Nucleophilic fluorination of β-ketoester derivatives with HBF₄

Raffaele Pasceri, Hannah E. Bartrum, Christopher J. Hayes* and Christopher J. Moody*

Received 5th October 2012, Accepted 5th November 2012
DOI: 10.1039/c2cc37284c

Treating readily available α-diazo-β-ketoesters with HBF₄ results in nucleophilic fluorination by the usually inert and stable tetrafluoroborate anion. The resulting α-fluoro-β-ketoesters are highly versatile synthetic intermediates, for example in the preparation of fluoro-heterocycles, as illustrated by the direct formation of versatile synthetic intermediates, for example in the preparation of fluoro-pyrimidines, -pyrazoles and -coumarins in a single step.

Although fluorine-containing compounds are extremely rare as natural products, an increasing number of synthetic bioactive pharmaceuticals and agrochemicals contain fluorine.1–4 As a consequence, a number of methods have been developed for the introduction of fluorine into molecules by the formation of carbon–fluorine bonds,5 most commonly involving fluorination, often of aromatic rings, using electrophilic reagents that ultimately derive from elemental fluorine. A complementary approach would involve the use of nucleophilic fluorination, and indeed some very recent methods do employ fluoride.6–10 We now report the development of methodology that is simple to carry out, does not involve the use of exotic reagents or catalysts, but delivers versatile α-fluoro-β-ketoester intermediates. Most importantly it uses nucleophilic fluorination with a benign source of fluoride, HBF₄, to form the C–F bond, in a remarkable reaction given the perceived inertness and stability of the tetrafluoroborate anion, representing a new alternative to existing fluorination methodologies.

Reasoning that the use of relatively unreactive sources of nucleophilic fluoride would require the participation of a reactive carbon electrophile, we were drawn to the possibility of using carbene or metal carbene species. Such intermediates are easily derived from readily available diazocarbonyl compounds, exhibit wide ranging reactivity and versatility, and have found extensive application in organic synthesis,11 and whilst diazoesters are known to be available by electrophilic fluorination of β-ketoesters using, for example, elemental fluorine or 55% aqueous HF/PhIO,12,16 our focus remained on nucleophilic fluorination. A range of conditions was screened (Table 1) starting with rhodium or copper mediated reactions of the diazoester 1a in the presence of a variety of sources of fluoride (Table 1, entries 1–7). Unfortunately such transition-metal catalyzed reactions were unsuccessful with no evidence for the formation of the desired α-fluoro-β-ketoester 2a. Instead the reactions generally resulted in return of starting material 1a, together with general decomposition and formation of ethyl phenylacetate formed by Wolff rearrangement, reaction with adventitious water and subsequent decarboxylation. Therefore we turned our attention to acid mediated processes.

<table>
<thead>
<tr>
<th>Entry</th>
<th>F source</th>
<th>Conditions</th>
<th>Yield 2a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KF</td>
<td>Cat. Rh₂(OAc)₄, CH₂Cl₂, rt, 24 h</td>
<td>a</td>
</tr>
<tr>
<td>2</td>
<td>CsF</td>
<td>Cat. Rh₂(OAc)₄, CH₂Cl₂, rt, 24 h</td>
<td>a</td>
</tr>
<tr>
<td>3</td>
<td>CsF</td>
<td>Cat. Rh₂(OAc)₄, toluene, 110 °C, 24 h</td>
<td>a</td>
</tr>
<tr>
<td>4</td>
<td>TBAF</td>
<td>Cat. Rh₂(OAc)₄, THF/CH₂Cl₂, 0 °C</td>
<td>a</td>
</tr>
<tr>
<td>5</td>
<td>KF</td>
<td>Cat. Cu(OTf)₂, CH₂Cl₂, rt, 24 h</td>
<td>a</td>
</tr>
<tr>
<td>6</td>
<td>CsF</td>
<td>Cat. Cu(OTf)₂, toluene, 110 °C, 24 h</td>
<td>a</td>
</tr>
<tr>
<td>7</td>
<td>CsF</td>
<td>Cat. Cu(OCCF₃)₂, toluene, 110 °C, 24 h</td>
<td>b</td>
</tr>
<tr>
<td>8</td>
<td>HFPyr</td>
<td>Ether, 0 °C to rt, 24 h</td>
<td>c</td>
</tr>
<tr>
<td>9</td>
<td>BF₃OEt₂</td>
<td>Ether, rt, 24 h</td>
<td>25</td>
</tr>
<tr>
<td>10</td>
<td>BF₃OEt₂</td>
<td>CH₂Cl₂, rt, 24 h</td>
<td>45</td>
</tr>
<tr>
<td>11</td>
<td>BF₃OEt₂</td>
<td>CH₂Cl₂, 99 °C, 10 min, in flow</td>
<td>50</td>
</tr>
<tr>
<td>12</td>
<td>HBF₄OEt₂</td>
<td>CH₂Cl₂, rt, 5 h</td>
<td>82</td>
</tr>
<tr>
<td>13</td>
<td>HBF₄OEt₂</td>
<td>CH₂Cl₂, 70 °C, 10 min, in flow</td>
<td>84</td>
</tr>
</tbody>
</table>

† Mixture of 1a plus decomposition. a Mixture of 1a plus Wolff rearrangement product, PhCH₂CO₂Et. c No reaction.

School of Chemistry, University of Nottingham, University Park, Nottingham, NG7 2RD, UK. E-mail: chris.hayes@nottingham.ac.uk, c.j.moody@nottingham.ac.uk

Electronic supplementary information (ESI) available: Full experimental details and copies of ¹H and ¹³C NMR spectra for all compounds. See DOI: 10.1039/c2cc37284c
Since a few examples of fluorination of 2-diazoketones (such as diazoacetophenone, PhCOCH=NH2) with pyridinium poly(hydrogen fluoride) (Olah's reagent) have been reported,\textsuperscript{17} the reaction of the diazoketone 1a with Olah's reagent was investigated (Table 1, entry 8). However, this resulted in no reaction; presumably the diazo compound 1a, stabilized by two carbonyl groups, is less reactive towards HF than simple diazoketones. We next investigated the Lewis acid boron trifluoride ethereal since it is known to catalyze insertion reactions of diazocarbonyl compounds.\textsuperscript{11} We were further encouraged down this route by early work from Hooz who showed that diazo compounds react readily with borane reagents,\textsuperscript{18} in particular the reaction of 2-diazoketones with alkylidichloroboranes that resulted in chloride migration from boron to give 2-chloroketones, in competition with alkyl group migration.\textsuperscript{19} Thus we reasoned that use of boron trifluoride would result in fluoride migration to give 2-fluorocarbonyl compounds.\textsuperscript{20} In the event, treatment of the diazo compound 1a with boron trifluoride ethereal in ether or CH$_2$Cl$_2$ did result in the formation of the desired 2-fluoro-2-ketoster 2a in modest yield (Table 1, entries 9 and 10). Considering the likely mechanism of the process based on the proposal by Hooz and Brown (Scheme 1), we reasoned that the intermediate boron enolate requires protonation by an additional Bronsted acid to give the final product. Hence we decided to explore the use of HBF$_4$ in this transformation as it combines the components of both BF$_3$ and HF, and were delighted to find that the 2-fluoro-2-ketoster 2a was isolated in 82% yield after 5 h (Table 1, entry 12).

Since diazo compounds can be easily generated and handled in flow conditions thereby reducing the hazards,\textsuperscript{13,21–23} we showed that the fluorination reaction also proceeded readily in a flow reactor to give 2-fluoro-2-ketoster 2a in 84% yield. These conditions also avoid the handling of possibly hazardous 2-fluorocarbonyl compounds.

These optimized conditions employing HBF$_4$ were readily extended to heteroaromatic 2-ketesters 1b and 1c that gave the corresponding 2-fluoro-2-ketesters 2b and 2c in 61 and 76% yield respectively. Extension to alkyl 2-ketosteres 1d and 1e gave the 2-fluoro-2-ketesters 2d and 2e in reasonable yield (Scheme 2), with the corresponding 2-bifluoro-2-hydroxysteres, RCF$_2$CHOHCO$_2$Et, being isolated as by products in 21 and 16% yield respectively. The byproducts are presumably formed by carbene O–H insertion into adventitious water, followed by conjugate addition of fluoride to the enol tautomer, dehydration and a second addition of fluoride.

2-Ketesteres are versatile intermediates in organic chemistry, widely used in the construction of heterocycles. Given that a large number of modern medicines and agrochemicals contain one or more heterocyclic ring, there is a huge demand for fluorinated heterocycles. Unfortunately, with few exceptions,\textsuperscript{6–8} the methods developed for the fluorination of benzene derivatives are not readily applicable to the fluorination of heteroaromatic rings. The methods that do exist normally rely on electrophilic fluorination of preformed heterocyclic rings using reagents that ultimately derive from elemental fluorine.\textsuperscript{5,7,24,25} Hence, using 2-fluoro-2-ketesteres 2, obtained by nucleophilic fluorination, as precursors might be a versatile alternative approach to a range of fluorinated heterocycles. This is illustrated by the preparation of fluoro-pyrimidines, -pyrazoles and -coumarins.

For the efficient construction of a diverse range of fluorine-containing heterocyclic rings from the 2-fluoro-2-ketosteres 2, we only considered those conversions that proceeded in a single step leading to heterocycles with medicinal potential. Thus reaction with resorcinols in trifluoroacetic acid\textsuperscript{26} gave the 3-fluorocoumarins 3 in good yield (Scheme 3). Likewise reaction with hydrazine or methylhydrazine\textsuperscript{15,27} gave the 4-fluoro-5-hydroxypyrazoles 4 in modest – good yield (Scheme 3), with the hydroxypyrazole tautomer presumably being stabilized over the pyrazolone form by hydrogen bonding to the adjacent fluorine atom. Recently 4-fluoropyrazoles have attracted some attention because of their role as biologically active compounds,\textsuperscript{28,29} although their preparation has involved electrophilic fluorination. As the pyrimidine heterocycle is an important core structure in a range of biologically active molecules,\textsuperscript{30,31} we next investigated the formation of fluorinated-pyrimidinols from 2-fluoro-2-keto esters. The reaction was simply achieved by adding an amide hydrochloride and DBU in EtOH in a modification of a literature procedure,\textsuperscript{32} and gave a range of novel 5-fluoropyrimidinols 5a–5h in moderate to excellent yields (63–95%) (Scheme 3). Although all of the above reactions were carried out on isolated and purified 2-fluoro-2-keto esters 2, the whole process can be telescoped.

**Scheme 1** Proposed mechanism for nucleophilic fluorination of 2-diazoketones with BF$_3$; with HBF$_4$, the reaction can be initiated by protonation.

**Scheme 2** Compounds: a, R = Ph (82%; 84% in flow); b, R = 2-furyl (61%; 59% in flow); c, R = 2-thienyl (76%); d, R = PhCH$_2$CH$_2$ (51%); e, R = cyclohexyl (61%).
into a single operation obviating the need to isolate the α-fluoro-β-keto ester. Thus the β-diazo-β-keto ester 1a was treated with tetrafluoroboric acid etherate in dichloromethane and DBU were added sequentially to give 5-fluoro-2-methyl-6-

Scheme 3 α-Fluoro-β-keto esters in the synthesis of 3-fluorocoumarins, 4-fluoropyrazoles, and 5-fluoropyrimidin-4-ols.

Notes and references

2 At present ca. 20% of marketed medicines and ca. 30% of agrochemicals contain at least one fluorine atom (ref. 3). The trend towards fluorinated bioactives continues: in 2011, three out of the 10 top-selling drugs contained fluoride, as did seven out the 35 newly approved drugs in that year (ref. 4).
10 There are examples of fluorination by halide exchange. However this requires the starting halogen-arene or -heterene to be (a) sufficiently activated to SN2Ar reaction, and (b) readily synthetically accessible.