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Catalytic fluorination of 1,3-dicarbonyl compounds using iodoarene catalysts

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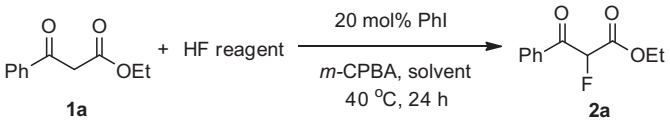
ABSTRACT

Catalytic fluorination of 1,3-dicarbonyl compounds with aqueous hydrofluoric acid proceeded efficiently with the aid of iodoarene catalysts in the presence of *m*-CPBA as a terminal oxidant. *o*-Iodotoluene, *o*-iodoanisole, and *o*-ethyliodobenzene showed a high catalytic efficiency to give 2-fluoro-1,3-dicarbonyl compounds in good yields.

Recently hypervalent iodine compounds have been used widely in organic synthesis because they have synthetically useful advantages such as mild oxidation ability and the chemical behaviors similar to transition metals.[1] In addition, due to the superleaving ability of hypervalent iodine,[2] nucleophilic substitution occurs easily under mild conditions. This unique behavior has been demonstrated in α-functionalization of carbonyl compounds.[1b] In the fluorination reaction of carbonyl compounds, *p*-(difluoroiodo)toluene was shown to be an efficient fluorinating reagent. Hara et al. reported that *p*-(difluoroiodo)toluene could be applied to the fluorination of β-ketoesters, β-ketoamides and β-diketones.[3] Recently, we reported that a convenient fluorination reaction of 1,3-dicarbonyl compounds without *p*-(difluoroiodo)toluene.[4] This method involves direct use of commercially available hydrofluoric acid and iodosylbenzene (PhIO) and does not require synthesis of *p*-(difluoroiodo)toluene or (difluoroiodo)benzene. However, this method still remains drawbacks, that is, it requires synthesis of iodosylbenzene or p-iodosyltoluene and needs a stoichiometric amount of iodosylarenes. Iodosylarenes are reasonably stable but cause a slight decomposition during long term storage. In the case of large-scale synthesis, such drawbacks may cause a serious problem. In the fluorination using hydrofluoric acid/PhIO reagent, PhIO was reduced to iodobenzene via (difluoroiodo)benzene. If the resulting PhI can be re-oxidized to PhIO in situ,[5] it can participate in the fluorination again. Namely, it is considered that PhI can serve as a catalyst for fluorination. However, to the best of our knowledge, there are no reports that fluorination proceeds

Table 1
Catalytic fluorination of **1a** with a HF reagent[a]



1a **2a**

Entry	HF reagent (mmol)	Solvent (mL)	Yield[b] (%)
1	55% HF (10 mmol)	DCM (2 mL)	51
2	55% HF (5 mmol)	DCM (2 mL)	55
3	55% HF (20 mmol)	DCM (2 mL)	45
4	55% HF (10 mmol)	DCM (4 mL)	57
5	55% HF (10 mmol)	DCE (4 mL)	72
6	55% HF (10 mmol)	DCE (5 mL)	58
7[c]	55% HF (10 mmol)	DCE (4 mL)	34
8[d]	55% HF (10 mmol)	DCE (4 mL)	64
9[e]	55% HF (10 mmol)	DCE (4 mL)	52
10	TEA·3HF (10 mmol)	DCE (4 mL)	17
11	TEA·5HF (10 mmol)	DCE (4 mL)	56
12	TEA·5HF (20 mmol)	DCE (4 mL)	69
13	HF·pyridine (10 mmol)	DCE (4 mL)	78

[a] Conditions: **1a** (1 mmol), a HF reagent, *m*-CPBA (1.5 mmol), PhI (0.2 mmol), a solvent, 40 °C, 24 h.
[b] Yields were determined by ^{1}H NMR using the integral of doublet methine proton of **2a**.
[c] *m*-CPBA (0.5 mmol) was used.
[d] *m*-CPBA (1 mmol) was used.
[e] *m*-CPBA (2 mmol) was used.

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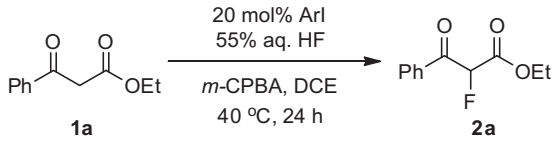
Table 2
Iodoarene-catalyzed fluorination of **1a**[a]



Entry	Iodoarene	Yield[b] (%)
1	PhI	79
2	*p*-Iodotoluene	83
3	*o*-Iodotoluene	85
4	Iodomesitylene	80
5	*p*-Iodoanisole	15
6	*m*-Iodoanisole	83
7	*o*-Iodoanisole	88
8	*o*-Ethyliodobenzene	85
9	*p*-Chloroiodobenzene	70
10	*p*-Diiodobenzene	74
11	*p*-Iodonitrobenzene	35

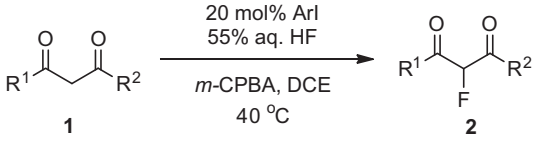
[a] Conditions: **1a** (1 mmol), 55% aqueous HF (10 mmol), *m*-CPBA (1.5 mmol), ArI (0.2 mmol), DCE (4 mL), 40 °C, 24 h.
[b] Isolated yields by column chromatography on silica gel.

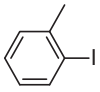
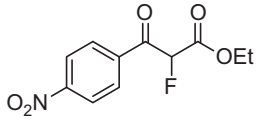
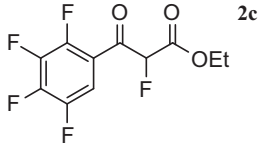
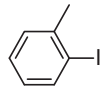
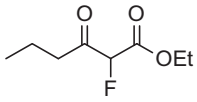
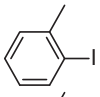
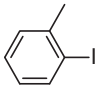
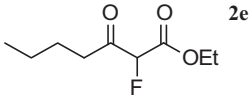
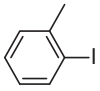
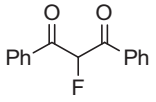
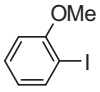
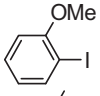
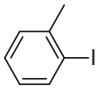
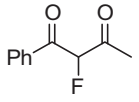
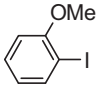
efficiently with iodobenzene catalysis. Here, we wish to report the first example of catalytic fluorination of 1,3-dicarbonyl compounds using iodoarene catalysts.

To explore the catalytic fluorination using iodoarenes as catalyst, we first optimized the reaction conditions in the fluorination reaction of ethyl benzoylacetate (**1a**) as the model substrate. Since we succeeded previously in the stoichiometric fluorination of 1,3-dicarbonyl compounds by aqueous HF with the aid of PhIO,[4] the reaction conditions similar to the stoichiometric ones were adopted. When the reaction of **1a** (1 mmol) with 55% aqueous HF (10 equiv HF) was conducted in the presence of PhI (20 mol %) as catalyst and *m*-CPBA (1.5 equiv) as oxidant in dichloromethane (DCM). The reaction at 40 °C for 24 h in DCM (2 mL) gave ethyl 2-fluorobenzoylacetate (**2a**) in 51% yield (Table 1, entry 1). Decreasing or increasing the amount of HF from 10 equiv HF resulted in a similar yield of **2a** (Table 1, entries 2 and 3). Using 4 mL of DCM slightly increased the yield to 57% (Table 1, entry 4). The reaction in dichloroethane (DCE) improved the yield to give the best result (72% yield) (Table 1, entry 5) but increasing the amount of DCE to 5 mL decreased the yield to 58% (Table 1, entry 6). By examining the amount of *m*-CPBA (0.5–2.0 equiv), the best amount of *m*-CPBA was found to be 1.5 equiv (Table 1, entries 5, 7–9). Then, we examined other HF sources such as TEA·3HF, TEA·5HF and HF·pyridine complexes (Table 1, entries 10–13). The fluorination using TEA·5HF (20 equiv) and HF·pyridine (10 equiv) gave **2a** in 69% and 78% yields, respectively. Although HF·amine complexes are also good HF sources, these complexes are much more expensive than aqueous HF. We decided that the method using HF·amine complexes was not suitable for large-scale synthesis. Therefore, we continued to examine the catalytic fluorination with aqueous HF.

Using the above optimized conditions, several iodoarenes were screened to check the catalytic efficiency. The results obtained from the fluorination of **1a** are given in Table 2. Compared with PhI (Table 2, entry 1), *p*-iodotoluene, *o*-iodotoluene, iodomesitylene, *m*-iodoanisole, *o*-iodoanisole and *o*-ethyliodobenzene served as good catalysts (Table 2, entries 2–4, 6–8). These catalysts gave **2a** in 80–88% yields. However, the presence of strong electron-withdrawing (NO_2) and electron-donating (MeO) substituents at the *para* position decreased the catalytic efficiency to afford **2a** in 15 and 35% yields, respectively (Table 2, entries 5 and 11). *p*-Chloroiodobenzene and *p*-diiodobenzene also acted as good catalysts to give **2a** in 70% and 74% yields, respectively (Table 2, entries 9 and 10).

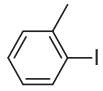
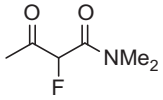
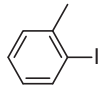
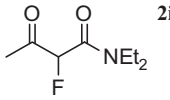
Table 3
Iodoarene-catalyzed fluorination of 1,3-dicarbonyl compounds **1**[a]



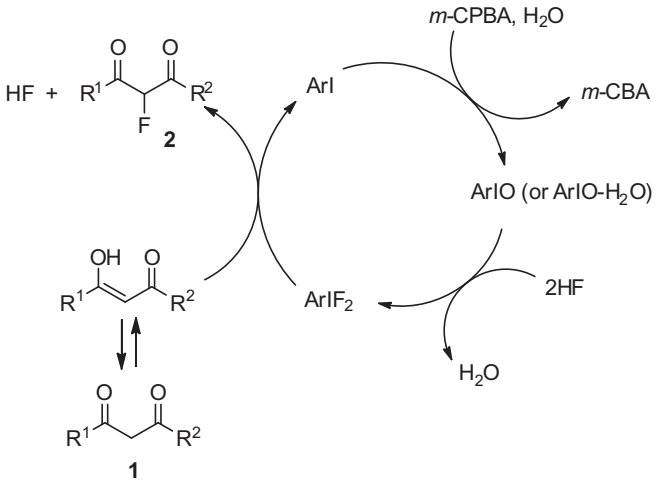
Entry	ArI	Time (h)	Product	Yield[b] (%)
1		24	 **2b**	82
2	PhI	24	 **2c**	75
3	 PhI	24	**2c**	78
4	PhI	1	 **2d**	74
5		1	**2d**	79
6		1	 **2e**	79
7		24	 **2f**	44
8		24	**2f**	50
9		24 (rt)[c]	**2f**	70
10		24	 **2g**	46
11		24	**2g**	62

(*continued on next page*)

Table 3 (*continued*)

Entry	ArI	Time (h)	Product	Yield[b] (%)
12		2	 **2h**	56
13		2	 **2i**	58

[a] Conditions: **1** (1 mmol), 55% aqueous HF (10 mmol), *m*-CPBA (1.5 mmol), ArI (0.2 mmol), DCE (4 mL), 40 °C.
[b] Isolated yields by column chromatography on silica gel.
[c] At room temperature.



Scheme 1. A proposed mechanism.

Table 3 demonstrates the scope of 1,3-dicarbonyl compounds in the iodoarene-catalyzed fluorination reaction.[6] In addition to **1a**, other β-ketoesters such as ethyl 3-(4′-nitrophenyl)-3-oxopropionate (**1b**), ethyl 3-oxo-3-(2′,3′,4′,5′-tetrafluorophenyl)propionate (**1c**), ethyl 3-oxohexanoate (**1d**) and ethyl 3-oxoheptanoate (**1e**) were fluorinated by using *o*-iodotoluene or iodobenzene as catalyst to give products **2b**–**2e** in high yields (74–82%) (Table 3, entries 1–6). In the case of dibenzoylmethane (**1f**), the catalytic fluorination with *o*-iodotoluene resulted in a moderate yield of product **2f** (Table 3, entry 7). Use of *o*-iodoanisole as catalyst slightly improved the yield of **2f** (Table 3, entry 8). In addition, lowering the reaction temperature to room temperature increased the yield of **2f** to 70% (Table 3, entry 9). Similarly, the fluorination of 1-phenyl-1,3-butanedione (**1g**), *o*-iodoanisole afforded a better yield of product **2g** than *o*-iodotoluene. The fluorination of β-ketoamides **1h** and **1i** was catalyzed by *o*-iodotoluene to give products **2h** and **2i** in 56 and 58% yields, respectively (Table 3, entries 10 and 11).

A proposed mechanism for the iodoarene-catalyzed fluorination is outlined in Scheme 1. First, an iodoarene is oxidized by *m*-CPBA to an iodosylarene which may exist as its hydrate due to the presence of water.[7] The iodosylarene is readily converted to a (difluoroiodo)arene by reaction with HF.[8] The resulting (difluoroiodo)arene then reacts with the enols of 1,3-dicarbonyl compounds **1** to give 2-fluorinated 1,3-dicarbonyl compounds **2**, with re-generation of the iodoarene catalyst.

In summary, we have demonstrated an iodoarene-catalyzed fluorination of 1,3-dicarbonyl compounds using aqueous HF as a cheap HF source and *m*-CPBA as a terminal oxidant. High catalytic efficiency of the iodoarene was observed in the cases of *o*-iodotoluene, *o*-iodoanisole and *o*-ethyliodobenzene. The catalytic fluorination reduces the drawbacks caused by the stoichiometric reaction with iodosylarenes. As compared with other expensive HF sauces, use of aqueous HF has a merit in cost performance, and it is also suitable for large-scale synthesis.

Acknowledgment

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6. *General procedure for catalytic fluorination of* ***2****:* In a PFA test tube were added ArI (0.2 mmol), 55% aqueous HF (0.64 mL, 10 mmol HF), *m*-CPBA (1.5 mmol) and DCE (4 mL). After stirring for 15 min at room temperature, **1** (1 mmol) was added and then the mixture was stirred at 40 °C for the time given in Table 3. After neutralizing the reaction mixture with aqueous $NaHCO_3$ the product was extracted with CH_2Cl_2 (6 mL × 3). The combined organic layer was washed with saturated NaCl and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the product was isolated by column chromatography on silica gel with EtOAc/hexane. All products **2** were identified on the basis of the spectra of the authentic samples or the reported data.[4]
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