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Trifluoromethylation

Regioselective Synthesis of N-Heteroaromatic Trifluoromethoxy Compounds by Direct O–CF_3 Bond Formation

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Abstract: The first one-step method for the synthesis of *ortho*-N-heteroaromatic trifluoromethoxy derivatives by site-specific O–CF_3 bond formation using hydroxylated N-heterocycles and Togni's reagent is described. The approach enables the unprecedented syntheses of a wide range of six or five-membered N-heteroaromatic trifluoromethoxy compounds containing one or two heteroatoms from most commonly used hydroxylated N-heterocycles. Notable advantages of this method include its simplicity and mild conditions, avoidance of the need for metals or toxic reagents, and compatibility with a variety of functional groups. Furthermore, this method is especially suitable for the larger scale application.

Fluorine plays a conspicuous and increasingly important role within pharmaceuticals and agrochemicals, as well as in materials science, because one or a few fluorine atoms substituted at specific sites in organic compounds can dramatically alter their chemical and biological properties, such as solubility, metabolic and oxidative stability, lipophilicity, and bioavailability.[1] Among fluorine-containing functional groups, the trifluoromethoxy group (OCF_3) has unique structural and electronic properties,[2] so OCF_3-containing compounds with higher lipophilicities show enhancement in their in vivo uptake and transport in biological systems. Indeed, many OCF_3-containing compounds are of current interest for their use in materials, agricultural, and pharmaceutical science (Figure 1 a).[3] For example, Riluzole is the first approved drug for the treatment of neurological diseases such as amyotrophic lateral sclerosis.[4] Celikalim is known as a potent potassium channel opener in human airway smooth muscles.[5] There are also many pesticides, such as Triflumuron, Indoxacarb, and Thifluzamide, that contain OCF_3.[3b,6] Aside from the examples of compounds containing the OCF_3 group at an aromatic ring that have been used in drugs or pesticides, aliphatic trifluoromethyl ethers have been used in the field of liquid crystalline materials.[3c]

Despite the special properties and the wide applications of the OCF_3 group, its facile introduction into organic molecules has always been a challenge. Therefore, the development of an efficient trifluoromethoxylation process is currently a major goal in organic synthesis. Most current routes to trifluoromethoxy compounds fall into two main categories: 1) the fluorine atoms are introduced by chlorine–fluorine exchange, deoxyfluorination of fluoroformates, or oxidative fluorodesulfurization under hazardous and harsh reaction conditions;[7] 2) trifluoromethoxy compounds were synthesized, based on construction of the C–OCF_3 bond, by nucleophilic trifluoromethoxylation,[8] metal-mediated trifluoromethoxylation,[9] radical addition trifluoromethoxylation,[10] or OCF_3 migration.[11] Although OCF_3 can be introduced to organic molecules, most approaches either suffer from poor substrate scope or require use of highly toxic and/or thermally labile reagents. In addition, in some approaches, regioselectivity is difficult to control.

Direct O–CF_3 bond formation has recently received much attention as a new synthetic route to trifluoromethoxy compounds, owing to the development and utilization of trifluoromethylating reagents in recent years.[12] Togni and co-workers reported the successful O–CF_3 bond formation with primary and secondary alcohols or *N*,*N*-dialkylhydroxylamines by using electrophilic hypervalent iodine reagents.[13] However, examples of direct *O*-trifluoromethylation of phenols are still limited. These examples include: 1) a conceptually important approach reported by Umemoto et al. for the direct, electrophilic trifluoromethylation of alcohols, phenols, and amines by using *O*-(trifluoromethyl)dibenzofuranium salts,[14] and 2) the synthesis of 1,3,5-trimethyl-2-(trifluoromethoxy)benzene by using Togni's reagent, as reported by Togni and co-workers.[15] The drawback of approach (1), however, is that the highly reactive species need to be generated in situ from diazonium salts containing a trifluoromethoxy group and reaction conditions are harsh,[14] whereas, in approach (2), the desired product was obtained as a byproduct in only 15% yield and the major products were a mixture of *C*-trifluoromethylated derivatives.[15]Among the aromatic compounds containing OCF_3 group(s), 2-(trifluoromethoxy)pyridine and 2-(trifluoromethoxy)quinoline derivatives

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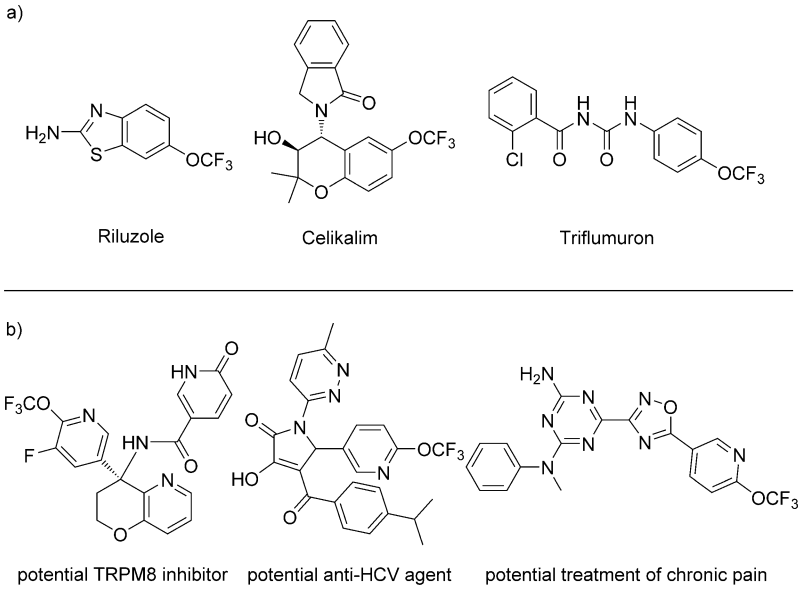
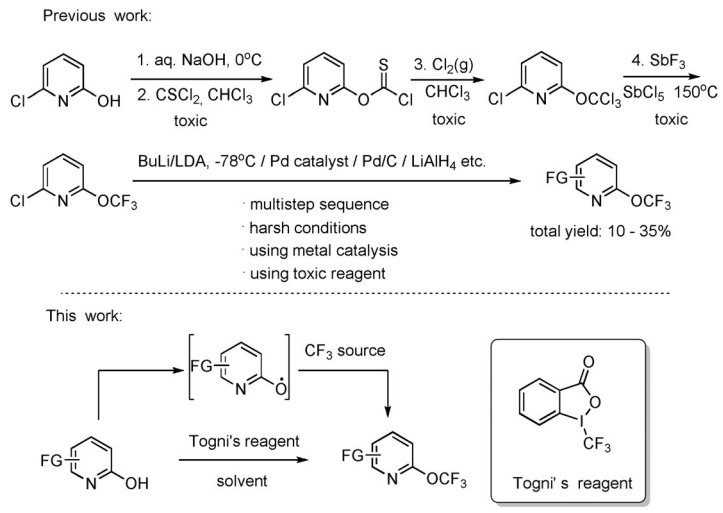


Figure 1. Examples of OCF_3-containing compounds.

are especially useful for agrochemicals and drugs (Figure 1 b).[16] However, approaches to synthesize these compounds and, especially, other N-heteroaromatics containing two or three heteroatoms, are very limited. Only Leroux et al.,[17] in 2010, reported a general approach to synthesize 2-(trifluoromethoxy)pyridines by a multistep sequence with lower yields. Moreover, due to the poor substrate scope and highly toxic reagents, application of this method is limited. Herein, we report the first convenient, general, and efficient method for the synthesis of OCF_3-containing pyridine, quinolone, and isoquinoline derivatives, as well as other N-heteroaromatics containing two heteroatoms, through site-specific O–CF_3 bond formation (Scheme 1).

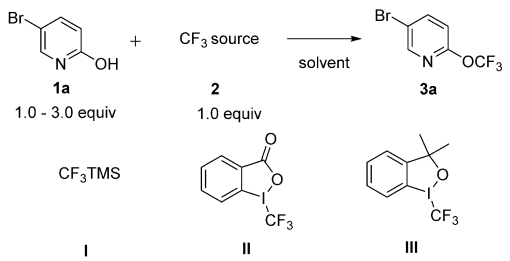
During the preparation of this paper, Qing and co-workers[18] reported the an excellent study on silver-mediated oxidative trifluoromethylation of phenols. In contrast to their study, the method that we report herein does not require metal-mediated conditions. As an effective complement to their work, we provide another choice for the synthesis of OCF_3-containing compounds. Optimization of the reaction parameters was explored by using 5-bromopyridin-2-ol (**1 a**) as a model substrate in conjunction with various CF_3 sources (Table 1). Initially, non-hazardous, widely used Me_3SiCF_3 (**I**) and Togni's reagent[12b,13,19] (**II**, **III**; 1.0 equiv) were tested as electrophilic CF_3-transfer reagents in $CHCl_3$ solution at reflux temperature for 48 hours (Table 1, entries 1–3). When **I** was used, no product was obtained (Table 1, entry 1). However, by using reagents **II** or **III**, the desired product was obtained. A higher yield was obtained when using reagent **II** as the CF_3-transfer reagent (Table 1, entries 2 vs. 3). We next investigated a variety of solvents and found that CH_3NO_2 was the best choice (Table 1, entry 7), although the yield did not exceed 24%. We then explored the effects of the bases,[20] Lewis acids,[12b,13a] and Brønsted acids[21,12b] on the reaction. To our disappointment, none of these additives were conducive to the reaction (see the Supporting Information). However, to our surprise, by increasing the amount of **1 a**, the yield was greatly improved (Table 1, entries 10–12). When the reaction temperature was increased to 100 °C and the reaction time was shortened from 48 hours to 5 hours, a yield of 67% was obtained (Table 1, entry 13). With these results in hand, the reaction was also performed under UV light or with the addition of radical initiators, such as azobisisobutyronitrile (AIBN) or benzoyl peroxide (BOP), but the effects were adverse (see the Supporting Information). Thus, the optimum reaction conditions were determined as the combination of 3.0 equivalents of **1 a**, 1.0 equiv **II**, in CH_3NO_2 at 100 °C for 5 hours.



Scheme 1. Site-specific O–CF_3 bond formation of 2-hydroxypyridine derivatives.

Next, the substrate scope of the trifluoromethoxylation of N-heteroaromatic compounds was investi-

Table 1. Representative results for the optimization of the trifluoromethylation of **1a** with **2**.[a]



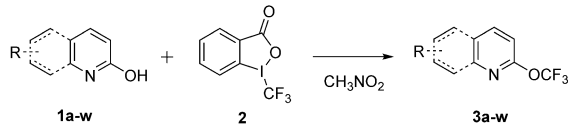
Entry	CF_3 source	T [°C]	t [h]	Solvent	Yield [%][b]
1	**I**	70	48	$CHCl_3$	0
2	**II**	70	48	$CHCl_3$	14
3	**III**	70	48	$CHCl_3$	8
4	**II**	70	48	DCE	19
5	**II**	70	48	dioxane	12
6	**II**	70	48	ethyl acetate	8
7	**II**	70	48	CH_3NO_2	24
8	**II**	70	48	CH_3CN	16
9	**II**	70	48	DMF	trace
10[c]	**II**	70	48	CH_3NO_2	41
11[d]	**II**	70	48	CH_3NO_2	46
12[e]	**II**	70	48	CH_3NO_2	47
13[f]	**II**	100	5	CH_3NO_2	67

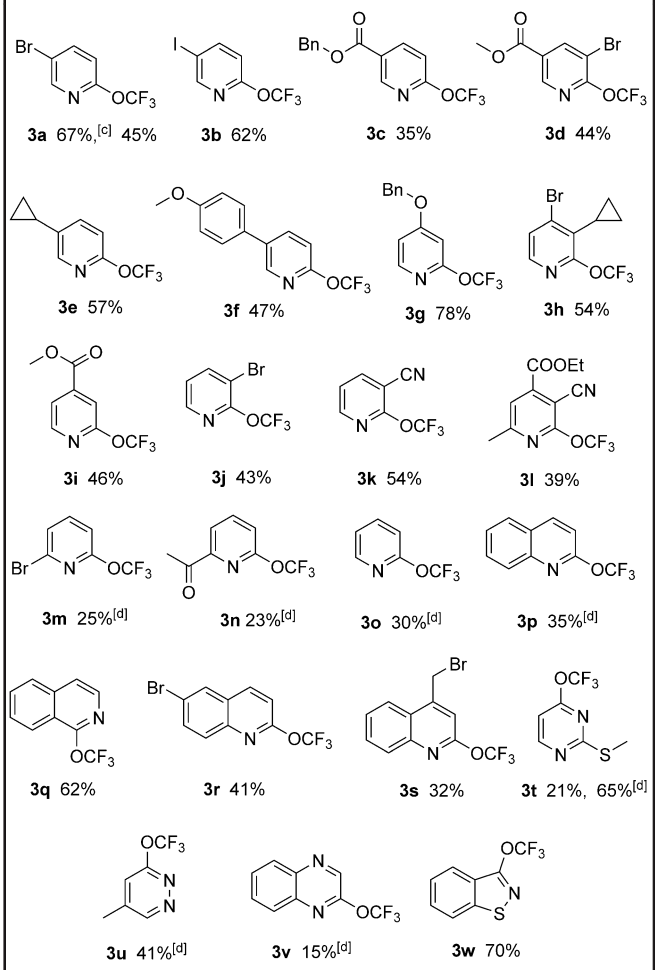
[a] Reaction conditions (unless otherwise stated): **1a** (0.1 mmol) and CF_3 source (0.1 mmol) in the specified solvent (1.0 mL) were stirred at 70 °C for 48 hours under air; [b] yields were determined by using GC (average of two GC runs) with *n*-dodecane as an internal standard; [c] **1a** (0.2 mmol), **II** (0.1 mmol); [d] **1a** (0.3 mmol), **II** (0.1 mmol); [e] **1a** (0.4 mmol), **II** (0.1 mmol); [f] **1a** (0.3 mmol), **II** (0.1 mmol).

gated (Table 2). Using 2-hydroxypyridine derivatives containing electron-neutral, electron-donating and electron-withdrawing groups as substrates, the reaction proceeded smoothly to give 2-trifluoromethoxypyridine derivatives **3a**–**n** in 23–78% yield. A variety of important functional groups, including ester, cyano, acetyl, ether, halide, alkyl, and aryl, were well tolerated under the mild reaction conditions. Furthermore, complicated 2-hydroxypyridine derivatives containing multiple functional groups (**3d**, **3h**, **3l**) were also transformed into trifluoromethoxy compounds in good yields by using this method. In general, substrates containing electron-withdrawing groups were found to give the desired products in lower yields than those with electron-donating groups (**3c**, **3i** vs. **3g**). When using pyridines with an amino substituent at the 3- or 5-position, the trifluoromethylation mainly occurred on the aromatic ring, affording the desired trifluoromethyl ether in very low yield, which could only be detected by ^{19}F NMR spectroscopy and LC-MS.

To expand the potential utility of this reaction for medicinal chemistry, heterocycles, such as quinoline/isoquinoline derivatives, and other N-heteroaromatics containing two heteroatoms, were also subjected to this reaction protocol (**3p**–**w**). The desired trifluoromethoxylated products **3p**–**u** were nevertheless produced in good yields under the developed conditions. Five-membered N-heteroaromatic compounds can also be applied under these conditions to give the desired product in good yield (**3w**).

Table 2. Direct *O*-trifluoromethylation of N-heteroaromatics.[a,b]

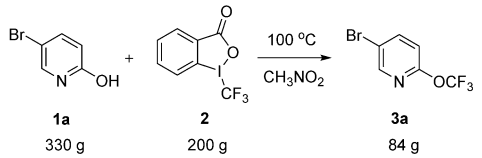




[a] Reaction conditions: **1** (3.0 mmol), **2** (1.0 mmol), CH_3NO_2 (10 mL), 100 °C, 5 h, under air. [b] yields of isolated product based on **2**; [c] yields were determined by using GC (average of two GC runs) with *n*-dodecane as an internal standard; [d] yield determined by ^{19}F NMR spectroscopy with 2-(trifluoromethyl)benzenamine as the internal standard.

The reaction is also very suitable for application in larger scale experiments. Treatment of 330 g of **1a** with 200 g of reagent **II** in 6 L of CH_3NO_2 produced 84 g of **3a** (55% yield; Scheme 2), with 152 g of **1a** recovered.

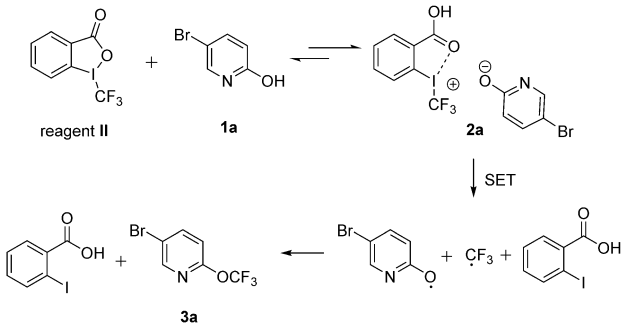
To gain insight into the reaction mechanism, we carried out several experiments (see the Supporting Information). A stoichiometric amount of the radical trap 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and 3,5-di-*tert*-butyl-4-hydroxytoluene (BHT) were added to the reaction mixture of **1a** and reagent **II**. With the increase of the amount of TEMPO, the yield of the product was decreased and the amount of TEMPO-CF_3 was increased. When BHT was used, the formation of BHT-CF_3 adduct could be detected by GC-MS & ^{19}F NMR. The result is a strong



Scheme 2. Scalability of the trifluoromethylation of **1a**.

indication of a radical pathway with a CF_3 radical as the key intermediate.Treatment of the sodium salt of **1a** with reagent **II** in CH_3NO_2 at 100 °C did not afford the desired product **3a**, indicating that the proton of the phenolic hydroxy group is important for the reaction. It is possible that the proton transfer is a necessary condition for the formation of the CF_3 radical. Togni and co-workers have discussed similar proton transfer pathways in their work on trifluoromethylation.[12b,13b,21,22] Rapid protonation of the carboxyl moiety causes a weakening of the I–O bond, thus freeing a coordination site at the iodine, followed by the occupation of the substrate to form an iodonium intermediate. After protonation of reagent **II** by either hydroxypyridine, a CF_3 radical, from hemolytic cleavage of the I–CF_3 bond by a SET step, and simultaneously a phenoxyl radical are formed. After recombination, the desired product is formed.

In light of these results, we assumed that the mechanism for O–CF_3 bond formation is similar to that proposed by Togni[13b] (Scheme 3). Firstly, through a proton transfer pre-equilibrium between the phenolic hydroxy and reagent **II**, a charge-transfer complex **2a** is formed. Secondly, a pair of radicals are generated through a SET step which then afford the desired product **3a** upon recombination.



Scheme 3. Proposed reaction mechanism.

In conclusion, we have developed a simple site-specific trifluoromethoxylation of N-heteroaromatic compounds through O–CF_3 bond formation by using commercially available *ortho*-hydroxy N-heterocycles and Togni's reagent as a CF_3 source under mild reaction conditions without the use of any transition metal catalysts and/or toxic reagents. The reaction is very generally applicable to a wide range of substrates and most functional groups are tolerated. More importantly, this method is very simple and mild. It would be useful in industrial processes, laboratory methods, and applications in drug discovery research. The introduction of an OCF_3 group into a molecule of interest at a late stage of a synthesis under mild reaction conditions could accelerate the discovery of lead compounds.

Experimental Section

A dried glass reaction tube equipped with a magnetic stir bar was charged with **1** (3.0 mmol), **2** (316 mg, 1.0 mmol), and CH_3NO_2 (10.0 mL). The reaction mixture was then stirred at 100 °C for 5 h. The reaction progress was monitored by TLC. The reaction mixture was then allowed to cool to room temperature, filtered through a pad of celite, and washed with ethyl acetate (10 mL × 3). The combined organic solvent was removed under reduced pressure. The residue was purified by silica gel flash chromatography to afford the desired product. The products were characterized by ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, GC-MS, LC-MS and HRMS.

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Keywords: C–O bond formation · N-heterocycles · hypervalent iodine reagents · trifluoromethylation

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