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Nucleophilic acylation of arylfluorides catalyzed by imidazolidenyl carbene

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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]

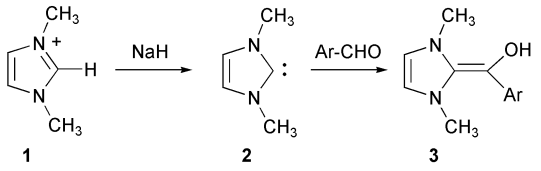
We have previously reported the nucleophilic aromatic substitutions of haloheteroarenes to afford aroylheteroarenes.[6] This reaction proceeds by the catalytic action of imidazolidenyl carbene **2**. **2** and aromatic aldehyde form the intermediate **3** known as an 'activate aldehyde',[7] which is 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-fluorobenzaldehyde (**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-chlorobenzaldehye (**5f**), and 3-methoxybenzaldehyde (**5g**) afforded the corresponding benzophenones **14**–**16** in good yield.

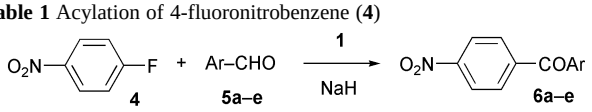
In conclusion, we succeeded in carrying out the nucleophilic acylation of fluorobenzenes with electron-attracting groups. The reaction proceeds by the catalytic action of imidazolidenyl carbene, and the substitution occurs *via* an addition–elimination mechanism. It is impossible to directly introduce 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



1 **2** **3**

Scheme 1

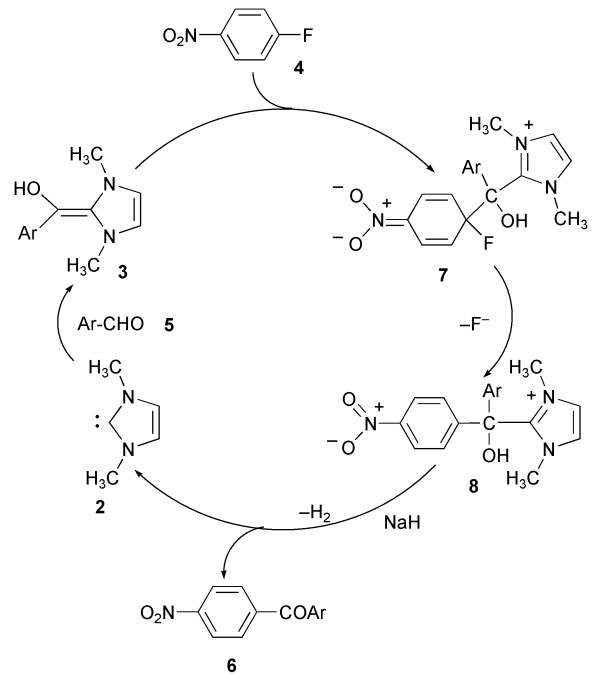
Table 1 Acylation of 4-fluoronitrobenzene (**4**)



4 **5a–e** **6a–e**

Ar		Solvent	Yield (%)
Ph	**a**	THF[a]	46
Ph	**a**	DMF[b]	57
4-ClC_6H_5	**b**	DMF[b]	61
4-$MeOC_6H_5$	**c**	DMF[b]	77
3-FC_6H_5	**d**	DMF[b]	63
2-FC_6H_5	**e**	DMF[b]	49

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



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

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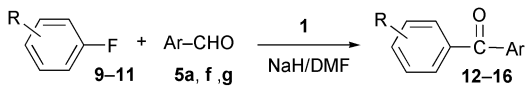
Table 2 Benzoylation of fluoroarenes



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_6H_5CO	**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_6H_5	**5f**	0 °C, 1.5 h	**15**	56
2-F-4-NO_2	**11**	3-$MeOC_6H_5$	**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 Na_2SO_4. 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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