Denitrogenative hydrofluorination of aromatic aldehyde hydrazones using (difluoriodio)toluene†

Kaivalya G. Kulkarni, Boris Miokovic, Matthew Sauder and Graham K. Murphy*

An operationally simple conversion of aromatic aldehyde hydrazones to monofluoromethylated amines is reported. The hypervalent iodine reagent TolIF2 serves as an oxidant, converting the hydrazone to the corresponding diazo compounds. The by-product of the oxidation process, HF, is consumed in situ by a denitrogenative hydrofluorination reaction of the diazo group.

Introduction

There is only a handful of naturally occurring fluorocarbons, so fluorine’s use in medicinal chemistry might never have come to pass had chemists limited themselves to naturally-inspired pharmaceuticals.1 As fluorine is small, univalent and makes very strong bonds to carbon, it is now routinely employed as a biostere for hydrogen.2 Over the past few decades, site-specific fluorination has become an essential tool for medicinal chemists due to fluorine’s ability to act as a biostere, and because of its desirable effects on the lipophilicity, metabolic stability and bioavailability of pharmaceutical and agrochemical agents.3

Given the breadth of biologically active fluorinated compounds,4 the development of new fluorination strategies and reagents remains an important field of research.5 As a complement to nucleophilic fluorination strategies, a large body of research developing electrophilic fluorinating reagents has been completed. While elemental fluorine is the simplest and most direct source of electrophilic fluorine, it is toxic, explosively reactive with organic compounds, and cannot be used without specialized laboratory equipment. To mitigate fluorine’s reactivity, chemists have synthesized designer electrophilic fluorinating reagents based on N–F,6 S–F,7 and I–F bonds8,9 (Fig. 1). However, contrary to the N–F reagents (1–3) that serve as sources of electrophilic “F−”, the S–F and I–F compounds (4–8) have umpolung reactivity: attack of the hypervalent sulphur or iodine atom by a Lewis base expels fluoride, and generates an electrophilic adduct to be displaced by the fluoride anion.

Benzylic fluorides, represented by the ArCH2F, ArCF2H and ArCF3 groups,10 are common synthetic targets and strategies towards the ArCH2F and ArCF3H functional groups have received considerable attention in the literature.9a/11 General strategies towards their synthesis include deoxygenative fluorination of benzyl alcohol (using 4–6),12 substitution reactions of benzyl halides,13 metal-catalyzed cross-coupling of fluorine-containing units,14–16 or radical-based fluorination reactions.15 The ArCH2F group might also be synthesized by the hydrofluorination reaction of diazo compounds, simply by treating them with HF sources (Et3N·3HF, Py·HF, HBF4, etc.).16 This reaction is highly effective for stabilized diazo compounds (e.g. flanked by two Ar, carbonyl, CF3 groups); however, the aryldiazomethanes required to synthesize benzylic mono-fluorides are unstable, rarely isolable, and cannot easily serve as hydrofluorination precursors. Nonetheless, development of this methodology could offer a mild, rapid and metal-free approach to benzylic monofluorides from simple starting materials.

Recently Yadav and co-workers reported a novel reaction where tosylhydrazone derivatives of aromatic aldehydes were converted to diazo intermediates in situ, and then treated with Et,N·3HF to produce hydrofluorination products 10 (Fig. 2a).17 In an earlier study, Myers reported the oxidation of TBS-hydrazones to aryldiazomethanes using (difluoriodio)benzene, and their subsequent hydroacylation with carboxylic acids (Fig. 2b).18 By combining these two concepts, we have...
developed the first synthesis of benzyl fluorides where the hypervalent iodine reagent, TolIF₂, acts as both an oxidant and as the fluoride source, and gives 10 under mild and operationally simple reaction conditions (Fig. 2c).

Results and discussion

Our studies of halogenation reactions using PhICl₂ or TolIF₂ as halogen sources have led to the gem-dihalogenation of diazocarbonyl compounds¹⁹ and the oxidative dichlorination of isatin-3-hydrazones.²⁰ The gem-difluorination reactions of diazoesters proceeded best using Lewis acid activation of TolIF₂ with BF₃·OEt₂ or borosilicate glass²¹ (eqn (1)). Similarly, the oxidative difluorination reactions of benzaldehyde hydrazone 13a proceeded best with TiF₃ activation of the iodane (eqn (2)).²² During these latter studies, we observed for the first time traces of hydrofluorination by-product 10a, which we attributed to the HF generated during the oxidation³³ competing with TolIF₂ as an electrophilic partner for the diazo intermediate. We believed that this intermediate could be induced to react preferentially to give 10a through chemoselectivity-guided modification of the reaction conditions.

Due to the increased stability of the putative diazo intermediate, hydrazone 13a was used as our model substrate during the reaction optimization. We first studied the effects of Lewis acid activators on the reaction, in both laboratory glassware and PFA vials, using the optimal conditions previously determined in our gem-difluorination reactions.¹⁹,²¹,²² 

Treating 13a with TolIF₂ and 1 mol% BF₃·OEt₂ generally failed in both types of reaction vessel, and gave aldehyde 17a as the major product (Table 1, entries 1 and 2). The reactions were repeated using TiF₃ as the activator, and while the reaction in glassware was very low yielding, the reaction in PFA gave 10a in 48% yield, along with 25% of aldehyde 17a (Table 1, entries 3 and 4). The experiment conducted in glassware without a Lewis acidic activator was also very low yielding,²¹ but the analogous reaction in a PFA vial proceeded in 47% yield (Table 1, entries 5 and 6).

Mass spectrometry analysis of the crude reaction mixtures of these preliminary trials revealed the occasional occurrence of a hydrofluorinated dimerization product. To preclude dimer

<table>
<thead>
<tr>
<th>Entry</th>
<th>Vessel</th>
<th>TolIF₂ (equiv.)</th>
<th>Additive (mol%)</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Yield¹⁰a</th>
<th>Yield¹⁰a</th>
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¹ Isolated yields. ² Reaction carried out in a borosilicate round bottom flask. ³ Reaction carried out in a 4 mL PFA vial. ⁴ Reverse addition of hydrazone to TolIF₂.
formation by minimizing the concentration of substrate relative to electrophile, the two most promising trial reactions (entries 4 and 6) were repeated using reverse addition of the hydrazone. The reaction using TiF₃ was unchanged (entry 7), but the reaction without a Lewis acid activator gave 10a in 60% yield (entry 8). These two trials (entries 6 and 8) were our first examples of fluorination reactions occurring in a PFA vessel in the absence of a Lewis-acidic activator. Presumably this is due to TolIF₂ acting solely as an oxidant, instead of as an electrophilic fluorine source, for which Lewis acid activation is unnecessary.¹⁸ We completed our reaction optimization by varying the loading of the TolIF₂ (entries 9–11). While the production of the aldehyde by-product 17a was unchanged with increasing TolIF₂ loading, the amount of benzyl difluoride (16a) increased with increasing TolIF₂ loading. This is consistent with our expectation that the gem-difluorination reaction should compete with hydrofluorination in the presence of excess TolIF₂. The highest yield (74%) of the desired benzyl fluoride 10a was achieved when 1.7 equivalents of iodane was used.

Having demonstrated that benzaldehyde hydrazones could be induced to react preferentially via the denitrogenative hydrofluorination reaction, we next investigated the reaction efficacy on a variety of substituted benzaldehyde hydrazone derivatives (Scheme 1). The para-, meta- and ortho-nitro substituted substrates all performed well, as did the di-substituted derivatives having a meta-NO₂ substituent, giving the products 10a–e in 51–74% yield. The para-cyano and para- or meta-cyano substituted benzyl fluorides (10f–l) were isolated in good yield, as were the benzyl fluorides of the para-tosylate, para-phenyl and 3,4-dichloro substrates (10i–k). The para-methoxy and para-dimethylamino benzaldehyde hydrazones substrates were consumed by the action of TolIF₂; however, no traces of the benzyl fluorides (10l,m) were observed. Interestingly, when the electron-releasing –O Me functional group was in the meta-position, the hydrofluorination reaction gave 10n in 45% NMR yield, and 33% isolated yield. Presuming the volatility of 10n to be problematic, we investigated the bulkier substrates 13o and 13p, which also possessed electron releasing –O Bn and –O Me groups in their respective meta-positions, and in both cases, the products 10o,p were recovered in moderate yield.²⁴ These experiments indicate that substrates bearing electron-neutral or electron-withdrawing substituents are well-tolerated in the hydrofluorination reaction. And while substrates with electron-releasing substituents at the para-position were not compatible, substrates with the same electron-donating groups in the meta-position were moderately effective in the reaction. We attribute this trend to the destabilizing effect of electron-donating groups on the aryldiazomethane intermediates, and the decreased stability of the benzyl fluoride products that bear an electron-donating group at the para-position. Our experimental observations, coupled with the unlikelihood of free carbene formation at this low reaction temperature, led us to propose an ionic mechanism for the oxidative hydrofluorination reaction (Fig. 3). Upon oxidation of hydrazone 13 to aryldiazomethane intermediate A, iodotoluene and HF (excess) would be generated as by-products. Protonation of the diazo group would give diazonium ion B, from which N₂ gas could be expelled upon fluoride attack, leading to benzyl fluoride 10.

**Scheme 1** Denitrogenative hydrofluorination of benzaldehyde hydrazone derivatives.

**Fig. 3** Plausible mechanistic pathway for the conversion of hydrazones to benzylic fluorides.

**Conclusions**

In conclusion, we have developed the first use of a hypervalent iodine reagent (TolIF₂) as both an oxidant and source of fluorine in the hydrofluorination of aromatic aldehyde hydrazones. The one-pot reaction made use of the oxidative potential of the iodane, converting the hydrazone to a diazo group, and generated an excess of the HF by-product which was consumed by a denitrogenative hydrofluorination reaction. The reaction proceeded best with electron-neutral or withdrawing substituents, and failed with electron-donating groups capable of destabilizing the diazo intermediate. This reaction is a mild, rapid, metal-free and operationally simple alternative to other deoxygenating fluorinating strategies in the synthesis of benzyl fluorides. Further exploration of this reaction, including...
expanding the substrate and functional group scope, is under-
way and will be disclosed in due course.

**Experimental**

A 4 mL PFA vial containing [difluoroiodo]toluene (1.7 equiv.)
was placed under nitrogen and immersed in a pre-heated
40 °C bath. To this was added a pre-made solution of hydra-
zone 13a (50 mg, 1.0 equiv.) in CH2Cl2 (1.5 mL) via a syringe
pump over ~10 minutes. The reaction was monitored by TLC
analysis, and upon consumption of the hydrazone (5–10 min),
the reaction mixture was cooled to RT and concentrated by
rotary evaporation. The resulting crude reaction mixture was
purified by flash silica gel chromatography (10% EtOAc in
hexanes) to provide benzyl fluoride 10a (35 mg) in 74% yield.

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24 Hydrazones of 1-naphthaldehyde, pentafluorobenzaldehyde and 3-bromo-4-methoxybenzaldehyde were also effective in the reaction, proceeding in 40–50% NMR yield. The products were not sufficiently purified to determine isolated yields.