderate yields (Runs 5 and 7). Contrarily, **2d** did not give the corresponding carbinol-ketone (**4d**; Run 9). Neither elevation of temperature nor employment of a large amount of AlCl$_3$ yielded the carbinol-ketone (Runs 10 and 11). The ^{1}H NMR spectrum of the product suggests the formation of carbinol-ketone structures devoid of iodo groups at least partially but structural determination and identification by isolation have not been achieved.

When **1** was allowed to react with **2a** for a short interval, a trace amount of carbinol-carboxylic acid **6a** was isolated from the reaction mixture, whereas **3a** was not obtained (Run 12). In a similar manner, **6c** was also obtained in the reaction of **1** with **2c** (Run 7). Yield of diarylhydroxymethylbenzene **7a** from trifluo-



Scheme 2.



Scheme 3.

romethylbenzene (**5**) under similar conditions to Run 1 has been also confirmed (Run 13).

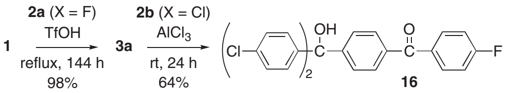
Two possible routes for the formation of **4a** from **1** are displayed in Scheme 2. In Route 1, **3a** is postulated to be yielded initially by arylation of the chlorocarbonyl group, which might be converted into **4a** by defluorinative diarylhydroxylation. In Route 2, diarylhydroxymethylbenzoyl chloride **8a** or the equivalent is assumed to be formed initially by defluorinative diarylhydroxylation of CF_3 in **1**, which might be converted into **4a** by arylation of the chlorocarbonyl moiety.

From the reaction behavior shown in Run 12, the diarylation of CF_3 is suggested to precede arylation of the chlorocarbonyl group as demonstrated in Route 2 of Scheme 2.

Besides this, Ramchandani and co-workers reported the $AlCl_3$-mediated reaction of chloro(trifluoromethyl)benzene with arenes to give diaryldichloromethanes, where the CF_3 group was postulated to transform into CCl_3 and then undergo $AlCl_3$-mediated Friedel–Crafts alkylation.[11] In a similar fashion, the CF_3 group of **1** is speculated to be converted in situ to CCl_3 by $AlCl_3$ prior to arylation as demonstrated in Scheme 3. After the dual arylation of the CF_3-carbon completes, then arylation of the chlorocarbonyl moiety of intermediate **14** is presumed to proceed smoothly, because the electrophilicity of the triphenylmethyl cation moiety is diminished due to the large steric hindrance.

Furthermore, 4-fluoro-4′-trifluoromethylbenzophenone (**3a**),[9a] the postulated intermediate of the nonadapted route for the transformation of **1** to **4a** (Scheme 2, Route 1), readily afforded **4a** in high yield by treatment with **2a** under the same reaction conditions (98% yield). This result suggests that defluorinative diarylhydroxylation of CF_3 also progresses satisfactorily after the formation of the corresponding ketone. Stepwise triarylations giving **16**, which have different kinds of aryl substituents, are also performed efficiently (Scheme 4).

These results imply that a CF_3 group on an aromatic ring can behave as a diarylhydroxymethyl group equivalent. From the viewpoint of synthetic chemistry, such behavior affords additional potential for CF_3 as a synthetic equivalent of a diarylcarbinol moiety. Moreover, control of the order of the reaction steps, i.e., whether ketone formation is undertaken before or after carbinol construction, is possible. Ready exchange of the sequence of interconversion of a CF_3 group to a diarylhydroxymethyl group and ketone formation promises the extension of the choice of routes and reactions in the design and the synthesis of polyarylated carbinol-ketone compounds. Such synthetic protocol is especially useful for introduction of bulky-polar polyarylated groups to aromatic polymeric material such as CF_3-bearing aromatic polyketones[12] which can be synthesized effectively via TfOH-mediated electrophilic aromatic aroylation.



Scheme 4.

Conclusively, CF_3 on arenes has proven to act as a chemoselective equivalent of a diarylhydroxymethyl group. The acid-mediated defluorination and triarylations of **1** giving diarylhydroxymethylated phenones chemoselectively have been revealed. In this transformation, defluorinative diarylation of CF_3 proceeds, then arylation of the chlorocarbonyl group progresses. Furthermore, diarylhydroxylation of the CF_3 group of **3a** also proceeds to give the same carbinol-ketone compounds in a sufficient conversion. As CF_3-bearing aroyl chloride **1** selectively affords the corresponding ketone **3a** with the aid of TfOH, whether ketone formation is undertaken before or after diarylhydroxymethyl group formation is controllable by the choice of acidic mediator.

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