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Domino cyclization/trifluoromethylation of 2-alkynylanilines using fluoroform-derived $CuCF_3$: synthesis of 3-(trifluoromethyl)indoles†

Yibin Ye, Kelvin Pak Shing Cheung, Lisi He and Gavin Chit Tsui *

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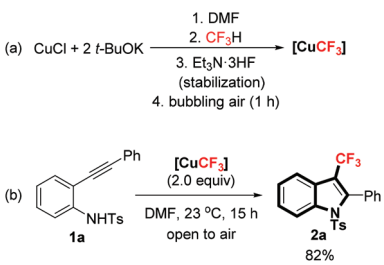
By employing easily accessible 2-alkynylanilines and the well-established fluoroform-derived $CuCF_3$ reagent, a novel class of 3-(trifluoromethyl)indoles can be synthesized in good yields with no ambiguity of the CF_3 position. The method utilizes a domino cyclization/trifluoromethylation strategy to construct the indole cores with the concomitant installation of the CF_3 group. The ultimate source of CF_3 is the low-cost industrial by-product fluoroform (CF_3H).

Trifluoromethylated heterocycles have found substantial applications in pharmaceuticals and agrochemicals.[1,2] A number of important marketed drugs, including anti-HIV efavirenz (Sustiva), anti-inflammatory celecoxib (Celebrex) and anti-diabetic sitagliptin (Januvia), contain the trifluoromethylated heterocyclic core. Indoles constitute some of the most abundant and biologically active natural products and pharmaceutical compounds.[3] The increasing interest in fluorinated indole derivatives towards drug discovery led to the recent development of methods accessing *trifluoromethylated indoles*, a class of trifluoromethylated heterocycles showing promising therapeutic potential.[4]

The construction of the substituted indole cores can be facilitated by the intramolecular cyclization of 2-alkynylanilines with the incorporation of functional groups at the C-3 position.[5] This conceivably convenient approach, however, has not been exploited for the preparation of *3-(trifluoromethyl)indoles*. To the best of our knowledge, there has been only one such example from Hou's group using stoichiometric amounts of CuBr as a promoter and the expensive Umemoto's reagent as an electrophilic CF_3 source.[6] The majority of the current methods for the synthesis of 3-(trifluoromethyl)indoles rely on the trifluoromethylation of pre-formed indole cores or the use of CF_3-containing building blocks. The direct C–H trifluoromethylation of indole cores provided powerful late-stage functionalization; however, mixtures of inseparable C-2 and C-3 trifluoromethylated products were often obtained.[7] The regioselectivity issues could be partially solved by using blocking groups[7h–m] and pre-installed functionalities (halides or boronic acids),[8] although the substrate scopes were limited and the reactions were less atom-economical. On the other hand, CF_3-containing building blocks (*e.g.* alkenes and alkynes) have been used in cycloadditions and cyclizations to construct the indole cores.[9] In most cases, tedious synthetic routes were needed to prepare the CF_3-containing substrates, thus lowering the overall efficiency.

In the context of our interest in synthesizing novel trifluoromethylated heterocycles,[10] we discovered that the 2-alkynylaniline **1a** can be converted into 3-(trifluoromethyl)indole **2a** in one step (82% isolated yield) using the *fluoroform-derived* [$CuCF_3$] reagent (Scheme 1). Fluoroform (CF_3H) is a large-volume by-product from Teflon manufacturing and is commercially available at a very low cost. It is also non-toxic and ozone-friendly, and therefore, would be a highly attractive CF_3 source for preparing valuable trifluoromethylated compounds.[11] Grushin's group pioneered the preparation and applications of fluoroform-derived [$CuCF_3$].[12] We have also successfully employed this reagent in the trifluoromethylation



Scheme 1 (a) Preparation of fluoroform-derived [$CuCF_3$] by Grushin's method. (b) Synthesis of 3-(trifluoromethyl)indole **2a** from 2-alkynylaniline **1a**.

Department of Chemistry, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong SAR. E-mail: gctsui@cuhk.edu.hk

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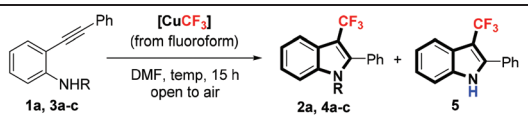
of alkynes, alkenes and arynes.[13] [$CuCF_3$] was prepared from copper(I) chloride/potassium *tert*-butoxide/fluoroform in DMF and stabilized with triethylamine trihydrofluoride ($Et_3N{\cdot}3HF$) according to Grushin's procedure with modifications (Scheme 1a).[12a,13a] Using this reagent under standard ambient conditions, the 3-(trifluoromethyl)indole core was furnished smoothly *via* a domino[14] cyclization/trifluoromethylation sequence (Scheme 1b). Other known conditions for copper-mediated trifluoromethylations were also investigated (Table S1†),[15] including the use of the $(PPh_3)_3CuCF_3$ complex,[16a] electrophilic Togni's reagent,[16b] and nucleophilic $TMSCF_3$,[16c] which all showed inferior reactivities compared to fluoroform-derived [$CuCF_3$] mainly due to the competing background cyclization to form the 3-*H* indole side product.[17]

The *N*-protecting group and reaction temperature had profound impacts on the reactivity (Table 1). The secondary sulfonamides were the most reactive substrates. Carbamates, amides, mono-/dialkylamines and unprotected aniline were completely unreactive (Table S2†).[15] While substrate **1a** cleanly afforded the desired product **2a** in a good yield at room temperature (*cf.* Scheme 1b), it gave a small amount of desulfonylated 3-(trifluoromethyl)indole **5** at 80 °C (Table 1, entry 1).[18] Substrates bearing mesyl (Ms) **3a**, nosyl (Ns) **3b** and triflyl (Tf) **3c** groups gave a mixture of products **4a–c** and **5**, even at room temperature (Table 1, entries 2–4). At 80 °C, the desulfonylated product predominated and by using substrate **3a** we could isolate compound **5** in 62% yield (Table 1, entry 2).[19]

The scope of the reaction was subsequently investigated using *N*-Ts 2-alkynylanilines **1b–x** (Table 2). The starting materials were conveniently synthesized in two steps from 2-iodoanilines *via* Sonogashira coupling of terminal alkynes and then *N*-tosylation with good yields. Upon treatment with fluoroform-derived [$CuCF_3$], the domino cyclization/trifluoromethylation took place furnishing a novel class of diversely functionalized 3-(trifluoromethyl)indoles **2b–x**. The substituent groups were well tolerated at the acetylenic and aniline ring positions of the substrate. For R^1, electron-rich arenes (**2b–g**) were generally higher-yielding than the electron-deficient ones (**2h–k**). The substituents at the *para*, *meta* and *ortho* positions of the benzene ring all gave good yields (**2b–g**). Other groups such as naphthyl (**2l**), phenanthryl (**2m**), pyridyl (**2p–q**) and thienyl (**2r**) were also demonstrated. For the alkyl substituent groups (**2n–o**), the yields were lower due to the increased amounts of background cyclization products. When R^1 was CO_2Me, only a trace amount of the desired product was detected and mainly the starting material was recovered (81%). The substrate containing terminal alkyne gave a complex mixture of products. On the aniline ring, methyl, fluoro and even chloro substituents (R^2) were tolerated at the C-5/6 positions (**2s–w**), despite the fact that aryl chlorides were known to react with fluoroform-derived [$CuCF_3$] in aromatic trifluoromethylation reactions.[12e] Furthermore, the 3-CF_3-7-azaindole **2x** was synthesized in 73% yield, which could be an interesting candidate for medicinal chemistry owing to the pharmaceutical potential of 7-azaindoles.[20]

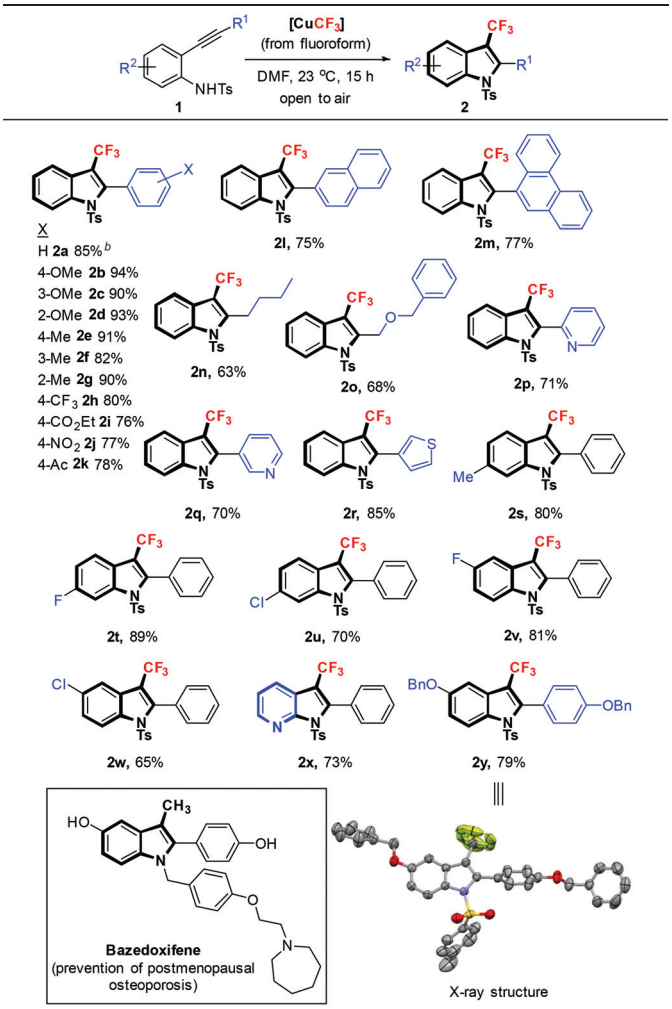
Table 1 Effects of the *N*-protecting group and reaction temperature[a]



Entry	R	Temp = 23 °C Yield[b] (%)	Temp = 80 °C Yield[b] (%)
1	Ts **1a**	83(82)/0 **2a**/**5**	72/13 **2a**/**5**
2	Ms **3a**	55(54)/17 **4a**/**5**	0/64(62) **4a**/**5**
3	Ns **3b**	60(60)/20 **4b**/**5**	11/63 **4b**/**5**
4	Tf **3c**	50(53)/5 **4c**/**5**	0/62 **4c**/**5**

[a] Conditions: [$CuCF_3$] in DMF solution (2.0 equiv., prepared from CuCl/*t*-BuOK/fluoroform and stabilized by $Et_3N{\cdot}3HF$), **1a** or **3a–c** (0.2 mmol, 0.2 M in DMF). R = Ts (*p*-toluenesulfonyl), Ms (methanesulfonyl), Ns (4-nitrobenzenesulfonyl), Tf (trifluoromethanesulfonyl). [b] Yield was determined by ^{19}F NMR analysis using benzotrifluoride as the internal standard. Isolated yields are shown in parentheses.

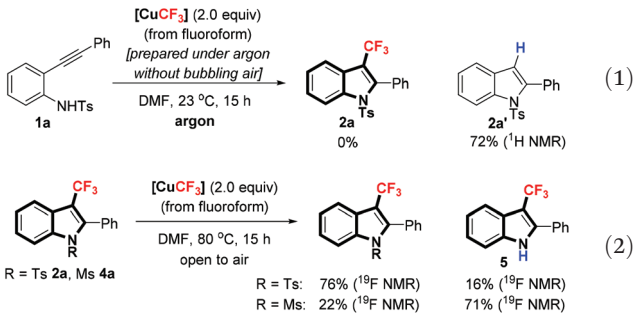
Table 2 Scope of 3-(trifluoromethyl)indoles **2**[a]



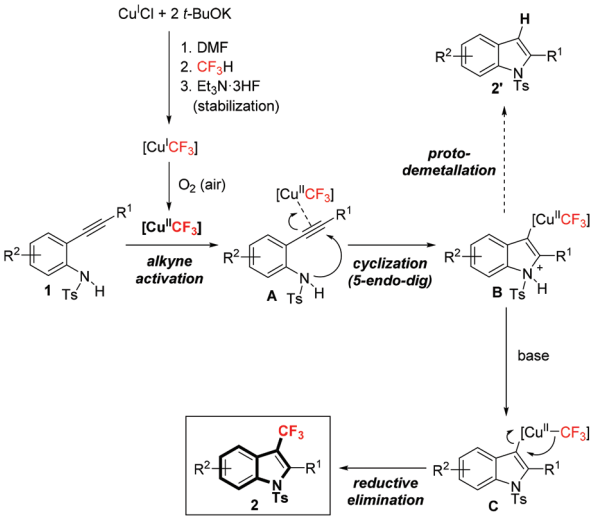
[a] Conditions: [$CuCF_3$] in DMF solution (2.0 equiv., prepared from CuCl/*t*-BuOK/fluoroform and stabilized by $Et_3N{\cdot}3HF$) and **1** (0.2 mmol, 0.2 M in DMF). Isolated yields. [b] 1 mmol scale.

Using this method, we could construct the 3-CF_3 indole core **2y** in 79% yield. X-ray crystallography unambiguously confirmed its structure and the C-3 position of the CF_3 group.[21] The FDA approved drug bazedoxifene for the management of postmenopausal osteoporosis contains the analogous indole core.[22] Therefore, compound **2y** could serve as a key intermediate towards the 3-CF_3 analog of bazedoxifene in a few steps according to literature procedures (detosylation, installing the azepane fragment and debenzylation)[22a] for the structure–activity relationship (SAR) studies.

The control experiment showed that when fluoroform-derived [$CuCF_3$] was prepared under argon and used in the reaction under an *argon* atmosphere, no desired product **2a** was obtained (eqn (1), *cf.* Scheme 1). Instead, the background cyclization product **2a′** was observed exclusively. To probe the deprotection process, the *N*-Ts **2a** and *N*-Ms **4a** indole products were resubjected to the standard conditions at 80 °C (eqn (2)). It was found that fluoroform-derived [$CuCF_3$] facilitated desulfonylation to give *N*-H product **5**, which was significantly more efficient for **4a** than **2a**, consistent with previous observations (*cf.* Table 1, entries 1–2). NMR studies had shown the intermediacy of **4a** in the formation of **5** from **3a** (Fig. S1†).[15]



Based on known literature evidence and the above studies, we propose a plausible mechanism for the domino cyclization/trifluoromethylation of 2-alkynylanilines **1** to form 3-(trifluoromethyl)indoles **2** (Scheme 2). The initial fluoroform-derived [Cu(I)CF_3] reagent is easily oxidized to the [Cu(II)CF_3] complex in air.[12a,b,13a] This *pre-oxidation* step during the preparation of a $CuCF_3$ reagent is important as [Cu(I)CF_3] was ineffective in the formation of the desired product **2a** (*cf.* eqn (1)). The activation of the alkyne moiety by coordination with [Cu(II)CF_3], followed by 5-*endo-dig* cyclization furnish the indole core **B**.[17a–c,10a] The unproductive protodemetallation of **B** would lead to 3-*H* by-product **2′**; this pathway was particularly dominant with other copper/CF_3 sources and [Cu(I)CF_3].[15] Alternatively, removing a proton by using a base, *i.e.* KF and Et_3N are present in the reaction mixture from the $CuCF_3$ reagent,[12a] gives the 3-copper indole intermediate **C**. The final reductive elimination delivers the 3-CF_3 indole product **2**.[12b] Although Cu(II) complexes are invoked here for intermediates **B** and **C**, the involvement of Cu(III) and polynuclear species should not be completely ruled out, especially under aerobic conditions.[23] It is noteworthy that the nature of the fluoroform-derived [$CuCF_3$] reagent, *i.e.* Cu(I) *versus* Cu(II), is much more important than the requirement of air for the reaction.



Scheme 2 Proposed mechanism.

The control experiment showed that using [Cu(II)CF_3] and carrying out the reaction with **1a** under an argon atmosphere also gave 74% yield (NMR) of **2a**. In general, running the reactions open to air was more convenient and gave higher yields.

In conclusion, a useful synthetic method has been developed for the preparation of trifluoromethylated indoles with the following features: (1) 3-(trifluoromethyl)indoles, mostly new compounds, can be accessed from the common starting material 2-alkynylanilines, with no ambiguity of the CF_3 position; (2) reaction conditions are mild, not moisture or air-sensitive, and tolerate a wide range of functional groups; (3) energy-efficient domino strategies are employed to form multiple bonds in one pot without the isolation and purification of intermediates; and (4) the ultimate CF_3 source is the industrial by-product fluoroform (CF_3H).

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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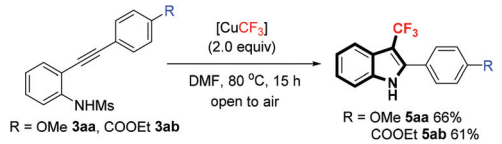

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