

Nucleophilic acylation of arylfluorides catalyzed by imidazolidenyl carbene

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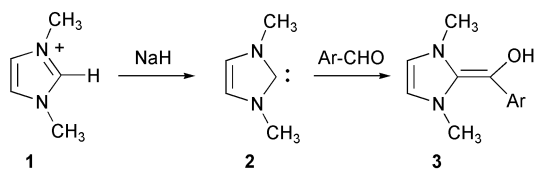
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Imidazolidenyl carbene catalyzes nucleophilic acylation reaction of arylfluorides with electron withdrawing groups to give benzophenone derivatives.

Nucleophilic aromatic substitution is an important process in synthetic aromatic chemistry.¹ As for substitution by carbon nucleophiles, one of the most significant examples is the vicarious nucleophilic substitution of hydrogen.² Displacement of methoxy group by organometallics is a convenient route to alkylate arenes.³ The organometallic complexes with the methoxy and the *ortho*-activating group to facilitate the substitution reaction. In contrast to these examples, nucleophilic aromatic substitutions of halogen atoms by carbanions are less common,^{1,2} as halonitroarenes often react with carbanions by electron-transfer processes^{2,4} or intra- or intermolecular redox processes.^{2,5}

We have previously reported the nucleophilic aromatic substitutions of haloheteroarenes to afford aroylheteroarenes.⁶ This reaction proceeds by the catalytic action of imidazolidenyl carbene **2**. **2** and aromatic aldehyde form the intermediate **3** known as an 'activate aldehyde',⁷ which is an 'aroyl anion equivalent'. **3** behaves as a carbon nucleophile, and its addition to heteroarenes at the carbon-bearing halogen, followed by elimination of halogen and **2**, results in nucleophilic acylation (Scheme 1).

Herein we report the first example of nucleophilic acylation of nitrobenzenes. In refluxing THF, 4-fluoronitrobenzene (**4**) was found to react with benzaldehyde (**5a**) in the presence of 1,3-dimethylimidazolium iodide (**1**) and sodium hydride to afford 4-nitrobenzophenone in 47% yield (Table 1). In DMF at 0 °C, the yield increased to 57%.[†] Under the same conditions in DMF, the reaction of **4** with 4-chlorobenzaldehydes (**5b**), 4-anisaldehyde (**5c**), 3-fluorobenzaldehyde (**5d**), and 2-fluor-



Scheme 1

Table 1 Acylation of 4-fluoronitrobenzene (**4**)

Ar	Solvent	Yield (%)
Ph	a	46
Ph	a	57
4-ClC ₆ H ₅	b	61
4-MeOC ₆ H ₅	c	77
3-FC ₆ H ₅	d	63
2-FC ₆ H ₅	e	49

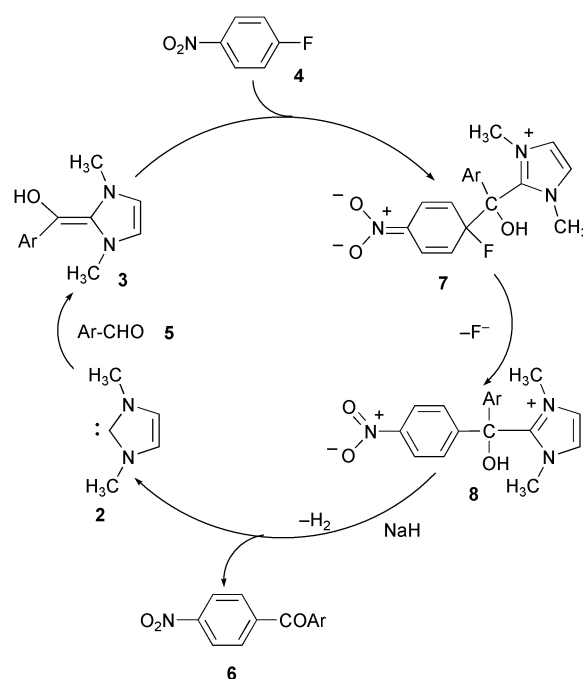
^a Conditions: reflux, 1 h. ^b Conditions: 0 °C, 1 h.

obenzaldehyde (**5e**) gave the corresponding benzophenones **6a–e** in good to moderate yields. It is well known that fluoride is often a better leaving group than the other halogens in nucleophilic aromatic substitution.⁸ The attempt at nucleophilic acylation of 4-chloronitrobenzene ended in the recovery of starting materials both in refluxing THF and in DMF at 0 °C.

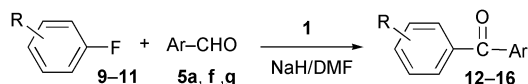
The reaction mechanism of the acylation of **4** is considered to be as shown in Scheme 2. The intermediate **3** adds to the carbon atom bearing fluorine, followed by loss of the fluorine as an anion. Base-promoted elimination of a proton and **2** from the tetrahedral intermediate **8** takes place to afford **6**. **2** is then recycled as a catalyst.

The acylation of other fluoroarenes with electron-withdrawing groups was also examined (Table 2). The reaction of 4-cyanofluorobenzene (**9**) and 4-fluorobenzophenone (**10**) with **5a** gave 4-cyanobenzophenone (**12**) and 4-benzoylbenzophenone (**13**), respectively, but the yields were poor. The reaction of 3,4-difluoronitrobenzene (**11**) with **5a**, 3-chlorobenzaldehyde (**5f**), and 3-methoxybenzaldehyde (**5g**) afforded the corresponding benzophenones **14–16** in good yield.

In conclusion, we succeeded in carrying out the nucleophilic acylation of fluoroarenes with electron-attracting groups. The reaction proceeds by the catalytic action of imidazolidenyl carbene, and the substitution occurs *via* an addition–elimination mechanism. It is impossible to directly introduce acyl groups to electron-deficient positions of benzene rings with 'ordinal' reactions such as the Friedel–Crafts reaction. As such, the acylation reaction using imidazolidenyl carbene as a catalyst is



Scheme 2 Reaction mechanism of acylation of 4-fluoronitrobenzene (**4**).

Table 2 Benzoylation of fluoroarenes

R	Fluoroarene	Ar	Aldehyde	Reaction conditions	Products	Yield (%)
4-CN	9	Ph	5a	0 °C, 20 min. and then r.t., 2 h	12	37
4-C ₆ H ₅ CO	10	Ph	5a	0 °C, 20 min. and then r.t., 2 h	13	32
2-F-4-NO ₂	11	Ph	5a	0 °C, 1.5 h	14	75
2-F-4-NO ₂	11	3-ClC ₆ H ₅	5f	0 °C, 1.5 h	15	56
2-F-4-NO ₂	11	3-MeOC ₆ H ₅	5g	-15 °C, 30 min. and then r.t., overnight	16	60

a useful method for introducing acyl groups to arenes with electron-deficient substituents.

Notes and references

† Procedure for nucleophilic acylation of **4**: sodium hydride (160 mg, 4 mmol) was added to a mixture of **4** (423 mg, 3 mmol), **5a** (382 mg, 3.6 mmol), and **1** (224 mg, 1 mmol) in DMF (20 ml). The mixture was stirred at 0 °C for 1 hour and then poured into ice-water. The product was extracted with ethyl acetate, washed with water and brine, and dried over Na₂SO₄. The combined organic layers were concentrated, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give **6a** (386 mg, 57 %). Recrystallization of the crude product from methanol yielded crystals of **6a** as slightly orange needles. Mp. 136–137 °C (lit.,⁹ 138 °C).

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