ChemPubSoc Europe

DOI: 10.1002/chem.201901865

CHEMISTRY A European Journal Full Paper

Synthesis Design |*Hot Paper*|

Concise and Additive-Free Click Reactions between Amines and $CF_3SO_3CF_3$

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Abstract: Trifluoromethyl trifluoromethanesulfonate has proved to be an excellent reservoir of difluorophosgene and a promising click ligation for amines in the preparation of urea derivatives, heterocycles, and carbamoyl fluorides under metal- and additive-free conditions. The reactions are rapid, efficient, selective, and versatile, and can be performed in benign solvents, giving products in excellent yields with minimal efforts for purification. The characteristics of the reactions meet the requirements of a click reaction. The use of trifluoromethyl trifluoromethanesulfonate as a click reagent is advantageous over other "CO" sources (e.g., $TsOCF_3$, $PhCO_2CF_3$, $CsOCF_3$, $AgOCF_3$, and triphosgene) because this reagent is readily accessible; easy to scale up; and highly reactive, even under metal- and additive-free conditions. It is anticipated that $CF_3SO_3CF_3$ will be increasingly as important as SO_2F_2 as a click agent in future drug design and development.

Introduction

Urea and its derivatives have played a central role in organic synthesis, since its first preparation from ammonium cyanate by Wöhler in 1828, which marked the beginning of classical organic chemistry and the first connection between chemistry and biology.[1a] Although interest in these compounds fell away in the last century because of their reputation for unreactivity and intractability, they have experienced a remarkable reemergence in the last two decades.[1] At present, urea derivatives have been widely used as chemical reagents, ligands, catalysts, and functional materials in numerous fields.[1–3] Their biological applications as plant growth regulators, agrochemicals, and pharmaceuticals have also been well documented.[2,3] The traditional synthesis of ureas mainly focused on the use of dangerous reagents, such as phosgene and isocyanates.[2] In recent years, these highly toxic reagents have been gradually substituted for safer alternatives, such as bis(4-nitrophenyl)carbonate, triphosgene, di-*tert*-butyl dicarbonate, 1,1-carbonylbisimidazole, 1,1-carbonylbisbenzotriazole, *S*,*S*-dimethyldithiocarbonate, and trihaloacetylchlorides, which can be stored and handled without special precautions.[2] The production of urea derivatives from CO, CO_2, and other miscellaneous carbonylation reagents has also been implemented.[3,4]

Moreover, carbamoyl fluorides, which represent another class of interesting compounds, have been applied as the precursors of hypofluorite, isocyanates, carbamate, *N*-fluoroalkylamines, and ureas, and as the starting materials for the synthesis of insecticides.[5,6] They can also be used as inhibitors of enzymes.[6] Carbamoyl fluorides are usually prepared from the condensation of amines with difluorophosgene or carbonic fluoride chloride, the halogen exchange of carbamoyl chlorides with fluoride, the electrochemical fluorination of carbamic acid derivatives, the hydrolysis of perfluoro(*N*,*N*-dialkylmethylamines) with oleum, and the reactions of aziridines with trifluoromethyl hypofluorite.[7] All of these transformations involve highly toxic reagents and/or harsh reaction conditions, which make them difficult to handle. Thus, the development of mild and convenient methods for the synthesis of carbamoyl fluorides is highly attractive because the exploitation of environmentally friendly processes has become one of the most important targets for today's chemists.

Trifluoromethyl trifluoromethanesulfonate (**2a**) has been confirmed as a useful reagent in recent years, although almost no progress was made for about 20 years after its initial and improved syntheses from the 1960s to the 1980s.[8] Contrary to the very reactive alkyl triflates, sulfonate **2a** is fairly stable and resistant to hydrolysis. It did not trifluoromethylate nucleophiles, such as pyridine, triethylamine, iodide, phenyllithium, phenylmagnesium bromide, lithium thiophenolate, and sodium napththalenide, but decomposed to form trifluoromethanesulfonyl fluoride and complex mixtures, which was thought to limit its synthetic utility.[8g] In reality, sulfonate **2a** has the potential to be either a OCF_3 or CF_3SO_2 transfer reagent.[9,10] Cleavage of the S–O bond in **2a** yields trifluoromethanolate salts as the most significant nucleophilic trifluoromethoxylation reagents.[9] The transition-metal-catalyzed or -free reactions of organic halides, metal complexes, α-diazo compounds, and alkenes with the $^{-}OCF_3$ anion, which is generated in situ from **2a** in the presence of anhydrous fluorides,

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Supporting Information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/chem.201901865.

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have successfully constructed a variety of trifluoromethoxylated compounds.[9] The similar employment of trifluoromethyl arylsulfonates and trifluoromethyl benzoate as $^{-}OCF_3$ sources has also been fully discussed.[11,12] Nonetheless, the application of trifluoromethyl sulfonates in other reactions, rather than trifluoromethoxylation and sulfonylation, has rarely been studied.[8]

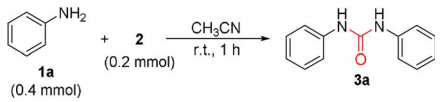
Furthermore, click chemistry is a chemical concept that was first introduced by Sharpless and co-workers in 2001, and has been extensively used in biology, medicine, and materials sciences.[13] Any reaction that can produce conjugate molecules efficiently from smaller units under simple conditions can be considered as a click reaction.[13] The best-known click reactions are the copper-catalyzed azide–alkyne cycloaddition (CuAAC) reaction and the thiol–ene reaction. Sulfur(VI) fluoride exchange (SuFEx), revived by Sharpless and co-workers, is an emerging click reaction based on the high reactivity of sulfonyl fluorides and fluorosulfates towards silyl ethers or amines.[13c,d] It is known that trifluoromethanolates are thermally unstable and tend to undergo α-fluorine elimination to form difluorophosgene and fluoride above −30 °C.[9–11] Because **2a** is an easily accessible $^{-}OCF_3$ source, which can be initiated by various nucleophiles,[8g,9] we have wondered whether it could be used as a liquid reservoir of difluorophosgene and a click reagent for amines to prepare ureas and carbamoyl fluorides under metal- and additive-free conditions.

Results and Discussion

Indeed, the reaction of **2a** with aniline (**1a**; 2.5 equiv) as a model substrate without any additive in CH_3CN at room temperature under an ambient atmosphere for 15 min provided 1,3-diphenylurea (**3a**) in 75% yield (Table S1 in the Supporting Information). The molar ratios of **2a** and **1a** had a slight influence on the reaction. A mixture of **1a** with excess **2a** at room temperature for a longer reaction time could also afford **3a** in moderate yields (Table S1 in the Supporting Information). A screening of different solvents demonstrated that hexane, CH_2Cl_2, CH_3CN, and DMF gave better yields, among which CH_3CN appeared to be the best solvent (Table S2 in the Supporting Information). Further investigation showed that the reaction of **1a** (2 equiv) with **2a** in CH_3CN at room temperature for 1 h provided 88% yield of **3a** (isolated in 90% yield) as an optimal result (Table 1). No additional base was necessary to trap the acid formed in the reaction. The addition of CsF to the reaction mixture of **1a** (2 equiv) and **2a** led to **3a** in a yield (89%) comparable to that (88%) without CsF (Table 1). This result proved that **1a** itself could trigger the reaction. Condensation was rapid, clean, and complete by simply mixing the reactants under mild conditions and with the formation of minimal or easily removable byproducts. According to the principles of click chemistry, as mentioned above, we ambitiously classify this reaction as a new type of click reaction.

To validate the efficiency of **2a** as a click reagent, the reactions of **1a** with other CO sources were compared under the same conditions (Table 1). It was found that the reaction of **1a** with **2b** under metal- and additive-free conditions gave **3a** in

Table 1. Click reactions between **1a** and different "CO" sources (**2**).[a]



Entry	2	Yield of 3a [%]
1	**2a**	88 (90), 89[b]
2	4-Me-$C_6H_4SO_3CF_3$ (**2b**)	(24, 63[b])
3	$C_6H_5CO_2CF_3$ (**2c**)	(50, 56[b])
4[c]	$CsOCF_3$ (**2d**)	71
5[c,d]	$AgOCF_3$ (**2e**)	81
6	$Cl_3COCO_2CCl_3$ (**2f**)	13, 39[e]
7	CDI[f] (**2g**)	73 (77)

[a] Reaction conditions: **1a** (0.4 mmol), **2a** (0.2 mmol), CH_3CN (2 mL), RT, 1 h. The yield was determined by HPLC with **3a** as an external standard (t_R = 4.626 min, λ_{max} = 256 nm, water/methanol (v/v) = 20:80). The yield of product isolated is given in parentheses. [b] CsF (0.02 mmol) was used. [c] Under N_2. [d] −30 °C to RT. [e] $Cl_3COCO_2CCl_3$ (0.067 mmol) was used. [f] CDI = *N*,*N*′-carbonyldiimidazole.

24% yield, and the addition of 10 mol% CsF to the reaction mixture could considerably improve the yield of **3a** (63%). Benzoate **2c** represents another useful precursor of the $^{-}OCF_3$ anion,[9b,12] and its reaction with **1a** in the absence of CsF formed **3a** in 50% yield. The choice of CsF as an additive could only slightly increase the yield of **3a** (56%). Similar treatment of **1a** with **2d** or **2e** provided **3a** in 71 or 81% yield, respectively, which was close to that with **2a**. Nevertheless, triphosgene (**2f**), a commonly used CO reagent, reacted with **1a** in the absence of additives to afford **3a** in 13 or 39% yield, depending on the number of equivalents of **2f** employed. Furthermore, the reaction of **1a** with **2g** under the same conditions produced **3a** in 73% yield (isolated in 77% yield). All of these results suggested that **2a** was the best CO source among the tested reagents under metal- and additive-free conditions.

With the optimized conditions in hand (**1**/**2a**/CH_3CN/RT/1 h), we next examined the substrate scope of the reaction with different types of amines (Table 2). To our delight, a variety of primary aniline derivatives and heteroarylamines (**1b–z**) with either electron-donating or -withdrawing groups on the aryl rings were all readily converted to form the corresponding symmetric ureas (**3b–z**) in good to high yields. The ester, ketone, amides, carboxylic acid, phenolic hydroxyl groups, allyl and alkynyl groups, and heterocycles were well tolerated in the reaction. It appeared that the electron-donating groups on the aryl rings of anilines facilitated the reaction and that very strong electron-withdrawing groups (e.g., CF_3, NO_2, and CN) slowed down the transformation, which gave lower yields of the desired products (after 1 h). The addition of CsF to the reaction mixtures could enhance the conversion of highly electron-deficient anilines (**3l–n**, **3p**, and **3z**). Sterically hindered 2,4-dimethylaniline (**1t**) and 2-allylaniline (**1u**) reacted with **2a** under standard conditions to give **3t** in 91% yield and **3u** in 87% yield; thus suggesting little effect of steric hindrance of the anilines on the reaction. In addition, click reactions of primary aliphatic amines (**1aa–aj**) with **2a** in the absence of addi-

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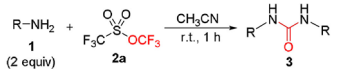
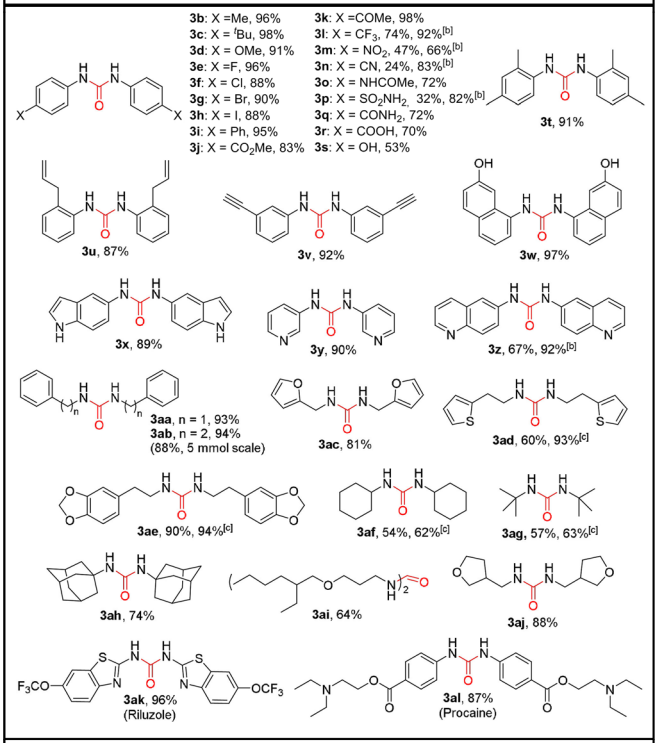
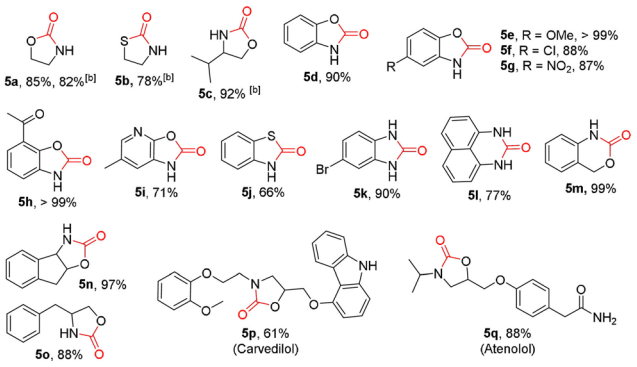
Table 2. The click synthesis of urea derivatives from **1** and **2a**.[a]





[a] Reaction conditions: **1** (0.4 mmol), **2a** (0.2 mmol), CH_3CN (2 mL), RT, ambient atmosphere, 1 h. Yields given are those of products isolated. [b] CsF (0.02 mmol) was added. [c] 15 min.

Table 3. The click synthesis of different types of heterocycles with **2a**.[a]



[a] Reaction conditions: **4** (0.2 mmol), **2a** (0.2 mmol), CH_3CN (2 mL), RT, ambient atmosphere, 1 h. Yields given are those of products isolated. [b] **4** (1.0 mmol), **2a** (1.0 mmol), CH_3CN (5 mL).

tives provided **3aa–aj** in excellent yields. Condensation was compatible with furanyl, thienyl, 1,3-benzodioxol-5-yl, and tetrahydrofuranyl groups. Shortening the reaction time of 2-(thiophen-2-yl)ethan-1-amine (**1ad**) could further improve the yield of **3ad**. If bulky aliphatic amines, such as cyclohexanamine (**1af**), 2-methylpropan-2-amine (**1ag**), and adamantan-1-amine (**1ah**), reacted with **2a** under standard conditions, the desired urea derivatives (**3af–ah**) were formed in relatively lower yields; thus implying that steric hindrance of the aliphatic amines had an impact on the transformation. It was remarkable that Riluzole (**1ak**), a glutamate antagonist, and Procaine (**1al**), an analgesic drug, underwent clean and smooth condensation with **2a** at room temperature to afford ureas **3ak** and **3al** in 96 and 87% yield, respectively; these may be proposed as potential candidates for the screening of new prodrugs of **1ak** and **1al**. These observations showed good availability of the reactions of **2a** with primary amines.

Interestingly, the click reactions of 1,2-aminoalcohols (e.g., **4a**, **4c**, **4n**,**o**), 1,2-aminothiol (e.g. **4b**), 2-aminophenols (e.g., **4d–i**), 2-aminobenzenethiol (e.g., **4j**), and 1,2-diamine (e.g., **4k**) with **2a** at room temperature under an ambient atmosphere for 1 h gave the respective oxazolidin-2-ones (**5a**, **5c**, **5n**,**o**), thiazolidin-2-one (**5b**), benzo[*d*]oxazol-2(3*H*)-ones (**5d–i**), benzo[*d*]thiazol-2(3*H*)-one (**5j**), and 1,3-dihydro-2*H*-benzo[*d*]-imidazol-2-one (**5k**) in up to >99% yield (Table 3). The reactions featured intramolecular cyclization and formed five-membered rings, rather than the ureas, through the condensation of two molecules of **4** with one molecule of **2a**. 1,3-Diamine and 1,3-aminoalcohol were also suitable substrates for the reaction. For instance, the treatment of naphthalene-1,8-diamine (**4l**) and (2-aminophenyl)methanol (**4m**) with **2a** under standard conditions gave the six-membered ring products **5l** and **5m** in 77 and 99% yield, respectively. Again, Carvedilol (**4p**), a nonselective beta blocker that is used for the treatment of heart failure and hypertension, and Atenolol (**4q**), a cardioselective beta-adrenergic blocker that is used for the treatment of angina and hypertension, were readily condensed with **2a** to supply the oxazolidin-2-one derivatives **5p** and **5q** in good yields. The aliphatic amino groups in **4p** and **4q** were selectively transformed over the aromatic and primary amide groups in these drugs, which hinted at a higher reactivity of the former to **2a** in these reactions. These achievements indicated that **2a** could be a useful cyclization "trap" for adjacent amino, hydroxyl, and thiol groups in the target molecules under metal- and additive-free conditions.

In addition, the click reactions of secondary amines with **2a** were investigated (Table 4). Different from primary aromatic and aliphatic amines, more sterically hindered secondary aliphatic amines (**6a–i**) reacted with **2a** in the absence of additives to produce carbamoyl fluorides (**7a–i**) in high yields. The reaction proceeded very rapidly (2–5 min) at room temperature and yielded carbamoyl fluorides as exclusive products. Neither prolonging the reaction time nor increasing the molar equivalents of amine could transform the carbamoyl fluoride into the corresponding urea (Table S7 in the Supporting Information). The reaction was also applicable to drug molecules (**6j–n**) containing secondary amino groups. Ciprofloxacin (a broad-spectrum antibiotic; **6j**), Amoxapine (an antidepressant; **6k**), Desioratadine (an antagonist for human histamine H1 receptor; **6l**), Fluoxetine (a selective serotonin reuptake inhibitor

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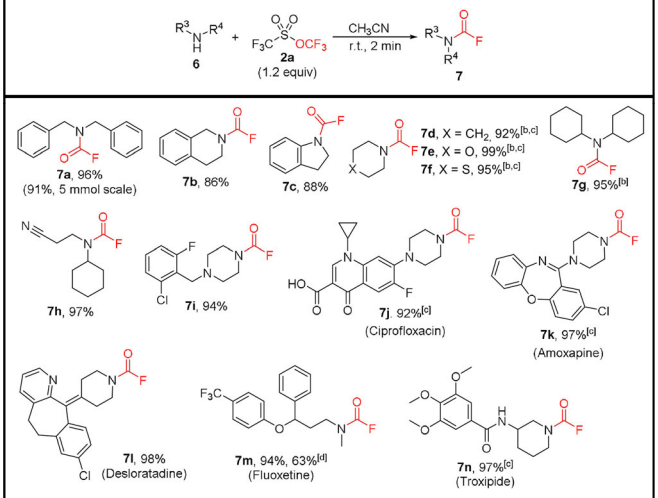
Table 4. The click synthesis of carbamoyl fluorides from secondary amines and **2a**.[a]

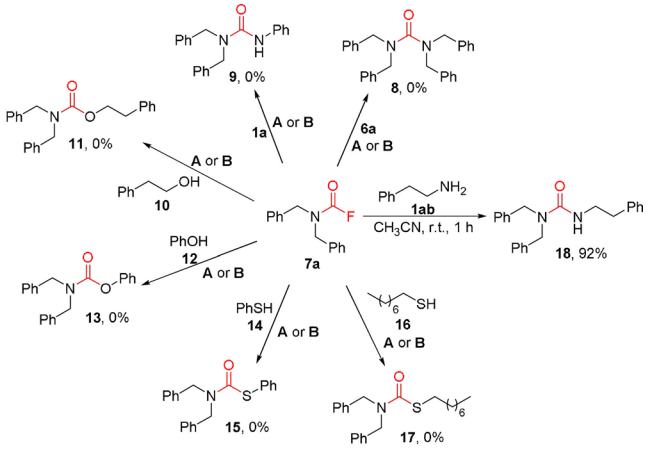


[a] Reaction conditions: **6** (0.2 mmol), **2a** (0.24 mmol), CH_3CN (2 mL), RT, ambient atmosphere, 2 min. Yields given are those of products isolated. [b] **6** (1.0 mmol), **2a** (1.2 mmol), CH_3CN (5 mL). [c] 5 min. [d] Fluoxetine hydrochloride was used directly as the starting material.

antidepressant; **6m**) and Troxipide (a systemic non-antisecretory gastric cytoprotective agent; **6n**) reacted with **2a** (1.2 equiv) in CH_3CN at room temperature for 2 or 5 min to construct the corresponding carbamoyl fluorides (**7j–n**) in 92–98% yield. In particular, the hydrochloride of fluoxetine without neutralization could also be successfully transformed under standard conditions to form **7m** in 63% yield. Functional groups such as ether, thioether, cyano, tertiary amino, imine, and amide in the substrates were well tolerated and did not hamper the formation and isolation of the desired carbamoyl fluorides; thus suggesting good selectivity and compatibility of the reaction. Additionally, it should be noted that a less nucleophilic secondary aromatic amine, such as diphenylamine, was inert to **2a** under standard reaction conditions; thus offering an opportunity to selectively functionalize the secondary aliphatic amines over the aromatic analogues.

The carbamoyl fluoride of a secondary amine (e.g., **7a**) was an unreactive reagent for secondary aliphatic amines (e.g., **6a**), aromatic amines (e.g., **1a**), alcohols (e.g., **10**), phenols (e.g., **12**), benzenethiols (e.g., **14**), and thiols (e.g., **16**) at either room temperature or 60 °C (conditions A, Scheme 1). The addition of NEt_3 to the reaction mixtures at room temperature overnight could not form the condensed products (**8**, **9**, **11**, **13**, **15**, and **17**) either (conditions B, Scheme 1). However, the carbamoyl fluoride was reactive to primary aliphatic amines because the reaction of **7a** with **1ab** at room temperature for 1 h gave **18** in 92% yield (Scheme 1). The results implied that the carbamoyl fluoride was substantially inactive to N-, O-, and S-nucleophiles, except the primary aliphatic amine; thus boding well for the compatibility of this type of compound with ordinary nucleophilic agents.

Furthermore, the competitive reaction of **1ab** (2 equiv) and 2-phenylethan-1-ol (**10**, 2 equiv) with **2a** in one pot provided

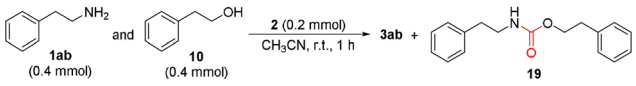


Condition **A**: **7a** (0.2 mmol), nucleophile (0.4 mmol), CH_3CN (2 mL), r.t. or 60 °C, overnight
Condition **B**: **7a** (0.2 mmol), nucleophile (0.4 mmol), CH_3CN (2 mL), Et_3N (0.2 mmol), r.t., overnight

Scheme 1. The reactions of **7a** with different N-, O-, and S-nucleophiles.

3ab in 89% yield and **19** in 3% yield (Table 5, entry 1). Meanwhile, the starting materials **1ab** and **10** were recovered in 6 and 94% yield, respectively. Addition of CsF to the reaction mixture did not significantly change the outcomes of the reaction (Table 5, entry 2). If **2b** reacted with a mixture of **1ab** and **10** under the same conditions, product **3ab** formed in 37% yield and **19** was produced in 2% yield (Table 5, entry 3). The use of **2c** instead of **2b** in the same reaction led to a 44% yield of **3ab** and 4% yield of **19** (Table 5, entry 4). These data showed the predominant formation of **3ab** in the reactions of **2a**, **2b**, and **2c**, albeit the last two reagents underwent frustrated conversions. The production of **3ab** in higher yield from **2a** might be attributed to the strongly electron-withdrawing CF_3 group, which led to easier degradation of **2a** by an amine for further condensation. In contrast, the reaction of **1ab** and **10** with **2d** or **2e** under similar conditions provided 57 or 38% yield of **3ab** and 27 or 54% of **19** (Table 5, entries 5 and 6).

Table 5. Competitive click reactions of **2** with amines and alcohols.[a]



Entry	2	Yield [%] 3ab[b]	19[c]	Recovery of 1ab/10 [%][d]
1	**2a**	89	3	6/94
2[e]	**2a**	86	4	10/89
3	**2b**	37	2	55/91
4	**2c**	44	4	50/86
5[f]	**2d**	57	27	26/74
6[f,g]	**2e**	38	54	33/64

[a] Reaction conditions: **1ab** (0.4 mmol), **10** (0.4 mmol), **2** (0.2 mmol), CH_3CN (2 mL), RT, ambient atmosphere, 1 h. [b] Yield of product isolated. [c] The yields were determined by HPLC with **19** as an external standard (t_R = 4.930 min, λ_{max} = 212 nm, water/methanol (v/v) = 20:80). [d] Starting material **1ab** was recovered by column chromatography. The recovery of **10** was determined by HPLC with **10** as an external standard (t_R = 15.575 min, λ = 212 nm, water/methanol (v/v) = 20:80). [e] CsF (0.02 mmol) was added. [f] Under N_2. [g] −30 °C to RT.

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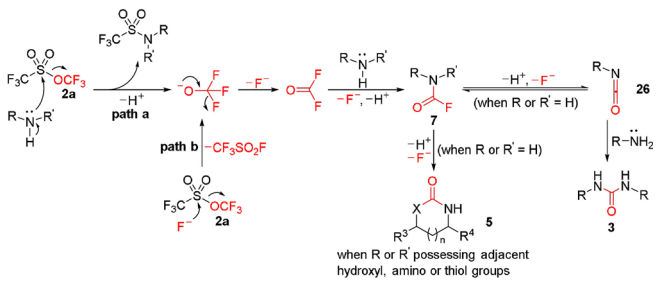
The comparable yields of **3ab** and **19** in both cases indicated the poor selectivity of $AgOCF_3$ and $CsOCF_3$ to the primary amine and alcohol, which was likely, in part, to be caused by the countercation of the $^-OCF_3$ salts.

For further comparison, the reactions of **2a** with O- or S-nucleophiles under standard or modified conditions were investigated (see the Supporting Information). If a mixture of **2a** and **10** (2 equiv), phenol (**12**, 2 equiv), benzenethiol (**14**, 2 equiv), or octane-1-thiol (**16**; 2 equiv) was kept without an additive at room temperature for 1–72 h, no desired product was formed (see the Supporting Information). Nevertheless, the same reaction of **2a** and **10** with CsF (0.1 equiv) or NEt_3 (1 equiv) as an additive provided diphenethyl carbonate (**20**) in 37 or 53% yield, respectively (see the Supporting Information). The addition of CsF or NEt_3 to reaction mixtures of **2a**/**12** and **2a**/**14**, respectively, gave diphenyl carbonate (**21**) in 20–88% yield and *S*,*S*-diphenyl carbonodithioate (**22**) in 49–87% yield after 12–72 h (see the Supporting Information). Different from **10**, **12**, and **14**, octane-1-thiol (**16**) reacted with **2a** at room temperature in the presence of CsF or NEt_3 to produce 1,2-dioctyldisulfane instead of *S*,*S*-dioctyl carbonodithioate (**23**; see the Supporting Information). If 1-phenylethane-1,2-diol (**24**) was mixed with **2a** at room temperature for 1–12 h, no product was formed (see the Supporting Information). The use of CsF or NEt_3 in the same reaction could greatly improve the production of 4-phenyl-1,3-dioxolan-2-one (**25**), which was obtained in up to 94% yield after 1 h. These findings, combined with the above discussions for amines, indicated that the N-, O- and S-nucleophiles might have distinct reaction profiles for **2a**, and that the N-nucleophiles might have priority for condensation with **2a** under additive-free conditions, compared with homologous O- and S-nucleophiles.

Based on the results above, a plausible reaction mechanism is suggested in Scheme 2. The synthesis of urea derivatives and carbamoyl fluoride from **2a** and amines might start from the nucleophilic substitution of **2a** by an amine at the sulfur center, which first forms the $^-OCF_3$ anion and trifluoromethanesulfonamide (path a, Scheme 2). Then, the $^-OCF_3$ anion rapidly fragments into COF_2 and fluoride through α-F elimination. Carbonylation of amine with COF_2 yields a carbamoyl fluoride (**7**) and releases an equal equivalent of HF. In the case of primary amines, fluoride **7** possibly undergoes elimination of HF to form a highly reactive isocyanate (**26**). This process could be reversed in the presence of HF. Both **7** and **26** react further with another equivalent of amine to produce the corresponding urea derivative (**3**). If the amine possesses an adjacent hydroxyl, amino, or thiol group, intramolecular cyclization of **7** and/or **26** occurs to supply five- or six-membered heterocycles. In the case of secondary amines without neighboring hydroxyl, amino, or thiol groups, the reaction stops at the carbamoyl fluoride intermediate, yielding various drug-like molecules. The fluorides generated in situ from decomposition of the $^-OCF_3$ anion and condensation of the amine with COF_2 are other important initiators for the degradation of **2a** (path b, Scheme 2). Because only a trace amount of $TfNHC_6H_5$ was formed (< 1%) in the standard reaction of **1a** and **2a**, as determined by ^{19}F NMR spectroscopy analysis of the reaction mixture (see the Supporting Information), the catalytic cycle of the reaction should be largely sustained by in situ formed fluorides. Additionally, the relative inertness of the O- and S-nucleophiles to **2a**, in comparison with the amines, might be attributed to the inability of these substrates to trigger the decomposition of **2a** to the key CO_2F intermediate under standard reaction conditions.



Scheme 2. A plausible reaction mechanism for the production of ureas, heterocycles, and carbamoyl fluorides from **2a** and amines.

Conclusion

We have developed an efficient and convenient method for the synthesis of ureas, heterocycles, and carbamoyl fluorides from amines and **2a**. The reaction proceeded very rapidly and supplied a large number of useful, potentially bioactive molecules under mild conditions. Sulfonate **2a** has proved to be a safe and stable replacement for difluorophosgene and a wonderful click reagent for amines without additional additives at room temperature. It was revealed that the click reactions of **2a** with primary amines at room temperature formed ureas in good to high yields, while the same reactions with secondary aliphatic amines provided selectively carbamoyl fluorides in excellent yields. If **2a** reacted with amines containing adjacent hydroxyl, amino, or thiol groups under standard conditions, a variety of five- and six-membered heterocycles were eventually produced. The reactions featured simplicity, high efficiency, a wide range of substrates, good functional group tolerance, excellent selectivity, no additives, and effortless purification of the products because of the formation of gaseous or easily removable byproducts. It was significant that even the hydrochloride of fluoxetine, without neutralization, could be transformed under the standard conditions; thus suggesting good applicability and compatibility of this method. Further application of **2a** as a promising precursor of difluorophosgene and anhydrous fluoride in organic synthesis is currently underway in our laboratory.

Experimental Section

A sealed tube was charged with amine **1** (0.4 mmol), CH_3CN (1.5 mL), and a solution of **2a** (43.6 mg, 0.2 mmol) in CH_3CN (0.5 mL) with stirring. The mixture was reacted at room temperature under ambient atmosphere for 1 h, quenched with water (2–3 drops), and concentrated to dryness under reduced pressure. The residue was purified by means of column chromatography on

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silica gel (3–5 cm length) with a mixture of petroleum ether and ethyl acetate as eluents to give the urea products (**3**).

Acknowledgements

We thank the Wuhan University of Technology, the National Natural Science Foundation of China (21602165), the "Chutian Scholar" Program from the Department of Education of Hubei Province, the "Hundred Talent" Program of Hubei Province, the Wuhan Youth Chen-Guang Project (2016070204010113), and the Excellent Dissertation Cultivation Funds of Wuhan University of Technology (2018-YS-082) for financial support.

Conflict of interest

The authors declare no conflict of interest.

Keywords: amines · click chemistry · fluorides · sulfur · synthesis design

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Manuscript received: April 24, 2019
Revised manuscript received: June 4, 2019
Version of record online: ■■ ■■, 0000

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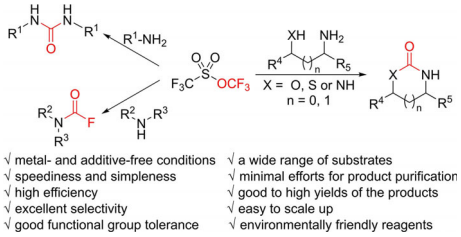

Back to basics: Trifluoromethyl trifluoromethanesulfonate is a promising click reagent for amines in the preparation of urea derivatives, heterocycles, and carbamoyl fluorides under metal- and additive-free conditions (see scheme). The click reactions are rapid, efficient, and selective, and simply carried out in benign solvents to afford products with minimal efforts for purification.

Synthesis Design

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■■ – ■■

Concise and Additive-Free Click Reactions between Amines and $CF_3SO_3CF_3$

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