ChemComm

Cite this: *Chem. Commun.*, 2012, **48**, 12077–12079

www.rsc.org/chemcomm

COMMUNICATION

Nucleophilic fluorination of β-ketoester derivatives with HBF_4†

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

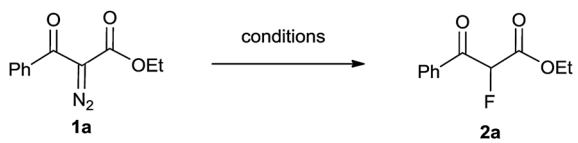
Treating readily available α-diazo-β-ketoesters with HBF_4 results in nucleophilic fluorination by the usually inert and stable tetrafluoroborate anion. The resulting α-fluoro-β-ketoesters are highly versatile synthetic intermediates, for example in the preparation of fluoro-heterocycles, as illustrated by the direct formation of 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, HBF_4, 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 diazo compounds are often viewed as hazardous, α-diazo-β-ketoesters are easier to handle than elemental fluorine, for example. Upon treatment with transition metal catalysts (*e.g.* those based on the dirhodium(II) framework), or with Bronsted or Lewis acids, such α-diazocarbonyl compounds generate highly electrophilic reactive intermediates that can react with a wide range of nucleophiles. For example, reactions with OH and NH nucleophiles have been exploited in O–H and N–H insertion processes leading to useful α-alkoxy and α-amino acid derivatives.[12,13] Hence the question was whether, under appropriate conditions, fluoride would function similarly as a nucleophile to give α-fluorocarbonyl compounds that could be utilized in synthesis.[14]

Initial experiments were carried out on ethyl 2-diazo-3-oxo-3-phenylpropanoate **1a** to identify suitable conditions for the formation of the α-fluoro-β-ketoester **2a**. Although such α-fluoro-β-ketoesters are known to be available by electrophilic fluorination of β-ketoesters using, for example, elemental fluorine or 55% aqueous HF/PhIO,[15,16] 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 1 Screening conditions for nucleophilic fluorination of ethyl 2-diazo-3-oxo-3-phenylpropanoate



1a **2a**

Entry	F source	Conditions	Yield **2a** (%)
1	KF	Cat. $Rh_2(OAc)_4$, CH_2Cl_2, rt, 24 h	[a]
2	CsF	Cat. $Rh_2(OAc)_4$, CH_2Cl_2, rt, 24 h	[a]
3	CsF	Cat. $Rh_2(OAc)_4$, toluene, 110 °C, 24 h	[b]
4	TBAF	Cat. $Rh_2(OAc)_4$, THF/CH_2Cl_2, 0 °C to rt, 24 h	[a]
5	KF	Cat. $Cu(OTf)_2$, CH_2Cl_2, rt, 24 h	[a]
6	CsF	Cat. $Cu(OTf)_2$, toluene, 110 °C, 24 h	[b]
7	CsF	Cat. $Cu(OCOCF_3)_2$, toluene, 110 °C, 24 h	[b]
8	HF·pyr	Ether, 0 °C to rt, 24 h	[c]
9	$BF_3{\cdot}OEt_2$	Ether, rt, 24 h	25
10	$BF_3{\cdot}OEt_2$	CH_2Cl_2, rt, 24 h	45
11	$BF_3{\cdot}OEt_2$	CH_2Cl_2, 99 °C, 10 min, in flow	50
12	$HBF_4{\cdot}OEt_2$	CH_2Cl_2, rt, 5 h	82
13	$HBF_4{\cdot}OEt_2$	CH_2Cl_2, 70 °C, 10 min, in flow	84

[a] Mixture of **1a** plus decomposition. [b] Mixture of **1a** plus Wolff rearrangement product, $PhCH_2CO_2Et$. [c] No reaction.

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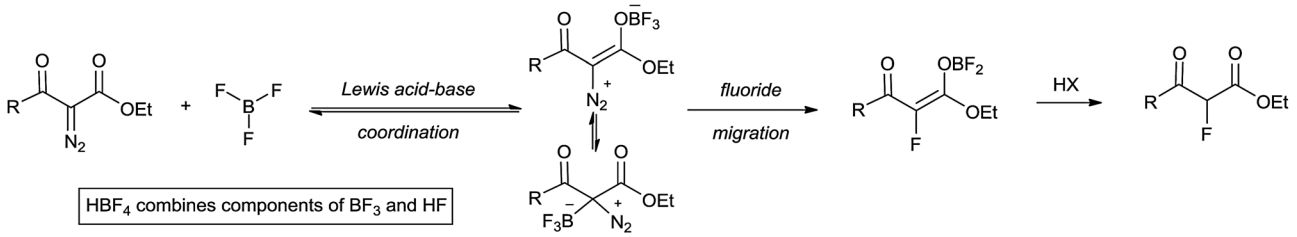
† Electronic supplementary information (ESI) available: Full experimental details and copies of ^1H and ^{13}C NMR spectra for all compounds. See DOI: 10.1039/c2cc37284c



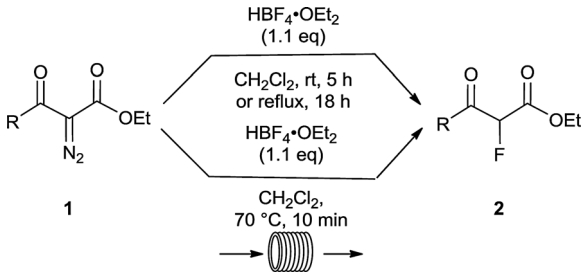
Scheme 1 Proposed mechanism for nucleophilic fluorination of α-diazo-β-ketoesters with BF_3; with HBF_4, the reaction can be initiated by protonation.

Since a few examples of fluorination of α-diazoketones (such as diazoacetophenone, $PhCOCH{=}N_2$) with pyridinium poly(hydrogen fluoride) (Olah's reagent) have been reported,[17] the reaction of the diazoester **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 etherate since it is known to catalyze insertion reactions of diazocarbonyl compounds.[11] We were further encouraged down this route by early work from Hooz who showed that diazo compounds react readily with borane reagents,[18] in particular the reaction of α-diazoesters with alkyldichloroboranes that resulted in chloride migration from boron to give α-chloroesters, in competition with alkyl group migration.[19] Thus we reasoned that use of boron trifluoride would result in fluoride migration to give α-fluorocarbonyl compounds.[20] In the event, treatment of the diazo compound **1a** with boron trifluoride etherate in ether or CH_2Cl_2 did result in the formation of the desired the α-fluoro-β-ketoester **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 α-fluoro-β-ketoester **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,[13,21–23] we showed that the fluorination reaction also proceeded readily in a flow reactor to give α-fluoro-β-ketoester **2a** in 84% yield. These conditions also avoid the handling of possibly hazardous α-fluorocarbonyl compounds.

These optimized conditions employing HBF_4 were readily extended to heteroaromatic β-ketoesters **1b** and **1c** that gave the corresponding α-fluoro-β-ketoesters **2b** and **2c** in 61 and 76% yield respectively. Extension to alkyl β-ketoesters **1d** and **1e** gave the α-fluoro-β-ketoesters **2d** and **2e** in reasonable yield (Scheme 2), with the corresponding β,β-difluoro-α-hydroxyesters, $RCF_2CH(OH)CO_2Et$, 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.

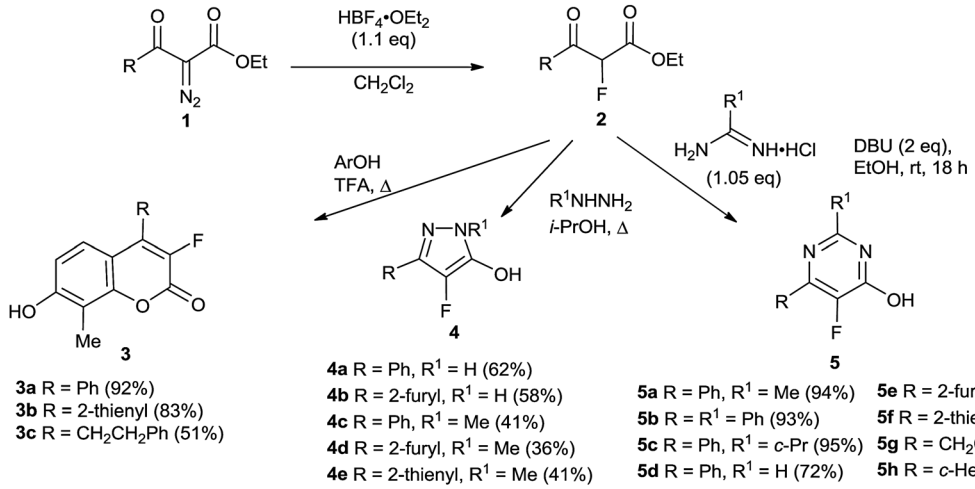
β-Ketoesters are versatile intermediates in organic chemistry, widely used in the construction of heterocycles. Given that a large number of modern medicines and agrochemicals contain



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 = $PhCH_2CH_2$ (51%); **e**, R = cyclohexyl (61%).

one or more heterocyclic ring, there is a huge demand for fluorinated heterocycles. Unfortunately, with few exceptions,[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.[6,7,24,25] Hence, using α-fluoro-β-ketoesters **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 α-fluoro-β-ketoesters **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[26] gave the 3-fluorocoumarins **3** in good yield (Scheme 3). Likewise reaction with hydrazine or methylhydrazine[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,[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,[30,31] we next investigated the formation of fluorinated-pyrimidinols from α-fluoro-β-keto esters. The reaction was simply achieved by adding an amidine hydrochloride and DBU in EtOH in a modification of a literature procedure,[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 α-fluoro-β-keto esters **2**, the whole process can be telescoped



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

into a single operation obviating the need to isolate the α-fluoro-β-keto ester. Thus the α-diazo-β-keto ester **1a** was treated with tetrafluoroboric acid etherate in dichloromethane as described above. After 5 h, ethanol, acetamidine hydrochloride and DBU were added sequentially to give 5-fluoro-2-methyl-6-phenylpyrimidin-4-ol **5a** in 66% yield. Likewise α-diazo-β-keto ester **1e** was converted into fluoropyrimidinol **5h** in 42% yield in a single operation.

In conclusion, we have developed new methodology, whereby α-fluoro-β-ketoesters can be easily obtained by nucleophilic fluorination with tetrafluoroboric acid, by treating readily available α-diazo-β-ketoesters with HBF_4 either using conventional batch chemistry or in flow. The overall process amounts to a novel variation on the Balz–Schiemann reaction, and the versatility of the resulting α-fluoro-β-ketoesters is illustrated in the synthesis of a wide range of fluoro-heterocycles. We believe that this is an exciting development that will both complement and challenge existing fluorination methodologies, allowing access to a wide diversity of fluorinated pharmaceuticals and agrochemicals.

We thank the EPSRC (Grant EP/G027919/1) for support.

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