Direct Photocatalytic Fluorination of Benzylic C-H Bonds with N-Fluorobenzenesulfonimide

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Direct Photocatalytic Fluorination of Benzylic C-H Bonds with N-Fluorobenzenesulfonimide

Matthew B. Nodwell, Abhimanyu Bagai, Shira D. Halperin, Rainer E. Martin, Henner Knust, and Robert Britton*

The late-stage fluorination of common synthetic building blocks and drug leads is an appealing reaction for medicinal chemistry. In particular, fluorination of benzylic C-H bonds provides a means to attenuate drug metabolism at this metabolically labile position. Here we report two complimentary strategies for the direct fluorination of benzylic C-H bonds using N-fluorobenzenesulfonimide and either a decatungstate photocatalyst or AIBN-initiation.

The incorporation of one or more fluorine atoms into a small molecule is of great interest to medicinal chemistry. For example, replacement of a hydroxyl group or hydrogen atom with a fluorine is a common tactic used to improve metabolic stability, cell permeability, or ligand-target interactions (Figure 1). Owing to the unfavorable properties of F₂ gas, however, the wide spread incorporation of organofluorines in medicinal chemistry campaigns has relied on the development of electrophilic and nucleophilic fluorination reagents and reactions. To compliment these processes, there has recently been considerable interest in the direct fluorination of unactivated C-H bonds. Such late-stage fluorination strategies are especially attractive to drug discovery programs, where the direct fluorination of metabolically labile C-H bonds would obviate extensive re-synthesis campaigns. In particular, the fluorination of benzylic C-H bonds provides a means to attenuate metabolic degradation at these so-called “hot spots.”

Recently, Lectka described the mechanism of C-H fluorination with Selectfluor and proposed that fluorine transfer from Selectfluor (BDE_{NF} ~260 kJ/mol) to a carbon radical generates a cationic nitrogen-centered radical that is responsible for hydrogen abstraction. Curiously, the related fluorine transfer reagent N-fluorobenzenesulfonimide (7) (BDE_{NF} ~267 kJ/mol) was unable to propagate aliphatic C-H fluorination. Moreover, among the growing number of C-H fluorination reactions, few are operative and only the most recently reported decatungstate-catalyzed C-H fluorination is optimal with NFSI. This unique photocatalytic fluorination reaction presumably involves C-H abstraction by the photoexcited decatungstate followed by fluorine transfer from NFSI (7) (see inset, Scheme 1). Here, we describe the development of a complimentary benzylic C-H fluorination reaction using decatungstate photocatalysis. Moreover, we demonstrate that NFSI is capable of propagating the radical fluorination of benzylic C-H bonds and that benzylic fluorination with NFSI can be initiated by AIBN. Notably, these NFSI-based C-H fluorination reactions provide differing selectivities in the fluorination of substrates with multiple benzylic C-H bonds, and thus provide new opportunities for site-specific fluorination.

As depicted in Scheme 1, we first investigated the fluorination of ethyl benzene (10) and the p-acetoxy derivative 11 using conditions developed previously by us for aliphatic C-H fluorinations. We were surprised that a major product of both reactions were the acetamides 12 and 13.

Figure 1. Beneficial properties of benzylfluorides in lead optimization.
Scheme 1. Decatungstate-catalyzed fluorination of unactivated C-H bonds and the fluorination of ethyl benzenes 10 and 11. a Yield of the volatile benzyl fluoride 15 based on analysis of 1H NMR spectra with internal standard. b Accompanied by 42% recovered 11.

a carbocation followed by reaction with acetonitrile would explain the formation of these Ritter-type products, Brønsted acid activation of initially formed benzylic C-F bonds by dibenzenesulfonamide (9, NHSI) may also be operative. Thus, we evaluated the effect of various bases as additives to the fluorination of 10. Unsurprisingly, soluble amine bases such as pyridine and Et3N were not compatible with this process, neither were a small collection of inorganic bases (e.g., Cs2CO3, Na2CO3, K2CO3, LiOH). Fortunately, when either NaHCO3 or Li2CO3 was added to the reaction mixture the desired benzyl fluoride 15 was formed as the exclusive product in good yield. To gain further insight into the formation of acetamides 12 and 13, the benzyl fluorides 15 and 16 were treated independently with a catalytic amount of NHSI (9) in CH3CN, which led to mixtures containing predominantly the acetamides 12 and 13 at temperatures as low as 35 °C. When these reactions were repeated without NHSI, the benzyl fluorides were recovered unreacted. This NHSI-promoted fluoride substitution reaction represents a unique example of Brønsted acid catalyzed C-F activation and may prove itself to be a useful transformation with further examination.

In order to gain insight into the scope of the decatungstate-catalyzed benzylic C-H fluorination reaction, we evaluated its effectiveness on a range of substrates with differing electronic and steric features. As summarized in Figure 2 (conditions A), we were pleased to find that this reaction is general and cleanly provides a range of benzyl fluorides 17-30 in modest to good yield. It is notable that the discrepancies between conversion (in parentheses) and isolated yields reflect the difficulty in isolating and separating the benzyl fluoride products from the parent hydrocarbon, a challenge common to late-stage C-H fluorination strategies. Importantly, both electron rich (e.g., 16 and 28) and electron poor (e.g., 17-19) alkylbenzenes are competent substrates for this reaction. The fluorination of isobutylbenzenes proceeded smoothly (e.g., 20 and 23), however, more sterically encumbered isopropyl benzenes proved difficult to fluorinate (e.g., 22) and proceeded in modest yield only with the electron rich p-acetoxy derivative. In this later case, the desired fluoroisopropyl adduct 28 was produced in 50% yield. In all cases, deoxygenation of the acetonitrile solvent was critical to avoid competing decatungstate-catalyzed benzylic
In contrast to all other benzyl C-H fluorination reactions, replacing NFSI with Selectfluor resulted in significantly lower yields. Interestingly, despite the necessary addition of base to these reactions (vide supra), benzyl C-H fluorination is competitive with α-fluorination of ketone-containing substrates, and provides access to the unusual γ-fluorotetralone 25 and β-fluorodindanes 27 and 29.

In an effort to gain further insight into the mechanism of decatungstate-catalyzed benzyl fluorination, we examined the fluorination of ethyl benzene (i.e., 10 → 15, Scheme 1) without the photocatalyst and observed no formation of the benzylfluoride 15 (with or without irradiation or heating). However, when a catalytic amount of the radical initiator AIBN was added and the reaction mixture was heated (75 °C), we observed clean conversion to the benzylfluoride 15, albeit in modest yield (~20%, eq 1). We were able to improve the yield of this AIBN-initiated reaction to 70% by simply replacing NaHCO₃ with Li₂CO₃. This dramatic base effect may be understood by considering that NaHCO₃ slowly decomposes to Na₂CO₃ at the elevated temperatures required for the AIBN-initiated reaction, and that Na₂CO₃ is incompatible with the NFSI fluorination reaction (vide supra). It is notable that several aliphatic substrates failed to fluorinate using these reaction conditions (i.e., AIBN, NFSI, Li₂CO₃) suggesting that unlike Selectfluor, NFSI is only capable of propagating the radical fluorination of relatively weak C-H bonds (BDE C-H ~377 kJ/mol). As summarized in Figure 2 (conditions B), these reaction conditions proved to be less optimal and general than the decatungstate-catalyzed fluorination (conditions A), and several substrates containing benzyl C-H bonds failed to provide any fluorinated products (e.g., 22-24).

During our examination of both the decatungstate-catalyzed and AIBN-initiated fluorination reactions, we evaluated the fluorination of p-ethyl toluene (31) (Scheme 2). Surprisingly, the decatungstate-catalyzed reaction selectively fluorinated the ethyl group in 31, while the AIBN-initiated fluorination provided the fluoromethyl product 33 exclusively. A similar trend was observed in the fluorination of m-ethyltoluene (34). Ni has reported analogous selectivity in the amination of p-ethyltoluene with NFSI, and suggested a preference for hydrogen abstraction from the methyl group in 31 based on steric considerations. In the present case, it is important to note that NFSI is not completely dissolved in the decatungstate-catalyzed reactions at room temperature but is fully solubilized at 75 °C in the AIBN-initiated reactions. Thus, we speculated that the unique fluorination selectivities may in fact result from a higher concentration of NFSI in the heated reactions and the consequent trapping of an initially formed methyl radical. Conversely, at lower concentrations of NFSI (decatungstate-catalyzed reaction), equilibration between benzyl radicals may be responsible for the preferred formation of the fluoroethyl products 32 and 35. To probe this hypothesis, the AIBN-initiated fluorination of 31 (conditions B) was repeated with decreasing amounts of NFSI to assess the effect of NFSI concentration. When substoichiometric amounts (0.5 equiv) of NFSI were added to this reaction, the fluoroethyl product 32 was also observed as a minor product (33:32 = 1:4:1). This result indicates that the equilibration of benzyl radicals is likely responsible for the differing selectivities in the fluorination of ethyl toluenes, and provides a useful tool for imparting or attenuating selectivity in the fluorination of substrates with multiple benzyl C-H bonds.

Finally, in an effort to decrease the reaction time for the decatungstate-catalyzed fluorination, we examined the fluorination of ibuprofen methyl ester (37) in flow.10,25 As depicted in Scheme 3, irradiation of the reaction mixture in FEP tubing (3 m length, 1.4 mL total volume) wrapped around a blacklight blue lamp (BLB lamp, λ = 365 nm) reduced the reaction time from 24 h (batch) to 5 h (flow) without impacting the yield. Considering the potential importance of late-stage fluorination to medicinal chemistry we were also interested in gauging the effect of benzyl fluorination on basic pharmacokinetic properties of ibuprofen. Thus, the ester 20 was hydrolyzed to afford the fluoroibuprofen 38. Not surprisingly, fluorination of ibuprofen resulted in a modest decrease in pKa (from 4.35 (ibuprofen) to 4.23 (38)). Fluorination of ibuprofen also slightly improved metabolic stability in both human and rat microsomes, leading to a decrease in clearance from 19 to 12 µg/min/mg protein in human microsomes and 71 to 39 µg/min/mg protein in rat microsomes.

In summary, we have developed two complimentary methods for benzyl fluorination that rely on the fluorine...
transfer agent NFSI in combination with either a decatungstate photocatalyst or radical initiator (AIBN). These processes tolerate a range of functional groups in providing benzyl fluorides in modest to excellent yield. Furthermore, the photocatalytic fluorination can be adapted to continuous flow without compromising yield. That this process is uniquely effective with NFSI and not Selectfluor differentiates it from existing and complimentary benzylic fluorination strategies and provides new opportunities for late stage fluorination in drug discovery.

![Scheme 3. Photochemical fluorination of ibuprofen methyl ester (37) in flow, and synthesis of fluoroibuprofen 38][12] a) LiOH, MeOH, THF, H2O, 24 h

Notes and references
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