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Synthesis of 3-((trifluoromethyl)thio)indoles *via* a reaction of 2-alkynylaniline with trifluoromethanesulfanylamide†

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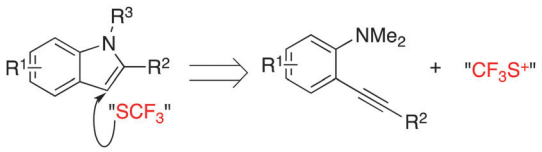
3-((Trifluoromethyl)thio)indoles can be synthesized by a palladium(II)-catalyzed reaction of 2-alkynylaniline with trifluoromethanesulfanylamide in the presence of bismuth(III) chloride. The presence of bismuth(III) chloride is crucial for the success of this transformation, which activates the trifluoromethanesulfanylamide during the reaction.

Currently, much attention has been paid to the introduction of fluorine atoms into drugs or leading compounds, with the aim of improving their medicinal properties.[1,2] Due to its high hydrophobicity, the (trifluoromethyl)thio (SCF_3) moiety has been used as the fluorine source recently.[3] As a result, several efforts have been made to incorporate the (trifluoromethyl)thio moiety into small molecules.[4,5] For instance, Qing and co-workers reported a transition-metal-free oxidative trifluoromethylthiolation of alkynes using elemental sulfur with the Ruppert–Prakash reagent (CF_3SiMe_3).[4a] Buchwald and co-workers described the trifluoromethylthiolation of aryl halides utilizing $AgSCF_3$ as a reagent.[4c] The reaction of alkenes or alkynes with trifluoromethanesulfanylamide as an equivalent of the trifluoromethanesulfanyl cation (CF_3S^+) was explored by Billard and co-workers.[5e] Recently, the progress of the formation of C–SCF_3 bond through direct trifluoromethylthiolation was summarized by Billard and co-workers.[5a]

Indole and its derivatives have attracted continuous interest due to their presence in natural products and pharmaceuticals with remarkable biological activities.[6] It is highly desirable to incorporate the (trifluoromethyl)thio moiety into an indole scaffold (Scheme 1). The most established methods for the formation of indoles are based on the palladium(II)-catalyzed reactions of 2-alkynylanilines.[7] Recently, Liu and co-workers reported a silver-catalyzed intramolecular oxidative aminofluorination of alkynes to produce 4-fluoroisoquinolines and 4-fluoropyrrolo[*α*]isoquinolines.[2h] During the investigation, they found that the presence of free N–H inhibited the fluorination process. Inspired by these intriguing studies and in continuation of our work on the synthesis of fluorinated heterocycles,[8] we envisioned that *N*,*N*-dimethyl-2-alkynylaniline[9] could be employed in the reaction of trifluoromethanesulfanylamide for the generation of (trifluoromethyl)thio-substituted indoles (Scheme 1). Thus, we started to explore this proposed transformation.



Scheme 1 Incorporation of the (trifluoromethyl)thio moiety into an indole scaffold.

In order to achieve this proposed trifluoromethylthiolation, our initial efforts focused on the model reaction of *N*,*N*-dimethyl-2-alkynylaniline **1a** with trifluoromethanesulfanylamide **2**. The optimization of conditions for the reaction is summarized in Table 1. Initially, the reaction was carried out in dichloroethane (DCE), in the presence of $Pd(OAc)_2$ (10 mol%) at 80 °C (Table 1, entry 1). However, no reaction occurred. It was reported that the electrophilic addition of arenesulfinamide could be activated in the presence of a Lewis acid.[5b–f] Thus, reactions using different metal salts were examined. However, no reaction took place when $BF_3{\cdot}OEt_2$, $FeCl_3$, $InCl_3$, CuF_2, CuBr, AgOTf, AgTFA, or $AgNTf_2$ were added (Table 1, entries 2–9). Interestingly, the desired product **3a** was obtained in 49% yield when $BiCl_3$ was used (Table 1, entry 10). A control experiment without the addition of the palladium(II) catalyst gave a lower yield (28%, Table 1, entry 11). The presence of a quantitative amount of bismuth(III) chloride is essential for the successful transformation. The reaction

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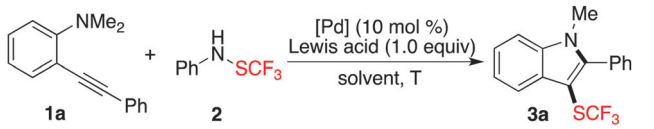
Table 1 Initial studies of the reaction of *N,N*-dimethyl-2-alkynylaniline **1a** with trifluoromethanesulfanylamide **2**



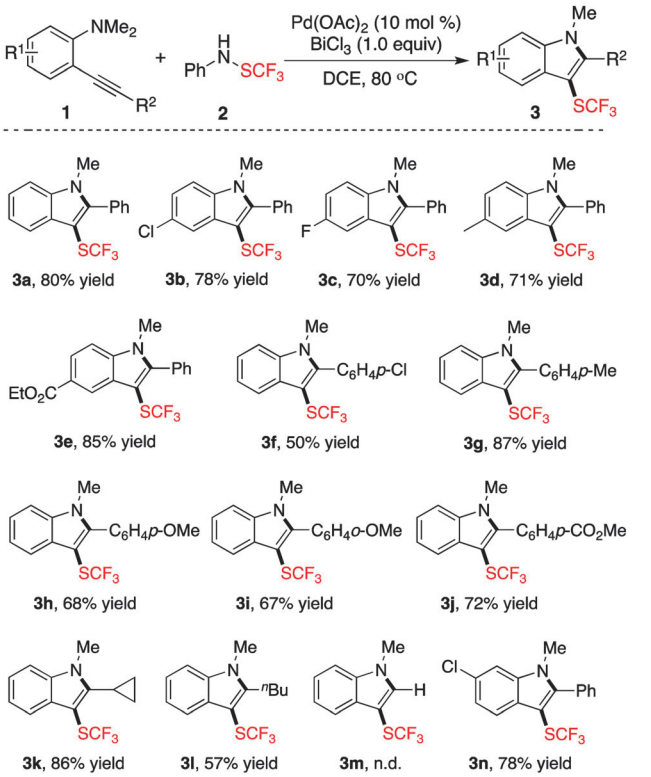
Entry	[Pd]	Lewis acid	T (°C)	Solvent	Yield[a] (%)
1	$Pd(OAc)_2$	—	80	DCE	0
2	$Pd(OAc)_2$	$BF_3{\cdot}OEt_2$	80	DCE	0
3	$Pd(OAc)_2$	$FeCl_3$	80	DCE	0
4	$Pd(OAc)_2$	$InCl_3$	80	DCE	0
5	$Pd(OAc)_2$	CuF_2	80	DCE	0
6	$Pd(OAc)_2$	CuBr	80	DCE	0
7	$Pd(OAc)_2$	AgOTf	80	DCE	0
8	$Pd(OAc)_2$	AgTFA	80	DCE	0
9	$Pd(OAc)_2$	$AgNTf_2$	80	DCE	0
10	$Pd(OAc)_2$	$BiCl_3$	80	DCE	49
11	—	$BiCl_3$	80	DCE	28
12[b]	—	$BiCl_3$	80	DCE	Trace
13[b]	$Pd(OAc)_2$	$BiCl_3$	80	DCE	Trace
14[c]	$Pd(OAc)_2$	$BiCl_3$	80	DCE	47
15[d]	$Pd(OAc)_2$	$BiCl_3$	80	DCE	39
16	$Pd(OAc)_2$	BiI_3	80	DCE	0
17	$Pd(OAc)_2$	$Bi(OAc)_3$	80	DCE	0
18	$Pd(OAc)_2$	$Bi(OTf)_3$	80	DCE	Trace
19	$PdCl_2$	$BiCl_3$	80	DCE	25
20	$PdBr_2$	$BiCl_3$	80	DCE	36
21	$Pd(TFA)_2$	$BiCl_3$	80	DCE	39
22[e]	$Pd(OAc)_2$	$BiCl_3$	80	DCE	59
23[f]	$Pd(OAc)_2$	$BiCl_3$	80	DCE	80
24[f]	$Pd(OAc)_2$	$BiCl_3$	70	DCE	47
25[f]	$Pd(OAc)_2$	$BiCl_3$	60	DCE	36
26[f]	$Pd(OAc)_2$	$BiCl_3$	100	DCE	67
27[f]	$Pd(OAc)_2$	$BiCl_3$	80	DMF	0
28[f]	$Pd(OAc)_2$	$BiCl_3$	80	MeCN	65
29[f]	$Pd(OAc)_2$	$BiCl_3$	80	Toluene	0
30[f]	$Pd(OAc)_2$	$BiCl_3$	80	THF	40
31[f]	$Pd(OAc)_2$	$BiCl_3$	80	1,4-Dioxane	33

[a] Isolated yield based on *N,N*-dimethyl-2-(2-phenylethynyl)aniline **1a**. [b] In the presence of 0.5 equivalents of $BiCl_3$. [c] In the presence of 1.5 equivalents of $BiCl_3$. [d] In the presence of 5 mol% of $Pd(OAc)_2$. [e] In the presence of 2.0 equivalents of $PhNHSCF_3$. [f] In the presence of 3.0 equivalents of $PhNHSCF_3$.

failed when 0.5 equivalents of $BiCl_3$ were used in the transformation (Table 1, entries 12 and 13). The results were not be improved when the amount of $BiCl_3$ was increased (Table 1, entry 14), or when the amount of the palladium(II) catalyst was reduced (Table 1, entry 15). It seemed that the chloride anion was important in the reaction. No reaction occurred when other bismuth(III) salts were employed (Table 1, entries 16–18). The results were poor when $Pd(OAc)_2$ was switched to $PdCl_2$, $PdBr_2$, or $Pd(TFA)_2$ (Table 1, entries 19–21). The corresponding 3-((trifluoromethyl)thio)indole **3a** could be obtained in 80% yield when 3.0 equivalents of trifluoromethanesulfanylamide **2** were used in the reaction (Table 1, entry 23). Changing the temperature did not improve the final outcome (Table 1, entries 24–26). Further screening of the solvents indicated that DCE was the best choice (Table 1, entries 27–31).

With the optimal conditions established for this palladium(II)-catalyzed fluorination process, we turned our attention to exploring the substrate scope of this reaction, by using different 2-alkynylanilines. The results are summarized in Table 2.

Table 2 Synthesis of 3-((trifluoromethyl)thio)indoles *via* a palladium(II)-catalyzed reaction of *N,N*-dimethyl-2-alkynylaniline with trifluoromethanesulfanylamide in the presence of bismuth(III) chloride[a]

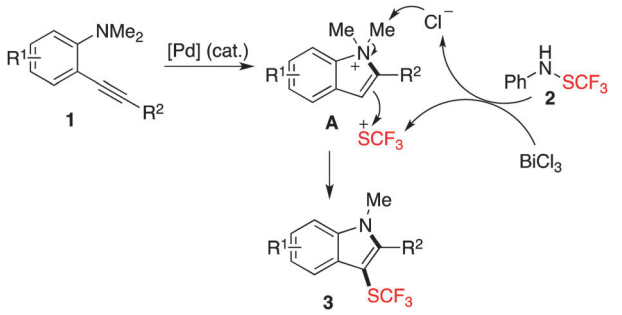


[a] Isolated yield based on 2-alkynylaniline **1**.

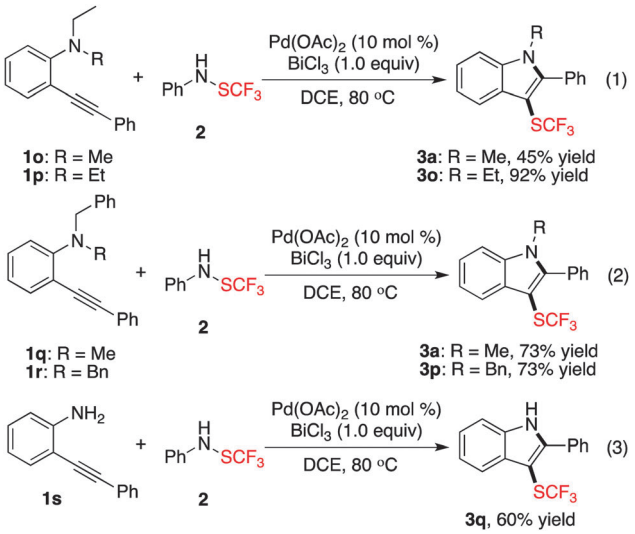
Various *N,N*-dimethyl-2-alkynylanilines with electron-withdrawing or electron-donating groups on the aromatic ring worked well under standard conditions. Different functional groups including fluoro, chloro, methyl, and ester were all compatible during the reaction process. Additionally, the substituents attached to the triple bond of *N,N*-dimethyl-2-alkynylanilines were tolerated as well. For instance, compound **3j** with an ester group was obtained in 72% yield. The alkyl substituted (cyclopropyl and *n*-butyl) *N,N*-dimethyl-2-alkynylanilines were all good substrates in the transformation. However, reaction of *N,N*-dimethyl-2-ethynylaniline with trifluoromethanesulfanylamide failed to produce the expected product.

A possible mechanism was proposed, which is shown in Scheme 2. We envisioned that an intramolecular cyclization of *N,N*-dimethyl-2-alkynylaniline would happen to produce intermediate **A**. Subsequently, the methyl group of intermediate **A** would be removed by attack of the chloride from bismuth(III) chloride. In the meantime, the trifluoromethanesulfanyl cation (CF_3S^+) would be formed *via* an activation of trifluoromethanesulfanylamide **2** by bismuth(III) chloride, which would react with the *in situ* generated indole to produce the 3-((trifluoromethyl)thio)indole **3**.

Reactions of other 2-alkynylanilines with trifluoromethanesulfanylamide were then explored (Scheme 3). The reactions also proceeded smoothly when 2-alkynylanilines **1o–1r** were employed. During the reaction process, the ethyl or benzyl



Scheme 2 A possible mechanism for the reaction of *N,N*-dimethyl-2-alkynylaniline with trifluoromethanesulfanylamide.



Scheme 3 Reactions of other 2-alkynylanilines with trifluoromethanesulfanylamide.

group was selectively removed. This is reasonable based on the above mechanism, since the benzyl cation or ethyl cation is more electrophilic during the transformation. Interestingly, substrate **1s** was a good substrate under the conditions, which reacted with trifluoromethanesulfanylamide to give the desired product **3q** in 60% yield (Scheme 3, eqn (3)). These results indicated that the reaction underwent an intramolecular cyclization, first catalyzed by Pd(II) to produce the indole ring, which then went through electrophilic addition with trifluoromethanesulfanylamide in the presence of bismuth(III) chloride to generate the 3-((trifluoromethyl)thio)indole.

In summary, we have described a facile route to 3-((trifluoromethyl)thio)indoles *via* a palladium(II)-catalyzed reaction of 2-alkynylaniline with trifluoromethanesulfanylamide in the presence of bismuth(III) chloride. Different functional groups could be compatible in this transformation. Exploration of the use of trifluoromethanesulfanylamide for the trifluoromethylthiolation of other heterocycles is ongoing in our laboratory.

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