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Synthesis of Acyl Fluorides via DAST-Mediated Fluorinative C−C Bond Cleavage of Activated Ketones

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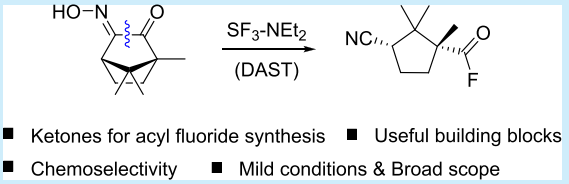
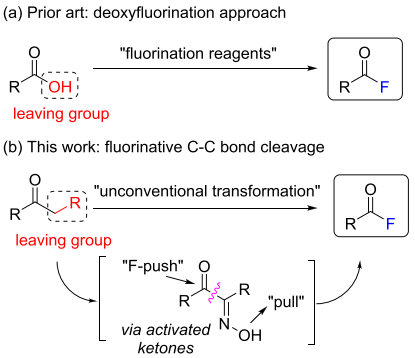
ABSTRACT: A new protocol for preparation of acyl fluorides was developed by recognizing activated ketones as starting materials. The method provides a different scope compared with previously reported methods that employ carboxylic acids as substrates. A working hypothesis of pull-and-push-driven fluorinative C−C bond cleavage was successfully demonstrated by the simple addition of diethylaminosulfur trifluoride (DAST) derivatives to α-oximinoketones. The designed reaction system led to a highly efficient and chemoselective reaction. The wide availability of the ketones allowed for a range of synthetically useful aryloyl and aliphatic acyl fluorides including those containing chiral skeletons. The method is mild, fast, scalable, and potentially one-pot operative.



Acyl fluorides are versatile reagents in organic synthesis due to their distinct reactivity and exceptional stability over other types of acyl halides. The small size and intrinsic electronic nature of the fluorine atom have often provided a solution for challenging problems encountered in the esterification and amidation of sterically demanding or electronically deactivated alcohols or amines.[1] In particular, the use of an acyl fluoride in peptide syntheses has offered advantages such as the suppression of byproduct formation and minimal epimerization compared with that with conventional coupling reagents.[2] In addition to its direct reaction with common nucleophiles, it has been employed as key building blocks in transition-metal (TM)-catalyzed coupling reactions; acyl fluorides can be classified as "RCO", "R", and "F" sources. An overview of the applications of acyl fluorides in TM catalysis was recently published by Ogiwara and Sakai.[3]

Such utility of acyl fluorides in organic synthesis led to the development of a number of reliable protocols that focus on the conversion of carboxylic acids to acyl fluorides (Scheme 1a). Since an early discovery using cyanuric fluoride by Olah and coworkers,[4] several seminal works have been reported by employing hydrogen fluoride (HF)−pyridine/1,3-dicyclohexylcarbodiimide (DCC),[5] uronium-based reagents (e.g., tetramethylfluoroformamidinium hexafluorophosphate (TFFH)),[6] diethylaminosulfur trifluoride (DAST)[7] and its derivatives (Deoxo-Fluor[8] and XtalFluor[9]), and other sulfur-based fluorinating reagents such as $(Me_4N)SCF_3$.[10] Most recently, a novel method using PPh_3/NBS and Et_3N/HF was presented by Prakash and coworkers.[11] Although these innovative reagents are practical due to the low toxicity, generous functional group scope, and minimal byproduct formation, the methods only rely on the use of carboxylic acids as starting materials.

Scheme 1. Prior Approaches and Proposed Work for the Synthesis of Acyl Fluorides



Herein we report a simple protocol to convert activated ketones to acyl fluorides (Scheme 1b). The method is an unconventional approach, but it is operationally simple and practical because it uses readily available ketones and sulfur-based fluorination reagents. The use of ketones as a starting material is a significant advantage because ketones are one of the most common functional groups and are widely present in many biologically important molecules.

This study was inspired by two seminal works of Momose and Shibata: (1) In 1997, Momose disclosed the fluorinative C−C bond cleavage of α,α-diakyl-substituted cyclic oximes

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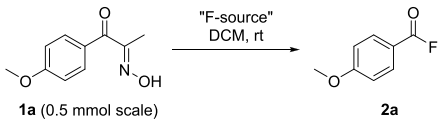
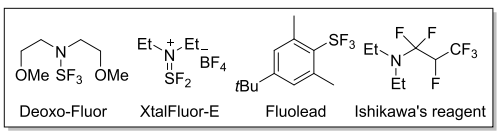
using DAST as a bifunctional fluoride source.[12] In this work, oxime activation by an electrophilic trifluorosulfur was followed by fluoride addition at the α-carbon of the oxime; this concerted reaction constructed a fluorinated quaternary carbon center instead of yielding a general Beckmann rearrangement product. (2) In Shibata's work, an interesting C−C bond cleavage by the fluoride-initiated retro-Claisen reaction was discovered when DAST derivatives were subjected to 2-carboalkoxy-1-indanones (1,3-dicarbonyl).[13] The unexpected formation of sulfenylated products was featured. In this context, we anticipated that a ketone bearing an α-oxime (1,2-dicarbonyl) might be an excellent substrate for the synthesis of acyl fluorides because it has, in principle, necessary components for C−C bond cleavage such as a fluoride acceptor (activated ketone) and a leaving group (activated oxime formed by electrophilic sulfur-based fluorination reagents), as depicted in Scheme 1b.[14] Compared with the 1,3-dicarbonyl system, the designed 1,2-dicarbonyl system was expected to differ in reactivity. For instance, because of the high reactivity of ketones activated by α-oximes, it would offer superior chemoselectivity over competing functional groups. Moreover, the enhanced reactivity of ketones would allow a broad ketone scope regardless of the original ketone reactivity. However, a challenge was to avoid competitive Beckmann rearrangement or Grob-like elimination, which can induce undesirable side products.[15]

Setting out the research, the model substrate **1a** was prepared. α-Oximation of ketones is readily accessed in several ways: direct formation at the ketone α-position by acid- or base-assisted oximation using alkylnitrites,[16] condensation between hydroxylamine and 1,2-diketones,[14b,17] or nitroso-interception by silyl enol ethers.[18] After surveying some nucleophilic fluorinating reagents, we found that the simple addition of DAST to **1a** provided the acyl fluoride **2a** in the highest yield (Table 1, entry 1). It is notable that no side products were found. Other sulfur-based fluorination reagents also gave the desired product with comparable conversions (Table 1, entries 2−4). In addition to SF_4 derivatives, the Ishikawa reagent worked in this system (Table 1, entry 5).

Table 1. F-Source Screening[a]



entry	fluorination reagents	time	yield (%)
1	DAST	10 min	93 (87)[b]
2	Deoxo-Fluor	10 min	93
3	XtalFluor-E, Et_3N/HF	10 min	83
4	Fluolead	10 min	88
5	Ishikawa's reagent	10 min	79
6	PPh_3/NBS, then Et_3N/HF	60 min	85
7	Et_3N/HF	1 day	trace
8	TsCl, Et_3N, then KF, 18-*crown*-6, THF	1 day	<10

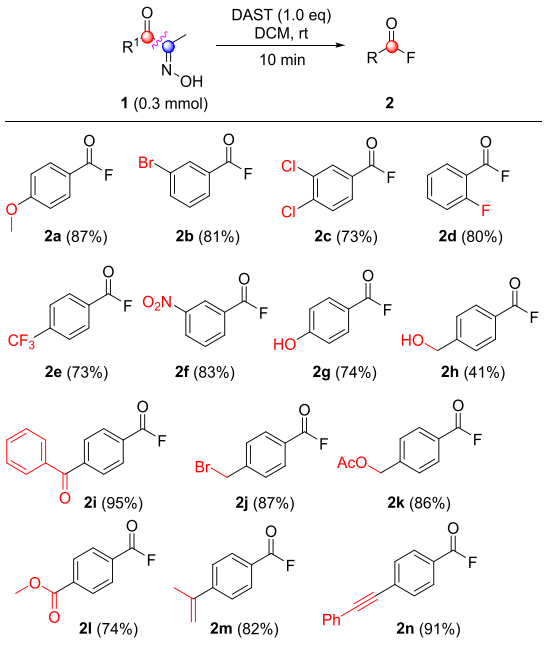


[a]Determined by ^{19}F NMR using fluorobenzene as the internal standard. [b]Isolated yield.

Fortunately, Prakash's one-pot protocol[11] could be successfully applied to the given system (Table 1, entry 6). However, the reaction did not proceed without preactivation of the oxime moiety (Table 1, entry 7). We also attempted nucleophilic fluoride addition to the oxime tosylate, but it was not fruitful (Table 1, entry 8).

During the investigation of the substituent scope of arenes (Scheme 2), careful handling was required for the precise

Scheme 2. Functional Group Scope[a]



[a]Isolated yield.

determination of product yield for a handful of volatile aryloyl fluorides. The mild reaction conditions ensured the broad scope of tolerable functional groups. Arenes bearing electron-donating and -withdrawing functional groups such as methoxy **2a**, halides **2b−d**, trifluoromethyl **2e**, and nitro **2f** groups were well suited. Gratifyingly, this method was highly chemoselective even for phenols, which are potential nucleophiles and can undergo undesired oxidation to generate **2g**.[19] The primary alcohol **1h** also reacted to provide acyl fluoride **2h** in 41% isolated yield, although it was not the sole product.[20] In addition, the substrate bearing a potentially competing ketone group was converted to the corresponding product **2i** with complete selectivity. The benzyl bromide **2j**, acetoxy **2k**, and arylester **2l** functional groups were all compatible. Moreover, arenes containing acid-sensitive unsaturated bonds were tolerated under the present conditions, giving **2m** and **2n** in good yields. The observed excellent chemoselectivity demonstrates our premise that ketone is strongly activated by adjacent oxime functionality.

Whereas a comparable functional group scope was displayed for the preparation of acyl fluorides, the protocols of Schoenebeck[10] and Prakash[11] appeared to be advantageous, as demonstrated for the late-stage functionalization of active pharmaceutical ingredients (APIs). Meanwhile, our method was considered to have differentiated applications owing to its use of cyclic ketones. To prove this point, we extended the substrate scope from acyclic ketones to benzo-fused and aliphatic cyclic ketones. By subjecting cyclic ketone substrates

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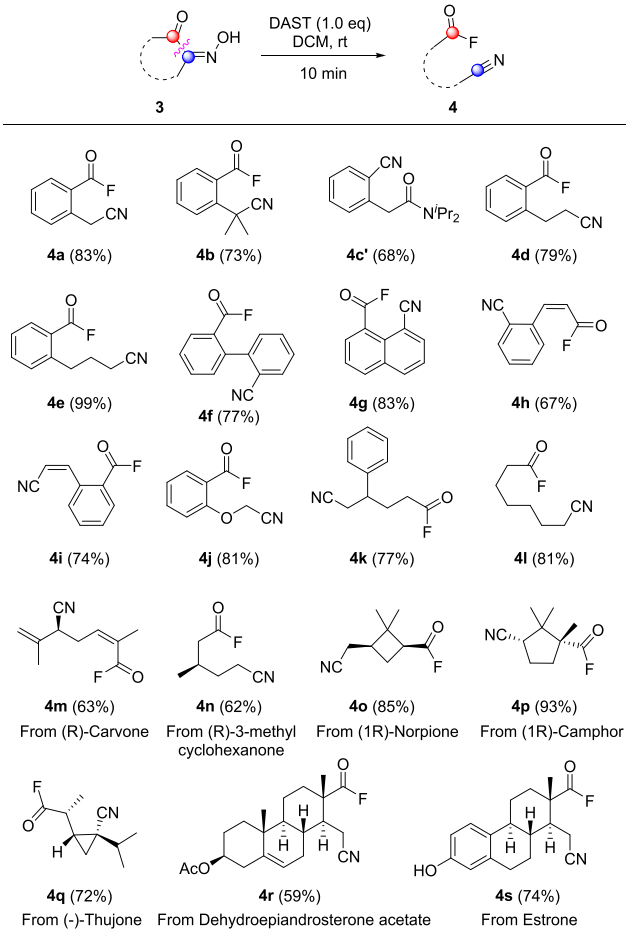
to the established reaction system, synthetically intriguing building blocks were obtained, as illustrated in Scheme 3. The

Scheme 3. Cyclic Ketone Scope[a]



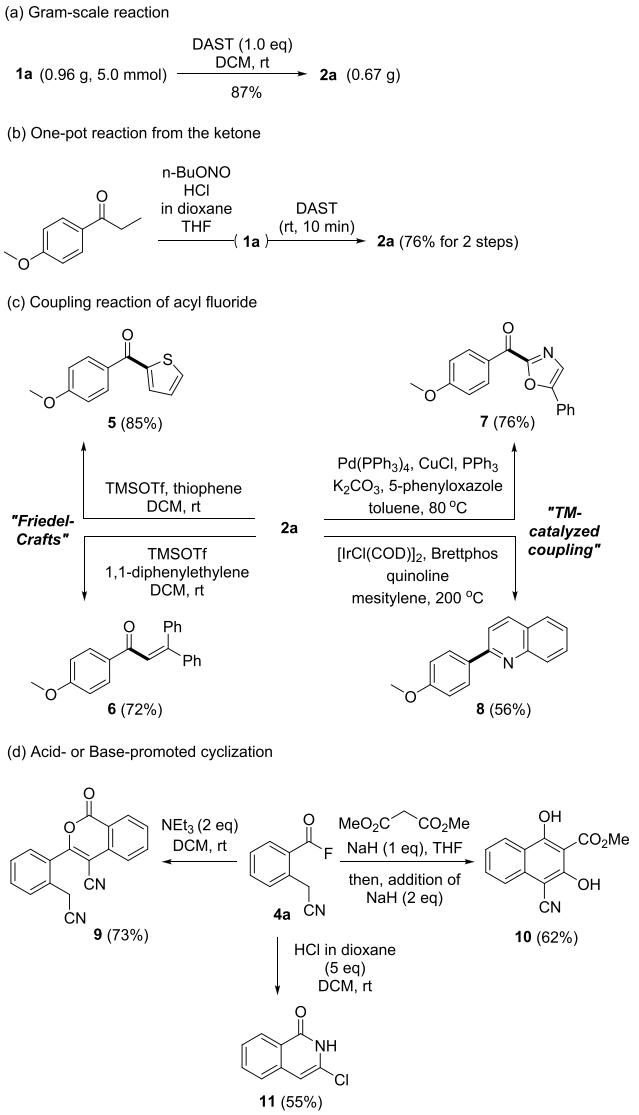
[a]Isolated yield.

resulting acyl fluorides contain a pendant nitrile group; due to the presence of the nitrile, they can be potentially utilized as 1,5-, 1,6-, 1,7-, and 1,8-dicarbonyl equivalents with orthogonal reactivity. The nitrile functionality is used in many organic transformations including conversion to amines and various carboxylic acid derivatives[21] as well as in the "Click" reaction.[22]

Indanone derivatives **3a**−**c** were successfully converted to the corresponding acyl fluorides in good yields, regardless of the position of the ketone moiety. Whereas the corresponding acyl fluoride **4c** was not fully isolated due to its instability in silica gel columns, the crude product was directly subjected to a bulky amine nucleophile such as diisopropylamine, giving **4c′** in 68% yield. Other benzofused cycles, **3d** and **3e**, were also compatible and showed clean conversion. 2-Arylbenzoyl- and naphthoyl fluorides **4f** and **4g** were obtained in good yields. It was notable that **3h** was converted to *Z*-acryloyl fluoride **4h** without isomerization. The reaction of **3j** gave cyanomethyl ether **4j**. In addition to aryloyl fluorides, aliphatic acyl fluorides were obtained with high efficiency. Through the use of a cyclohexanone-based substrate, 5-cyano-4-phenylpentanoyl fluoride **4k** (1,6-dicarbonyl equivalent) was obtained. A cyclooctanone substrate was cleaved to afford the useful acyl fluoride **4l** bearing a cyanoalkyl substituent. Among the commercially available chiral ketones, the selected substrates **3m**−**q** were subjected to the C−C cleavage reactions; in this way, the novel acylating agents **4m**−**q** were obtained in good to excellent yields. These examples strongly demonstrate the power of this methodology that provides unprecedented chiral acyl fluorides from a pool of readily available chiral cyclic ketones. As a set of final examples, steroidal compounds were deconstructed to provide interesting acyl fluorides **4r** and **4s**, respectively, which can potentially give stereochemically enriched fragments after relevant manipulations.

Next, the synthetic utility of the methodology was investigated. The protocol was scalable, as shown in Scheme 4a. We anticipated that the acidic medium of the oximation

Scheme 4. Further Scope and Application



step would be compatible with DAST. Indeed, a two-step reaction was found to be operative in one pot (Scheme 4b). The acyl fluoride **2a** was a good acylating source in some transformations (Scheme 4c). For instance, the Friedel−Crafts-type acylation of electron-rich thiophene provided ketone **5** in excellent yield.[23] Under the same conditions, **2a** could be used for the acylation of alkenes; the use of 1,1-diphenylethylene as the coupling partner afforded an *α,β*-unsaturated ketone **6**.[24] In addition, **2a** could be coupled to

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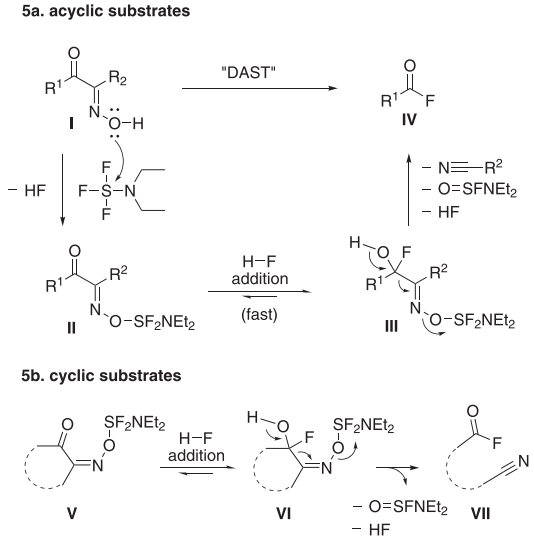
electron-deficient heterocycles. A C−H coupling reaction[25] provided diaryl ketone **7**, and the decarbonylative coupling reaction via the direct C−H activation of the quinoline gave 2-arylquinoline **8**.[26] Beyond intermolecular coupling reactions, the bifunctional molecule **4a** could participate in base-promoted annulations to give previously unreported bicyclic compounds such as isocoumarin **9** and 1,3-naphthalenediol **10**. Under acidic conditions, 3-chloro-isoquinolone **11** was obtained (Scheme 4d).

On the basis of the prior mechanistic proposals of fluoride-mediated reactions,[12,15d] a plausible reaction mechanism was proposed (Scheme 5a). The oxime activation is initiated by the

Scheme 5. Proposed Mechanism of the Fluorinative C−C Bond Cleavage



electrophilic trifluorosulfur moiety of DAST, which releases HF. The released HF probably adds to the activated ketone, and the resulting fluorohydrin **III** would be in equilibrium with **II**.[27] Then, the reaction ends up in C−C bond cleavage by the entropically favorable Beckmann fragmentation process, giving acyl fluoride **IV**.[28] In the case of cyclic substrates, the fragmentation proceeds in an intramolecular fashion, affording acyl fluorides **VII** bearing a cyano group (Scheme 5b).

In conclusion, the acyl fluorides were prepared by the DAST-mediated Beckmann fragmentation of α-oximinoketones. The increased reactivity of the ketone ensured a rapid and highly chemoselective reaction. The mildness of the reaction conditions permitted wide functional group tolerance. A number of linear and cyclic ketones were relevant sources for the preparation of synthetically valuable acyl fluorides. We believe that this method may add many intriguing acylating agents for the synthesis of functional molecules. Detailed mechanistic studies and the application of the method are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02603.

Experimental procedures, characterization data, copies of NMR spectra for all new products (PDF)

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Notes

The authors declare no competing financial interest.

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