This article can be cited before page numbers have been issued, to do this please use: C. Zhu, S. Zhumagazy, H. Yue and M. Rueping, Org. Chem. Front., 2021, DOI: 10.1039/D1QO01633D.

This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal’s standard Terms & Conditions and the Ethical guidelines still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.
Herein we report the deoxygenated fluorination of readily available carboxylic acids. A series of acyl fluorides have been synthesized using shelf-stable N-trifluoromethylthiophthalimide as a fluorinated reagent for the first time. Scale-up reactions and sequential cross-couplings were performed successfully to demonstrate the practicability of this fluorination protocol.

Fluorine-containing molecules are one class of the most important organic compounds due to the unique character of the fluorine atom in modulating the chemical and biological properties such as metabolic stability, lipophilicity, and bioavailability. Therefore, the development of methods to access such compounds is always a research focus for organic chemists. In this context, acyl fluorides represent intriguing targets that play an important role in organic synthesis. Due to the outstanding balance between stability and reactivity, acyl fluorides were widely employed as versatile synthons in different types of organic transformations (Scheme 1a). Also, acyl fluorides could be used for the activation of silyl enol ethers or other silicon species in the presence of a Lewis base.

Conventional methods to access acyl fluorides depend on the halogen exchange reaction of acyl chlorides with $^5$-$^F$ sources. Recent advances were mainly focused on the deoxygenation of readily available carboxylic acids with various fluorinated reagents (e.g., $CF_2SOOCF_3$, $PPh_3/Selectfluor$, $Me_4NSCF_3$, cyanoic fluoride, HF-Pyridine/DCC, sulphur tetrafluoride derivatives, and Carpin’salt TFFH). Notably, Shibata and coworkers developed a general and practical method to prepare acyl fluorides, in which acids, aldehydes, and alcohols all could be transformed into acyl fluorides by using inexpensive reagents, TCCA and CsF. In addition, acyl fluorides were skillfully accessed via selective C–C bond cleavage using DAST or its derivatives as fluorination reagents. Although these achievements provide good alternatives, most of them suffered from some drawbacks, mainly including high reaction temperature or the use of fluorinated reagents that are toxic, unstable, or expensive. Thus, the development of new approaches for the preparation of acyl fluorides is still highly desirable.

Shelf-stable N-trifluoromethylthiophthalimide has been developed as an easily synthesized and efficient trifluromethylthiolation reagent, and an array of valuable compounds were obtained employing this versatile SCF$_3$-reagent.

In 2000, Munavalli and coworkers reported the reaction of SCF$_3$-thphalimide with enamines, affording the $\alpha$-trifluoromethyl-thiolated ketones. Our group realized the enantioselective trifluoromethylthiolation of $\beta$-ketoester and oxindoles, Cu-catalyzed cross-coupling of boronic acids and alkynes, as well as the metal-free ring-opening/trifluoromethylthiolation of cycloalkanols with this SCF$_3$-reagent.

Scheme 1. Acyl fluorides as synthons in organic synthesis and the reaction of N-trifluoromethylthiophthalimide and carboxylic acids.
More recently, Hu and coworkers developed a protocol on deoxygenated trifluoromethylthiolation of carboxylic acids in the presence of FeCl₃ and PPh₃, wherein SCF₃-phthalimide acted as a nucleophilic “SCF₃” source. In contrast, we herein report that electrophilic N-trifluoromethylthiophthalimide acts as a fluorinated reagent in the reaction of carboxylic acids (Scheme 1b).

Table 1 Optimization of the reaction of carboxylic acid and N-trifluoromethylthiophthalimide to form acyl fluoride

| Entry | Variables                        | Yield (%) |
|-------|----------------------------------|-----------|
| 1     | none                             | 91        |
| 2     | DIPEA as base                    | 57        |
| 3     | 2,6-lutidine as base             | 0         |
| 4     | pyridine as base                 | 0         |
| 5     | “tBu,N as base                   | 0         |
| 6     | DMF as solvent                   | 55        |
| 7     | DMA as solvent                   | 60        |
| 8     | DMSO as solvent                  | 35        |
| 9     | THF as solvent                   | 42        |
| 10    | Acetone as solvent               | 33        |
| 11    | 10 mol% NaI as additive          | 60        |
| 12    | 10 mol% KI as additive           | 42        |
| 13    | 0.5 mL CH₂CN                     | 46        |
| 14    | 1a:2 = 1:2                      | 42        |
| 15    | No TBAI                          | 50        |
| 16    | NO Et₃N                          | 0         |

[a] Reaction conditions: 1a (0.40 mmol), 2 (0.20 mmol), TBAI (10 mol%), Et₃N (1 equiv.) in CH₂CN (2 mL) at 35 °C for 16 h. [b] GC Yields using dodecane as internal standard.

We started our investigation by evaluating the reaction of 4-(tert-butyl)benzoic acid 1a and N-trifluoromethylthiophthalimide 2a (Table 1). After a series of screening, the optimal reaction conditions were assigned as follows: 10 mol% TBAI as catalyst, 1 equiv. of Et₃N as reductant in 2 mL CH₂CN at 35 °C. The use of DIPEA as base gave lower yield, while the application of other bases including 2,6 lutidine, pyridine, and “tBu,N led to no formation of the desired product. Other solvents such as DMF, DMA, DMSO, THF, acetone were also suitable for this transformation, albeit delivering the acyl fluoride product in low to moderate yields. Using NaI or KI instead of TBAI decreased the yields dramatically. Reversing the ratio of 1a and 2 from 1:1 to 1:2 also damaged the yield. Control experiments showed that both TBAI and Et₃N are essential for the high efficiency of this transformation.

With the optimized reaction conditions in hand, the generality of the fluorination reaction was first examined. As shown in Table 2, a variety of aryl carboxylic acids could undergo this efficient fluorination transformation smoothly, affording the corresponding products in good to excellent yields. In addition to alkyl (3a and 3b), methoxyl (3c), methylthio (3d), and phenoxy (3e) functional groups, reactive chloride (3f), bromide (3g), iodide (3h) were also tolerated in this fluorination protocol, allowing the further sequential functionalization of the generated acyl fluoride products. Aryl carboxylic acid bearing N-Boc protected amine was fluorinated in 99% yield (3i). Also, biphenyl carboxylic acids could undergo this transformation with good to high efficiency (3j and 3k). In addition, bicyclic carboxylic acid bearing acetal group (3l), as well as naphthyl carboxylic acid (3m and 3n), could all give the corresponding product in high yield. Notably, steric hindrance seems to have no significant influence on the reactivity of the substrates (3b, 3c, 3k, and 3n).

Table 2 Substrate scope of the fluorination reaction of aryl carboxylic acids

| Entry | Variables                        | Yield (%) |
|-------|----------------------------------|-----------|
| 1     | Acetone as solvent               | 57        |
| 2     | DIPEA as base                    | 57        |
| 3     | DMF as solvent                   | 55        |
| 4     | DMA as solvent                   | 60        |
| 5     | DMSO as solvent                  | 35        |
| 6     | THF as solvent                   | 42        |
| 7     | Acetone as solvent               | 33        |
| 8     | 10 mol% NaI as additive          | 60        |
| 9     | 10 mol% KI as additive           | 42        |
| 10    | 0.5 mL CH₂CN                     | 46        |

[a] Reaction conditions: Reaction conditions: 1 (0.40 mmol), 2 (0.20 mmol), TBAI (10 mol%), Et₃N (1 equiv.) in CH₂CN (2 mL) at 35 °C for 16 h. [b] Isolated yield.

Gratefully, our fluorination protocol could be readily extended to vinyl carboxylic acids. As shown in Table 3, the reaction of cinnamic acid proceeded in good yield (5a). Vinyl carboxylic acids bearing methoxyl (5b and 5c) and fluoride (5d) on the aromatic ring underwent the protocol in good to excellent yields. The reactions of vinyl carboxyl acids containing benzodioxole and naphthyl groups (5e and 5f) with N-
trifluoromethylthiophthalimide took place in good to high yields. Importantly, heterocycles such as furan and thiophene (5e-5i) were also tolerated in this protocol, providing the possibility for the synthesis of pharmaceutical-related molecules. Moreover, larger π-extended vinyl acid could also be converted to the corresponding acyl fluoride in good yield (5j).

Table 3 Substrate scope of the fluorination reaction of vinyl carboxylic acids$^{[a,b]}$

![Table Image]

[a] Reaction conditions: Reaction conditions: 4 (0.40 mmol), 2 (0.20 mmol), TBAI (10 mol%), Et$_3$N (1 equiv.) in CH$_3$CN (2 mL) at 35 °C for 16 h. [b] Isolated yield.

Scheme 3. Proposed mechanism for the reaction of carboxylic acids and N-trifluoromethylthiophthalimide.

In order to demonstrate the practicality of this newly developed fluorination methodology from carboxylic acids, the gram-scale experiment of phenyl naphthalene-2-carboxylate 1l was conducted, and 98% yield of the desired product 3i was obtained (Scheme 2a). Furthermore, we also achieved the sequential deoxygenated fluorination/decarbonylative alkylation/C-O bond arylation, showing great advantages of this protocol (Scheme 2b).

Based on our results and previous studies,$^{13,16}$ a mechanism for this fluorination protocol is proposed (Scheme 3). First, Et$_3$N attacks the electrophilic sulfur center with the aid of TBAI, affording the phthalimide anion and intermediate I. Next, the phthalimide anion attacks one of the protons of the ethyl group at Et$_3$N to generate the nucleophilic trifluoromethylthio group along with phthalimide and the aminium. Then the SF$_3$ anion degrades to CSF$_3$ with the release of one fluoride ion. The rapid reaction of CSF$_3$ with carboxylic acid delivers the intermediate II that was attacked by a fluoride ion to afford the acyl fluoride product.

In summary, we have developed an efficient deoxygenated fluorination of readily available carboxylic acids. In contrast to previous reports wherein bench-stable N-trifluoromethylthiophthalimide was always used as a trifluoromethylthiation reaction reagent, this newly developed protocol employed it as a fluorinated reagent for the first time. A series of aryl and vinyl carboxylic acid could be converted to acyl fluorides with good to high efficiency. Gram-scale reaction and sequential synthesis, including deoxygenated fluorination/decarbonylative alkylation/C-O bond arylation, were realized in good yield. This protocol provides a good alternative for the fluorination of carboxylic acids.

Notes and references
1. (a) P. Kirsch, Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications, Wiley-VCH, Weinheim, 2004; (b) D. O’Hagan, Understanding organofluorine chemistry. An introduction to the C–F bond, Chem. Soc. Rev., 2008, 37, 308-319; (c) J. T. Welch, Fluorine in Medicinal Chemistry and Chemical
Promoted by a cooperative dual-catalyst system, catalysed decarbonylative borylation of aroyl fluorides, 2010, Commun.

Organic fluorides with arenes and heteroarenes via CH activation, M. Tobisu, Iridium-catalyzed decarbonylative coupling of acyl fluorides, 2018, Org. Lett.

Nickel-catalysed decarbonylative Suzuki–Miyaura coupling of acid fluorides, C. A. Malapit, J. R. Bour, C. E. Brigham and M. S. Sanford, Base-free Lewis-acidic organoboranes, 2020, Chem. Eur. J.

Catalyzed decarbonylative alkylation of aroyl fluorides assisted by nickel-catalyzed reductive radical relay, Nat. Commun., 2018, 9, 3488; (f) D. Chen, L. Xu, T. Long, S. Zhu, J. Yang and L. Chu, Metal-free, intermolecular carboxyphilization of alkenes via visible-light-induced reductive coupling, Chem. Sci., 2018, 9, 9012-9017.

Acyl fluorides as acyl electrophiles in Suzuki–Miyaura coupling, (a) A. L’Heureux, F. Beaulieu, C. Bennett, D. R. Bill, S. Clayton, F. Bouchard and E. L. Register, Tetramethylfluoroformamidinium hexafluorophosphate: a rapid dehalogenation agent, Org. Lett., 2007, 5053.

Preparation of Acyl Fluorides with Anhydrous Hydrogen Fluoride. The General Use of the Method of Colson and Fredenhagen, J. Org. Chem., 1961, 26, 237-238; (b) C. T. H. Jackson and R. G. Cookson, Synthesis of fluorides by metathesis with sodium fluoride, J. Org. Chem., 1960, 25, 2016-2019; (c) A. C. Pittman and D. Sharp, Fluoro Ketone-Metal Fluoride Adducts as Fluorinating Agents in the Preparation of Fluorosilanes and Fluorinated Acyl Fluorides, J. Org. Chem., 1966, 31, 2316-2318.

5-H. X. Song, Z. Y. Tian, J. C. Xiao and C. Z. Zhang, Tertiary-Amine Initiated Synthesis of Acyl Fluorides from Carboxylic Acids and CF3SO2OCF3, Chem. Eur. J., 2020, 26, 16261-16265.

Z. Yang, S. Chen, F. Yang, C. Zhang, Y. Dou, Q. Zhou, Y. Yan and L. Tang, Phosphonium fluorides as an effective reagent for the preparation of fluorinated aldehydes, Angew. Chem. Int. Ed., 2020, 59, 3493-3496; (a) A. L’Heureux, F. Beaulieu, C. Bennett, D. R. Bill, S. Clayton, F. Bouchard and E. L. Register, Tetramethylfluoroformamidinium hexafluorophosphate: a rapid dehalogenation agent, Org. Lett., 2007, 5053.
13. I. Saidalimu, S. Suzuki, E. Tokunaga and N. Shibata, Successive C–C bond cleavage, fluorination, trifluoromethylthio- and pentafluorophenylthiolation under metal-free conditions to provide compounds with dual fluoro-functionalization, Chem. Sci., 2016, 7, 2106-2110.

14. (a) S. Munavalli, D. Rohrbaugh, D. Rossman, F. Berg, G. Wagner and H. Durst, Trifluoromethylsulfenylation of masked carbonyl compounds, Synth. Commun., 2000, 30, 2847-2854; (b) T. Bootwicha, X. Liu, R. Pluta, I. Atodiresei and M. Rueping, N-Trifluoromethylthiophthalimide: A Stable Electrophilic SCF3-Reagent and its Application in the Catalytic Asymmetric Trifluoromethylsulfenylation, Angew. Chem. Int. Ed., 2013, 52, 12856-12859; (c) M. Rueping, X. Liu, T. Bootwicha, R. Pluta and C. Merkens, Catalytic enantioselective trifluoromethylthiolation of oxindoles using shelf-stable N-(trifluoromethylthio)phthalimide and a cinchona alkaloid catalyst, Chem. Commun., 2014, 50, 2508-2511; (d) R. Pluta, P. Nikolaenko and M. Rueping, Direct catalytic trifluoromethylthiolation of boronic acids and alkynes employing electrophilic shelf-stable N-(trifluoromethylthio)phthalimide, Angew. Chem. Int. Ed., 2014, 53, 1650-1653; (e) R. Mao, S. Bera, A. Cheseaux and X. Hu, Deoxygenative trifluoromethylthiolation of carboxylic acids, Chem. Sci., 2019, 10, 9555-9559; (f) W. Xu, J. Ma, X. A. Yuan, J. Dai, J. Xie and C. Zhu, Synergistic catalysis for the umpolung trifluoromethylthiolation of tertiary ethers, Angew. Chem. Int. Ed., 2018, 57, 10357-10361; (g) Q. Xiao, Q. He, J. Li and J. Wang, 1,4-Diazabicyclo[2.2.2]octane-Promoted Aminotrifluoromethylthiolation of α,β-Unsaturated Carbonyl Compounds: N-Trifluoromethylthio-4-nitrophthalimide Acts as Both the Nitrogen and SCF3 Sources, Org. Lett., 2015, 17, 6090-6093; (h) S. Mukherjee, T. Patra and F. Glorius, Cooperative catalysis: a strategy to synthesize trifluoromethylthioesters from aldehydes, ACS Catal., 2018, 8, 5842-5846.

15. T. Ji, X.-Y. Chen, L. Huang and M. Rueping, Remote Trifluoromethylthiolation Enabled by Organophotocatalytic C–C Bond Cleavage, Org. Lett., 2020, 22, 2579-2583.

16. (a) R. Honeker, J. B. Ernst and F. Glorius, Transition-Metal-Free Trifluoromethylthiolation of N-Heteroarenes, Chem. Eur. J., 2015, 21, 8047-8051; (b) H. X. Song, Z. Y. Tian, J. C. Xiao and C. P. Zhang, Tertiary-Amine-Initiated Synthesis of Acyl Fluorides from Carboxylic Acids and CF3SO2OCF3, Chem. Eur. J., 2020, 26, 16261-16265.