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Synthesis of Carbamoyl Fluorides via a Selective Fluorinative Beckmann Fragmentation

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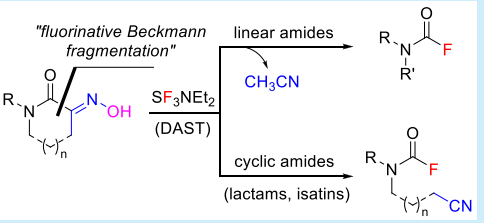
ABSTRACT: A fluorinative Beckmann fragmentation of α-oximinoamides was devised to provide synthetically useful carbamoyl fluorides. High selectivity for fragmentation over a potentially competing Beckmann rearrangement was observed. This protocol has a distinct mechanism and thus a different substrate scope compared with other synthetic methods. α-Oximinoamides derived from the readily available secondary amines, lactams, or isatins were converted into structurally diverse carbamoyl fluorides.



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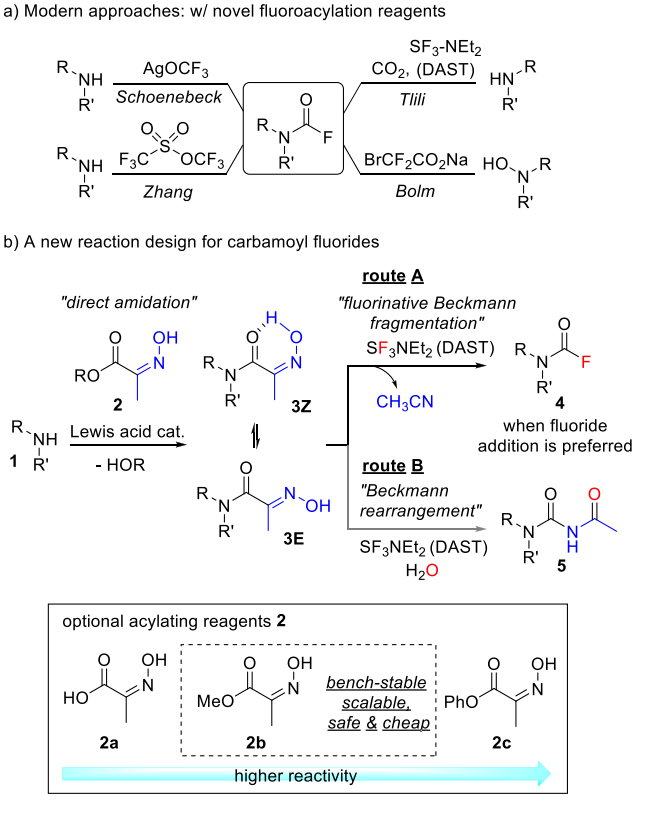
Fluorine chemistry has played a pivotal role in the discovery research of pharmaceuticals and agrochemicals. Incorporating fluorine atoms into a molecule often enhances biological efficacy, bioavailability, and selectivity, which is enabled by tuning the physicochemical properties with marginal structural variations.[1] Such benefits have inspired numerous studies into chemoselective and site-selective fluorination at the desired position of small molecules over recent decades.[2]

Carbamoyl fluorides are a class of fluorine-containing carbonyl compounds that have great potential for biological applications. Owing to their exceptional stability and distinct chemical properties, they are recognized as valuable bioisosteres of the carbamate functionality with uses beyond simple electrophilic coupling to external nucleophiles.[3] Early studies on the reactivity of carbamoyl fluorides are found in Hatch's work during the elaborative lead optimization of carbamate insecticides.[4] Although initial synthesis reports were disclosed in the 1940s, their synthetic application has not been thoroughly studied, and thus they have been underutilized for a long time. This is likely due to limitation in the efficient preparation of carbamoyl fluorides. Conventional protocols using amine substrates with highly toxic fluorophosgene gas[5] or its equivalents, such as gaseous fluorooxyperfluoromethane[6] and carbonic chloride fluoride[7] are impractical. The halogen exchange of carbamoyl chlorides with alkali metal fluorides[8] is another available method; however, additional efforts are required to prepare carbamoyl chlorides as substrates that are mostly moisture sensitive.

While development of new methods had not attracted attention for a long time, a handful of alternative methods were recently reported (Scheme 1a).[9] For instance, a unique reaction employing difluorocarbene precursors and hydroxylamine substrates was discovered by Bolm et al. in 2016.[10] Since then, two surrogate reagent systems for fluorophosgene (OCF_2) have been reported. For example, Zhang et el. demonstrated that trifluoromethyl trifluomethanesulfonate

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



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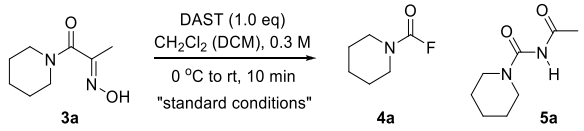
($CF_3SO_3CF_3$) is a good source of fluorophosgene, generated in situ by fragmentation of OCF_3 anions.[11] Most recently, the Schoenebeck group reported a novel method for the preparation of *N*-trifluoromethyl carbamoyl fluorides using isothiocyanates as substrates and $AgOCF_3$ generated in situ from the reaction between silver fluoride and bis(trichloromethyl) carbonate.[12] One year later, the same group reported a practical approach to access $AgOCF_3$ and its reaction with secondary amines to afford aryl or alkylcarbamoyl fluorides.[13] Although the reagents are still based on the in situ generation of poisonous difluorophosgene, these two methods improved the convenience of access to carbamoyl fluorides with a broad substrate scope and mild reaction conditions. In 2019, Onida and Tlili developed an exceptionally practical method using CO_2 activation strategy that does not rely on OCF_2 precursors, in which the N−C(O)−F bonds were constructed via a three component reaction using secondary amines, carbon dioxide, and (diethylamino)sulfur trifluoride (DAST) in the presence of *N*,*N*-dimethylaminopyridine (DMAP).[14]

Herein, we propose a new, cost-efficient, and reliable synthetic route to provide carbamoyl fluorides from α-oximinoamides **3**. We recently demonstrated the concept of fluorinative C−C bond cleavage of activated ketones; the key to this operation was the use of DAST, which plays a dual role as an oxime activator and nucleophilic fluoride donor.[15,16] We thus hypothesized that the fluorinative C−C bond cleavage of activated amides **3** enables the synthesis of carbamoyl fluorides **4** (Scheme 1b). However, the decreased electrophilicity of amides compared to ketones was a concern in this transformation; there were no existing reports of a reaction between tertiary amides and DAST derivatives. In this respect, the low reactivity of the amide functionality might be a selection factor between the fluorinative Beckmann fragmentation (route A) and Beckmann rearrangement (route B). While not obvious, we believe that the pathway selection is likely dependent on the geometry of the oximes and the structural and electronic properties of the substrates **3**.

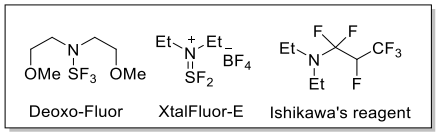
To prepare α-oximinoamides **3**, three types of pyruvate oximes (**2a**−**c**) were considered as available coupling partners with amines **1**. When employed in amide bond formation, compound **2a** requires additional coupling reagents to activate the inert acid functionality, which usually accompanies unpleasant byproducts. In contrast, the enhanced reactivity of activated esters such as **2b** and **2c** was expected to allow a direct coupling reaction with amines. Although **2c** has a better leaving group, its use has been limited because it requires multiple steps for preparation. Moreover, the phenol byproduct of the amidation step is less atom economical and less environmentally benign compared to methanol, which is generated when using **2b**. Therefore, **2b** was chosen for the amide synthesis. Note that it is bench-stable and available on a multigram scale from inexpensive methyl pyruvate. During the amidation reaction tests using piperidine **1a** and methyl pyruvate oxime **2b** as model substrates,[17] the use of Lewis acid catalysts including $ZrCl_4$, $Nb(OEt)_5$, $Ti(OiPr)_4$, and $Zr(OtBu)_4$ was found to lead to excellent conversion into α-oximinoamide **3a**.[18]

After determining a simple and scalable synthesis for **3a**, we commenced optimization of the designed reaction (Table 1). To our delight, simple addition of DAST into a solution of **3a** in DCM gave the desired product **4a** in high yield (entry 1). The use of other solvents such as DCE, THF, and CH_3CN was comparable to that of DCM (entries 2, 3, and 4). In addition, no Beckmann rearrangement product **5a** was observed. However, when a polar aprotic solvent such as DMF was used, the desired product was not obtained (entry 5). Next, deoxyfluorination reagents were evaluated. Interestingly, sulfur-based reagents such as DAST and bis(2-methoxyethyl)-aminosulfur trifluoride (Deoxo-Fluor) were highly efficient with good selectivity, whereas a reagent system employing XtalFluor-E and 3HF-Et_3N exhibited no conversion (entries 6 and 7). Consequently, HF-Et_3N was considered not to be a relevant nucleophilic fluoride source for the substrate **3a**, indicating that amide-based substrates require a more reactive fluoride source than that used in the activated ketones.[19] When 3HF-Et_3N was replaced with sodium fluoride,[20] **4a** was obtained in 50% yield along with piperidine-1-carboxylic anhydride as a side product (entry 8). Non-sulfur-based reagent such as Ishikawa's reagent also worked smoothly to provide **4a** in excellent yield (entry 9). The reaction was completed with similar efficiency in 10 min even at a lower concentration (entry 10).

Table 1. Reaction Optimization[a]



entry	variations from standard conditions	4a	5a
1	none	88 (85)[b]	-
2	DCE instead of DCM	88	-
3	THF instead of DCM	84	-
4	CH_3CN instead of DCM	78	-
5	DMF instead of DCM	0	-
6	DeoxoFluor instead of DAST	78	-
7	XtalFluor-E/3HF-NEt_3 instead of DAST	no conversion	
8	XtalFluor-E/NaF in EtOAc instead of DAST and DCM	50	-[c]
9	Ishikawa's reagent instead of DAST	83	-
10	0.1 M instead of 0.3 M	86	-



[a]Determined by ^1H NMR using 1,3,5-trimethoxybenzene as the internal standard. [b]Isolated yield. [c]Piperidine-1-carboxylic anhydride was obtained in 33% yield.

Having completed the reaction optimization, we surveyed the scope of the amines (Scheme 2). Piperidine derivatives **3a**−**c** were smoothly converted to the corresponding carbamoyl fluorides **4a**−**c** in good yields. The morpholine-containing substrate **3d** also afforded the desired product **4d** in high yield. However, piperazine substrates, **3e** (with an acid-sensitive Boc group) and **3f** (with a basic tertiary amine/acid-sensitive aryl olefin) exhibited reduced efficiency. However, the yields of the two substrates could be increased by lowering the concentration. This indicates that the intermolecular reaction

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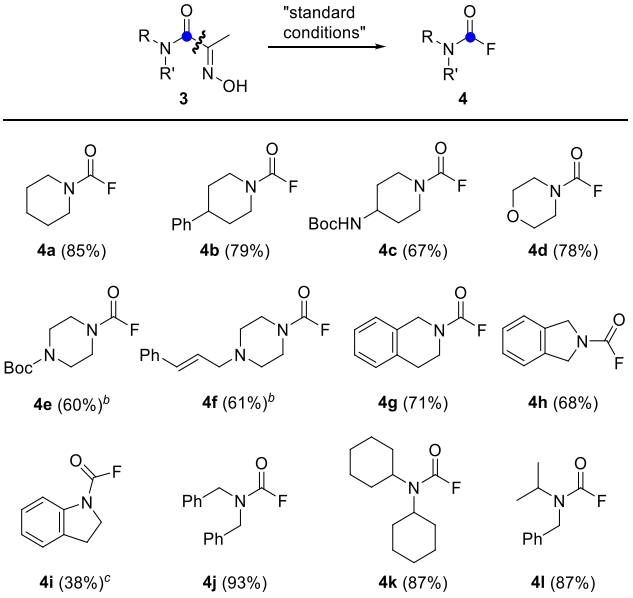
Scheme 2. Amine Scope[a]



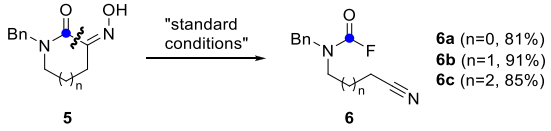
[a]Isolated yield. [b]0.1 M instead of 0.3 M. [c]Beckmann rearrangement product was isolated in 26%.

likely interrupts the selective C−C bond cleavage in substrates **3e** and **3f**. Benzo-fused *N*-heterocycles **3g** and **3h** were also compatible, affording products **4g** and **4h** in moderate to good yields. Compared to **3g** and **3h** bearing a nitrogen atom at 2-position, the indoline substrate **3i** underwent Beckmann fragmentation and rearrangement at a ratio of 3:2.[21] Gratifyingly, when sterically bulky acyclic amides **3j−l** were subjected to the reaction conditions, **4j−l** were obtained in excellent yields. It is notable that fragmentation occurred in a highly selective fashion regardless of the oxime geometry of substrates **3j−l**.[22] Based on our observation that the fragmentation was the dominant process in both *E*- and *Z*-oxime isomers, the rapid *E*/*Z* isomerization upon oxime-activation with DAST is believed to be significant for efficient conversion.[16e,f]

In addition to the preparation of carbamoyl fluorides from substrates obtained by direct amidation using secondary amines and methyl pyruvate oxime, cyclic amides could be transformed into the carbamoyl fluorides bearing a pendant cyanoalkyl moiety. Unaffected by ring size, 5-, 6-, and 7-membered α-oximinolactams **5a−c** were smoothly cleaved to afford **6a−c** in excellent yields (Scheme 3).

We further explored the substrate scope by employing *N*-substituted isatin-3-oximes **7**. Isatins, which are readily available cyclic keto-amides, perfectly fit the structural components required for the designed transformation. Due to the interesting electronic distribution of the keto-amide system, isatins and their derivatives have often been adopted as

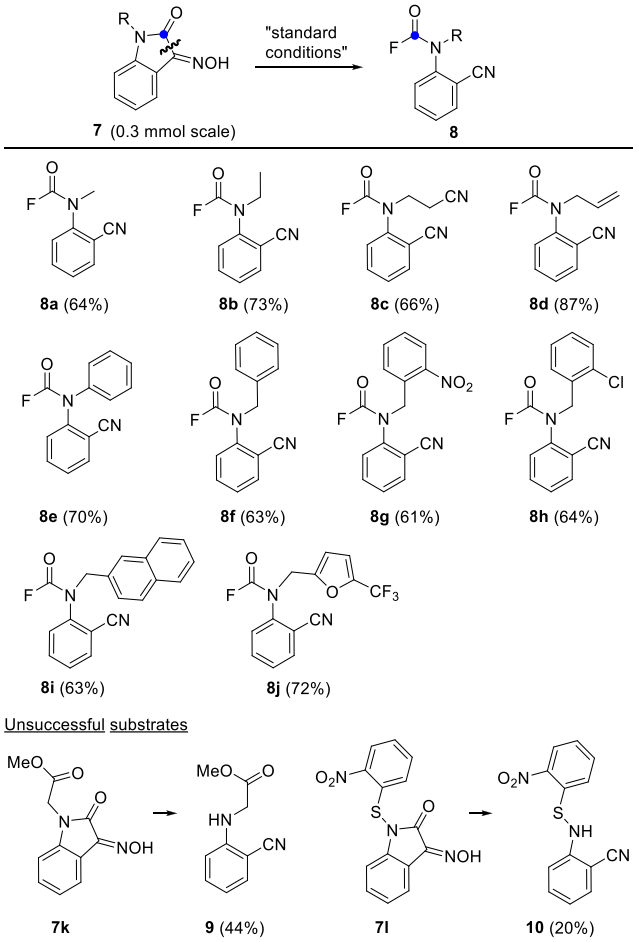
Scheme 3. Carbamoyl Fluorides Derived from α-oximinolactams[a]



[a]Isolated yield.

platforms in asymmetric conversions[23] and cycloaddition reactions.[24] The fluorinative C−C bond cleavage reaction of *N*-substituted isatin-3-oximes **7** provided previously unreported *N*-substituted *o*-cyanophenylcarbamoyl fluorides **8** (Scheme 4). With respect to *N*-substituents, the aliphatic

Scheme 4. Carbamoyl Fluorides Derived from *N*-Substituted Isatin-3-oximes[a]



[a]Isolated yield.

alkyl substituents such as methyl (**7a**), ethyl (**7b**), cyanoethyl (**7c**), and allyl (**7d**) groups were all tolerated. *N*,*N*-diarylcarbamoyl fluoride **8e** was obtained from **7e** in good yield. In addition, benzyl (**7f**), 2-nitrobenzyl (**7g**), 2-chlorobenzyl (**7h**), and 2-naphthylmethyl (**7i**) groups were compatible with the reaction. As a final example, a furan-containing substrate **7j** was found to participate smoothly to give **8j** in good yield.

The transformation appears to be influenced by certain *N*-substituents. For example, substrate **7k**, containing *N*-carbomethoxylmethyl group, did not provide the desired product. Instead, free amine **9** was isolated as a major product, likely as a result of the participation of neighboring ester group during oxime activation. The reaction of **7l** containing a highly electron-withdrawing nitrophenyl group was also unsuccessful although the exact reason is unclear; the only isolable product was *N*-arylsulfenylamine **10**.

Next, we explored the reactivity of non-*N*-substituted isatin-3-oxime **11** under the given reaction conditions (Scheme 5a). Although the secondary amide and oxime functionalities of

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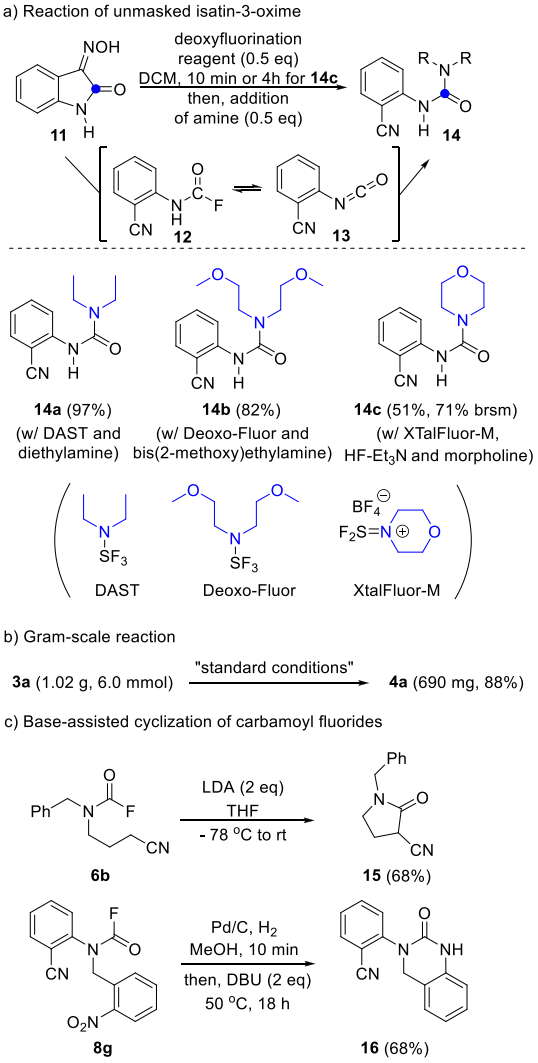
Scheme 5. Further Scope



substrate **11** were presumed to compete as both are nucleophilic,[25] the oxime was found to have complete selectivity in the reaction with DAST. Interestingly, 0.5 equiv of DAST was sufficient to fully consume **11**, and a major product was identified as urea **14a** (38% isolated yield). Upon treatment with DAST, **11** is believed to undergo fluorinative C−C bond cleavage followed by addition of diethylamine to the carbamoyl fluoride **12** or isocyanate **13** albeit with low efficiency.[11] While those highly reactive intermediates were not isolable, the conversion of **11** to **14** was further increased to 97% by adding 0.5 equiv of diethylamine to the reaction mixture at 10 min after the addition of DAST. Following the same procedure, unsymmetrical ureas **14b** and **14c** were obtained by using other deoxyfluorination reagents and paired amines. Our method proved to be scalable; **4a** was obtained in 88% yield on a gram scale (Scheme 5b). As a set of final applications, the base-assisted intramolecular annulation of the carbamoyl fluorides **6b** and **8g** was demonstrated (Scheme 5c). By examining the structures of **14**, **15**, and **16**, the presented applications are expected to inspire new synthetic designs for the preparation of *N*-heterocycles derived from nitriles,[26] which are linked to bioactive chemical moieties such as ureas, γ-lactams, and 3,4-dihydro-2-quinazolinones.

To summarize, α-oximinoamides were fragmented to yield chemically important carbamoyl fluorides. The deoxyfluorination reagent DAST was utilized as a dual-role activator. The developed protocol is mechanistically distinct from previously reported procedures. In addition, it is rapid and operationally simple, uses mild reaction conditions, and exhibits high tolerance for a range of functional groups. Therefore, various *N,N*-disubstituted carbamoyl fluorides were obtained. The application of the C−C bond cleavage strategy in cyclic amides was also successfully demonstrated using simple α-oximinolactams and isatin-3-oximes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01721.

Experimental procedures, characterization data, and 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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(22) When the separable *E*- and *Z*-isomers of acyclic substrates **3j−l** reacted in separate batches, the Beckmann fragmentation products were obtained in the same yields.

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