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TfOH-Promoted Transition-Metal-Free Cascade Trifluoroethylation/Cyclization of Organic Isothiocyanates by Phenyl(2,2,2-trifluoroethyl)iodonium Triflate

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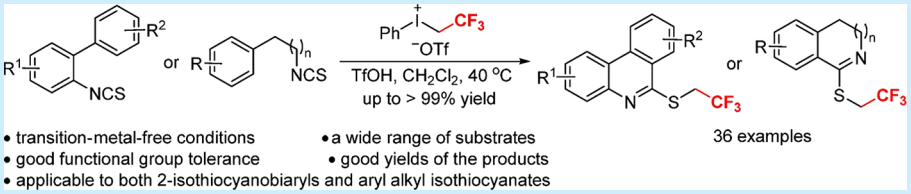
Supporting Information



ABSTRACT: An efficient and transition-metal-free method for the synthesis of the structurally diversified trifluoroethylthiol phenanthridines and 3,4-dihydroisoquinolines is described. Various 2-isothiocyanobiaryls and aryl alkyl isothiocyanates reacted with phenyl(2,2,2-trifluoroethyl)iodonium triflate in CH_2Cl_2 in the presence of trifluoromethanesulfonic acid at 40 °C to form the corresponding trifluoroethylation/cyclization products in good to quantitative yields. This work represents the first construction of trifluoroethylthiol phenanthridine and isoquinoline derivatives from isothiocyanates in the absence of transition-metal catalysts by a one-pot procedure.

The installation of bioisosteric fluorine or fluorine-containing groups into bioactive molecules can dramatically change their physiochemical and pharmacokinetic properties.[1] Given the benefits invoked by fluorine, a great variety of fluorine-containing compounds have been utilized in the search for new pharmaceuticals and agrochemicals.[1,2] Among these entities, trifluoroethylated molecules are of particular interest as a growing number of CF_3CH_2 compounds with potent biological activities have emerged in drug discovery.[3] Thus, the development of effective and practical methods for the synthesis of trifluoroethylated compounds is of vital importance.[3] At present, the transition-metal-catalyzed or -free trifluoroethylation of a wide range of organic scaffolds, such as arylboronic acids or esters, aryl iodides, arene, alkynes, alkenes, anilines, and aryl Grignard reagents, has been documented.[4−7] Reagents used in these reactions include CF_3CH_2I, CF_3CHN_2, CF_3CHCl_2, $(CF_3CH_2SO_2)_2Zn$, $CF_3CH_2SO_2Na$, $CF_3CH_2SO_2Cl$, CF_3CO_2H, and $[ArICH_2CF_3]X$ (Ar = C_6H_5, 2,4,6-$Me_3C_6H_2$; X = OTf, NTf_2).[4−7] Aryl(2,2,2-trifluoroethyl)iodonium salts ($[ArICH_2CF_3]X$), first synthesized by Umemoto, have proven to be the highly efficient electrophilic trifluoroethylation reagents for heteroatom and carbon nucleophiles under mild conditions.[7,8] The palladium-catalyzed reactions of aryl(2,2,2-trifluoroethyl)iodonium triflates with arylboronic acids via Suzuki−Miyaura cross-coupling or with anilides, aromatic amides, and indoles via C−H activation have represented the state-of-the-art transition-metal-catalyzed trifluoroethylation approaches using $[ArICH_2CF_3][OTf]$ as the CF_3CH_2 sources.[9] Notably, the catalyst-free reactions of $[ArICH_2CF_3]X$ with amines, peptides, alcohols, phenols, thiols, sulfides, carbohydrates, thioglycosides, fatty acids, phosphines, and electron-rich arenes have supplied a large number of trifluoroethylated bioactive molecules.[7,8] These studies demonstrate that $[ArICH_2CF_3]X$ have much more powerful trifluoroethylation reactivity than other electrophilic CF_3CH_2-transfer reagents.

On the other hand, phenanthridine and isoquinoline derivatives are privileged compounds found in natural products, with many of them showing antitumor, antiviral, antibacterial activities, and/or optoelectronic properties.[10,11] A variety of 6-fluoroalkylated phenanthridines have been constructed by the radical insertion reactions of numerous fluoroalkylation reagents into 2-isocyanobiaryls.[10c] However, synthesis of fluorinated phenanthridines from 2-isothiocyanobiaryls via direct fluoroalkylation at the isothiocyano (NCS) moieties has not been realized. Only a few examples of preparing nonfluorinated phenanthridines by a copper-catalyzed tandem arylation/cyclization of 2-biaryl isothiocyanates with diaryliodonium salts (at 100 °C) and a Mn(II)-promoted tandem phosphorylation/cyclization reaction of 2-biaryl isothiocyanates with phosphine oxides (at 110 °C) have been reported.[12] Although preparation of isoquinoline derivatives by intramolecular cyclization of aryl alkyl

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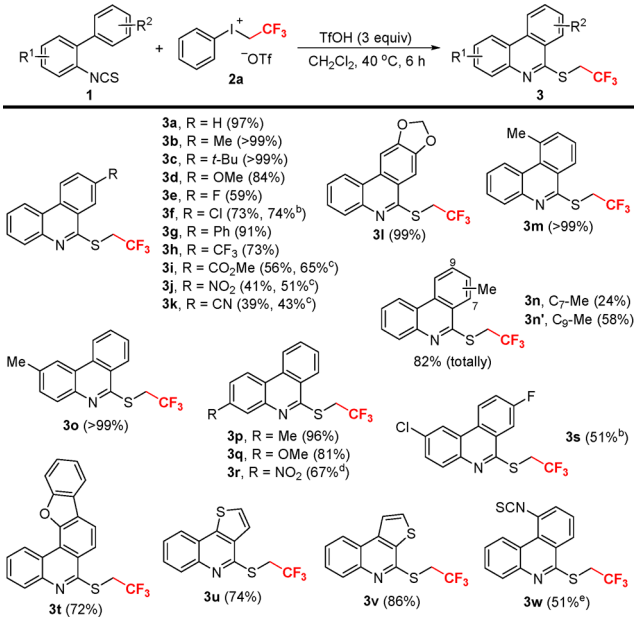
isothiocyanates in the presence of copper catalysts or Brönsted acids has been explored, the fluorinated versions of these conversions have never been known.[13] Since aryl(2,2,2-trifluoroethyl)iodonium salts are powerful electrophilic trifluoroethylation reagents toward a variety of nucleophiles,[7,8] we wondered whether $[ArICH_2CF_3][OTf]$ would trigger a transition-metal-free cascade 2,2,2-trifluoroethylation/cyclization of organic isothiocyanates. It is a challenging task to activate isothiocyano groups by iodonium salts without transition-metal catalysts because the NCS segments in 2-isothiocyanobiaryls have much poorer nucleophilicity.[12]

Indeed, reaction of 2-isothiocyanato-1,1′-biphenyl (**1a**) with phenyl(2,2,2-trifluoroethyl)iodonium triflate (**2a**, 2 equiv) in CH_3CN, $ClCH_2CH_2Cl$, CH_2Cl_2, toluene, or 1,4-dioxane at room temperature or 80 °C for 15 or 24 h gave none or a trace amount (<1%) of 6-[(2,2,2-trifluoroethyl)thio]phenanthridine (**3a**) (Table S2-1). Addition of bases such as K_3PO_4, KF, CH_3CO_2K, and HCO_2Na to the reaction mixture of **1a** and **2a** in CH_3CN at 80 °C afforded none or <1% of **3a** as well. Significantly, if the reaction of **1a** and **2a** was carried out in CH_3CN in the presence of 1.5 equiv of TfOH at room temperature for 15 h, 3% of **3a** was formed. Furthermore, if the same reaction with TfOH was run in CH_2Cl_2 or $ClCH_2CH_2Cl$, **3a** was obtained in 72% or 52% yields, respectively. These results suggest that the superacid TfOH could efficiently promote the trifluoroethylation/cyclization reaction of **1a**. The reaction was neither air- nor moisture-sensitive as the mixtures of **1a**, **2a**, and TfOH treated under a nitrogen atmosphere or an ambient atmosphere provided **3a** in comparable yields (Table S2-2). Finally, treatment of **1a** with **2a** (2 equiv) in CH_2Cl_2 in the presence of TfOH (3 equiv) at room temperature for 24 h or at 40 °C for 6 h gave 96% or 97% of **3a** (Table S2-2). Other strong acids such as CF_3CO_2H, concentrated H_2SO_4, CH_3SO_3H, and Tf_2NH could also facilitate the production of **3a** (2−50% yield) but showed much less efficiency compared to TfOH (Table S2-3). Moreover, the similar reactions using mesityl(2,2,2-trifluoroethyl)iodonium triflate (**2b**) as a CF_3CH_2 source instead of **2a** provided **3a** in moderate yields, indicating relatively poor reactivity of **2b** in this transformation (Table S2-5).

With the optimized conditions in hand (**1**, **2a** (2 equiv), TfOH (3 equiv), CH_2Cl_2, rt/24 h or 40 °C/6 h), the substrate scope of this trifluoroethylation/cyclization reaction was examined (Scheme 1). To our delight, various 2-isothiocyanobiaryls **1b−s** bearing either electron-donating or -withdrawing groups on the aryl rings were all smoothly converted to furnish the corresponding trifluoroethylthiol phenanthridine derivatives **3b−s** in 39% to >99% yields. The electronic nature and the position of the substituents on the aryl rings had a considerable influence on the reaction. The electron-withdrawing groups (e.g., fluoro, chloro, trifluoromethyl, ester, nitro, cyano) on either of the aromatic rings of 2-isothiocyanobiaryls slowed down the trifluoroethylation/cyclization processes, which afforded 39−73% yields of the desired products **3e**, **3f**, **3h−k**, **3r**, and **3s**. Prolonging the reaction time could somewhat improve the yields of these derivatives (e.g., **3f**, **3i−k**). In addition, reaction of 2-isothiocyanato-4′-methyl-1,1′-biphenyl (**1b**) or 2-isothiocyanato-2′-methyl-1,1′-biphenyl (**1m**) with **2a** under the standard conditions provided **3b** or **3m**, respectively, as the sole product, in quantitative yield, while the same reaction of 2-isothiocyanato-3′-methyl-1,1′-biphenyl (**1n**) with **2a** afforded a

Scheme 1. Transition-Metal-Free Trifluoroethylation/Cyclization of Aryl Isothiocyanates by $[PhICH_2CF_3][OTf]$ in the Presence of TfOH[a]



[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), TfOH (0.6 mmol), CH_2Cl_2 (2 mL), 40 °C, 6 h. Isolated yields. [b]12 h. [c]24 h. [d]3 days. [e]TfOH (1.2 mmol), 12 h.

mixture of 7-methyl-6-[(2,2,2-trifluoroethyl)thio]-phenanthridine (**3n**, 24%) and 9-methyl-6-[(2,2,2-trifluoroethyl)thio]phenanthridine (**3n′**, 58%). Similar treatment of 5-(2-isothiocyanatophenyl)benzo[*d*][1,3]dioxole (**1l**) with **2a** gave 6-[(2,2,2-trifluoroethyl)thio][1,3]dioxolo[4,5-*j*]phenanthridine (**3l**) in 99% yield. Heteroaromatic systems were also suitable substrates for the reaction. 4-(2-Isothiocyanatophenyl)dibenzo[*b*,*d*]furan (**1t**), 2-(2-isothiocyanatophenyl)thiophene (**1u**), and 3-(2-isothiocyanatophenyl)thiophene (**1v**) reacted with **2a** under the standard conditions to form phenanthridine derivatives **3t−v** in good yields. Interestingly, reaction of 2,2′-diisothiocyanato-1,1′-biphenyl (**1w**) with **2a** in the presence of 6 equiv of TfOH at room temperature for 12 h supplied 10-isothiocyanato-6-[(2,2,2-trifluoroethyl)thio]phenanthridine (**3w**) in 51% yield, with one NCS group transformed and the other retained. All these combined suggested good compatibility and availability of the reaction.

Furthermore, the TfOH-promoted trifluoroethylation/cyclization reaction was applicable to aryl alkyl isothiocyanates (**4**) (Scheme 2). Numerous (2-isothiocyanatoethyl)arenes **4b−j** with either electron-donating or slightly electron-withdrawing groups on the aromatic rings reacted with **2a** in the presence of 3 equiv of TfOH at 40 °C for 2 h to furnish the respective trifluoroethylthiolated 3,4-dihydroisoquinolines in good yields. The position of the functionalities on the aryl rings had little influence on the reaction. The *para*- or *meta*-substituted (2-isothiocyanatoethyl)arenes (e.g., **4b**, **4d**, **4f**) reacted mildly to give the desired products (**5b**, **5d**, **5f**) in yields close to those obtained from the *ortho*-substituted analogues **4c**, **4e**, and **4g**. 1-Bromo-3-(2-isothiocyanatoethyl)benzene (**4f**), 4-(2-isothiocyanatoethyl)-1,2-dimethoxybenzene (**4h**), 5-(2-isothiocyanatoethyl)benzo[*d*][1,3]dioxole (**4i**), and 1,2-dichloro-4-(2-isothiocyanatoethyl)benzene (**4j**) reacted specifi-

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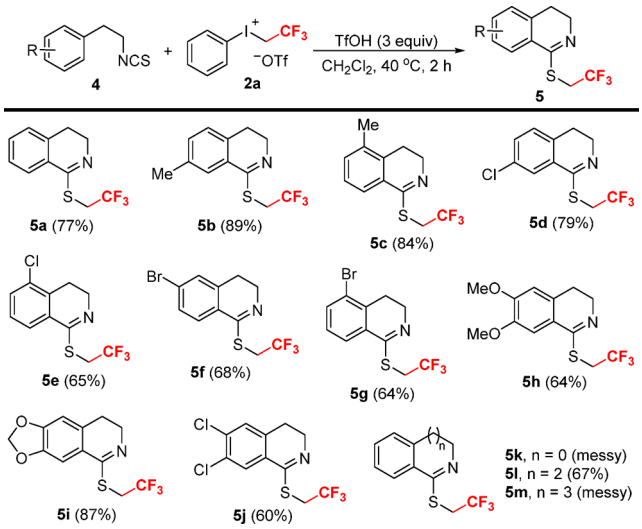
Scheme 2. Transition-Metal-Free Trifluoroethylation/Cyclization of Aryl-Alkyl Isothiocyanates by $[PhICH_2CF_3][OTf]$ in the Presence of TfOH[a]

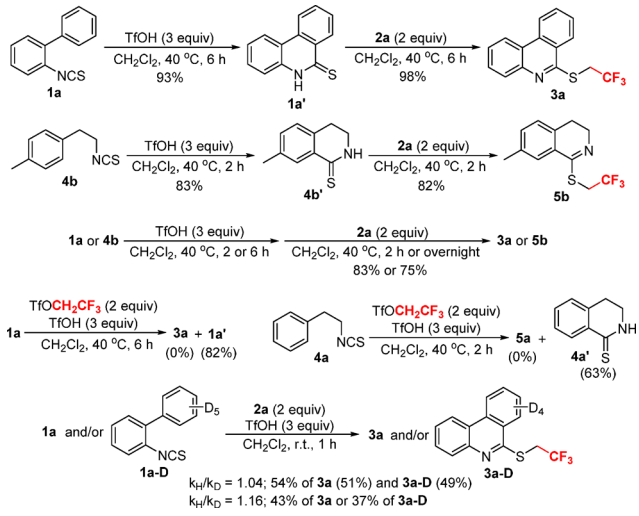


[a]Reaction conditions: **4** (0.2 mmol), **2a** (0.4 mmol), TfOH (0.6 mmol), CH_2Cl_2 (2 mL), 40 °C, 2 h. Isolated yields.

cally with **2a** at both the electron-rich and the least sterically hindered aromatic carbon sites to produce isoquinolines **5f** and **5h–j**, showing excellent regioselectivity. Moreover, reaction of (3-isothiocyanatopropyl)benzene (**4l**) with **2a** and TfOH under the standard conditions furnished 1-[(2,2,2-trifluoroethyl)thio]-4,5-dihydro-3*H*-benzo[c]azepine (**5l**), with a seven-membered ring, in 67% yield. Nevertheless, the similar reactions of (isothiocyanatomethyl)benzene (**4k**) and (4-isothiocyanatobutyl)benzene (**4m**) with **2a** at 40 °C gave complicated mixtures in which the desired products were not isolated by column chromatography. It should be mentioned that all fluorinated 3,4-dihydroisoquinoline derivatives synthesized in Scheme 2 tended to decompose when they were chromatographed on silica gel or aluminum oxide (especially the former). To obtain good yields of the products, their purification by the column chromatography on aluminum oxide should finish as fast as possible.

To shed light on the reaction mechanism, several control experiments were carried out. Initially, reaction of **1a** with TfOH in CH_2Cl_2 in the absence of **2a** at 40 °C for 6 h provided phenanthridine-6(5*H*)-thione (**1a′**) in 93% yield, which was determined by the NMR spectroscopy (see Scheme 3 and the Supporting Information (SI)). Subsequently, treatment of **1a′** with **2a** at 40 °C in CH_2Cl_2 without TfOH gave **3a** in 98% yield. The overall yield of **3a** (91%) was comparable to that (97%) obtained by the one-pot procedure. Further investigation revealed that the reaction of **1a′** and **2a** proceeded very fast, which could finish within 5 min (see SI). The acid was neither beneficial nor harmful to the trifluoroethylation step. Alternatively, the intermediate **1a′** without isolation reacted with **2a** in the same mixture to provide **3a** in 83% yield. These results suggest that phenanthridine-6(5*H*)-thione might be the key intermediate of the reaction of 2-isothiocyanobiaryl. In the case of aryl alkyl isothiocyanate, a similar reaction of **4b** with TfOH in the absence of **2a** afforded 7-methyl-3,4-dihydroisoquinoline-1(2*H*)-thione (**4b′**) in 83% yield (see Scheme 3 and the SI). Then **4b′** reacted with **2a** at 40 °C in CH_2Cl_2 in the absence of

Scheme 3. Control Experiments for the Mechanistic Study



TfOH and gave **5b** in 82% yield. Likewise, intermediate **4b′** without purification reacted with **2a** in the same system to form **5b** in 75% yield. These observations implied that 3,4-dihydroisoquinoline-1(2*H*)-thione was likely the key intermediate of the reaction of aryl-alkyl isothiocyanate.

Furthermore, the standard reaction of **1a** or **4a** with 2,2,2-trifluoroethyl trifluoromethanesulfonate ($TfOCH_2CF_3$) as a trifluoroethyl source in the presence of TfOH did not form the desired product. Instead, the corresponding thioamide (**1a′** (82%) or **4a′** (63%)) was isolated in the reaction (see Scheme 3 and the SI), indicating that the transformation stopped at the cyclization step. Additionally, reaction of **1a** (or **4b**) with diphenyliodonium salts under the standard conditions provided very low yields of **1a′** (or **4b′**) as well as the phenylthiolated product and most of the starting material was recovered (see SI). All these results combined demonstrated a much higher electrophilic reactivity of phenyl(2,2,2-trifluoroethyl)iodonium triflate (**2a**). $TfOCH_2CF_3$ and the diphenyliodonium salts seemed to slightly or seriously suppress the formation of thioamide as the reactions of **1a**/$TfOCH_2CF_3$/TfOH and **1a**/$[Ph_2I][OTf]$/TfOH gave lower yields of **1a′** (82% and 5%) than that of the blank reaction (93%) (see the SI). Moreover, the higher yield of **3a** from the one-step reaction (97%) compared to that from the two-step processes (91% and 83% overall yields) suggested that **2a** might play an important synergetic role in the acid-promoted cyclization of isothiocyanates. The production of **3a** from **1a** and **2a** in the absence of TfOH, albeit in trace amounts, also supported that **2a** itself could trigger the cyclization of isothiocyanates (see the SI). Nevertheless, the exact mechanism of this process remained unclear. In addition, the kinetic isotope effect (k_H/k_D) of the cyclization step was studied by the competitive and parallel reactions of **1a** and 2-isothiocyanato-1,1′-biphenyl-2′,3′,4′,5′,6′-d_5 (**1a-D**) with **2a**/TfOH at room temperature for 1 h (see Scheme 3 and the SI). The reactions gave a k_H/k_D value of 1.04 or 1.16, implying that the C–H bond cleavage was not involved in the rate-determining step.

Based on the above discussions, a plausible reaction mechanism was proposed for the TfOH-promoted trifluoroethylation/cyclization reactions (Scheme 4). First, isothiocyanate (**1** or **4**) is activated by TfOH via protonation of the nitrogen atom of the NCS group, forming a cation

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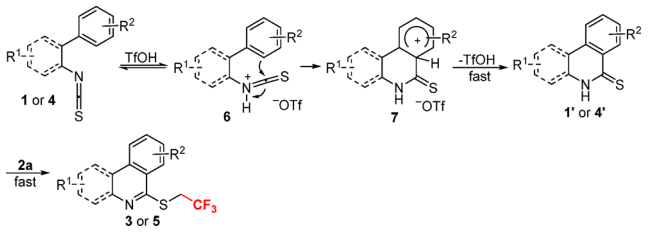
Scheme 4. A Plausible Reaction Mechanism for the TfOH-Promoted Trifluoroethylation/Cyclization of Isothiocyanates



intermediate (**6**). Intramolecular Friedel−Crafts reaction between the activated NCS moiety and the adjacent aryl ring gives a cyclohexadienyl cation **7**, which is probably the rate-determining step of the reaction. Then deprotonation of **7** by the $^{-}$OTf anion proceeds quickly and affords a stable thioamide **1′** or **4′**. Finally, trifluoroethylation of the thioamide intermediate **1′** or **4′** at the sulfur center by **2a** followed by aromatization furnishes the final product **3** or **5** within a few minutes. Since there was no *N*-trifluoroethylated product observed, the reaction at the nitrogen site could be excluded.

In conclusion, we have developed a convenient and efficient method for the one-pot synthesis of trifluoroethylthiol phenanthridines and 3,4-dihydroisoquinolines under transition-metal-free conditions. The cascade trifluoroethylation/cyclization of 2-isothiocyanobiaryls and aryl alkyl isothiocyanates (**1** and **4**) with phenyl(2,2,2-trifluoroethyl)iodonium triflate (**2a**) in CH_2Cl_2 in the presence of TfOH at 40 °C afforded a variety of trifluoroethylthiolated phenanthridine and 3,4-dihydroisoquinoline derivatives (**3** and **5**) in good to quantitative yields. The reactions were dramatically promoted by TfOH; its absence led to only trace amounts of the desired products. The control experiments suggested that phenanthridine-6(5*H*)-thiones and 3,4-dihydroisoquinoline-1(2*H*)-thiones might be the key intermediates of the reactions, respectively, when using TfOH as a promotor. This protocol is the first report for the production of fluorinated phenanthridine and isoquinoline derivatives from isothiocyanates without using transition metals. The reactions verified again the powerful electrophilic trifluoroethylation reactivity of aryl(2,2,2-trifluoroethyl)iodonium salts. Application of these promising reagents in new trifluoroethylation reactions is currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02793.

Screening of the optimal reaction conditions, procedures, characterization data, control experiments, NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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