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Copper-Mediated Domino Cyclization/Trifluoromethylation/Deprotection with $TMSCF_3$: Synthesis of 4-(Trifluoromethyl)pyrazoles

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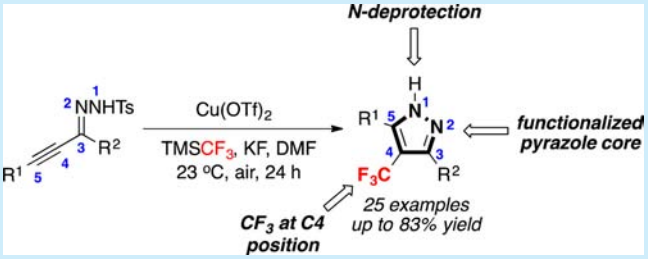
Supporting Information

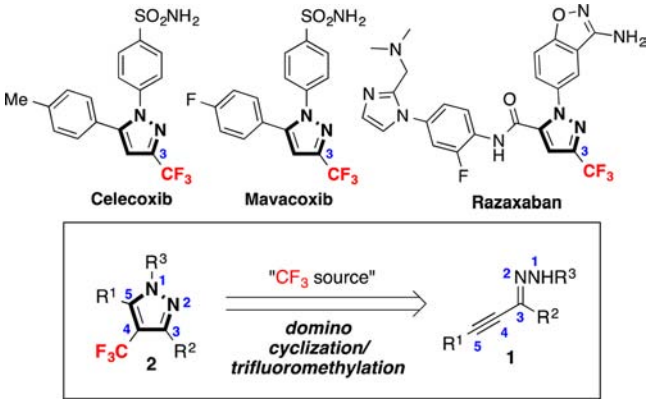
ABSTRACT: A copper-mediated synthesis of 4-(trifluoromethyl)pyrazoles is described. In one step from readily accessible α,β-alkynic tosylhydrazones, a remarkable domino sequence of cyclization, trifluoromethylation, and detosylation takes place to furnish the 4-CF_3 *N*-H pyrazole cores with good functional group compatibility. The reaction conditions are mild and convenient, at room temperature in air, using the commercially available trifluoromethyltrimethylsilane ($TMSCF_3$) as the CF_3 source. The method can be applied to the synthesis of a 4-CF_3 analogue of the anti-inflammatory drug celecoxib.



Trifluoromethylated heterocycles are a class of fluorinated molecules with substantial applications in pharmaceuticals and agrochemicals.[1] It is well-documented that introduction of a trifluoromethyl (CF_3) group at a strategic position within a drug candidate can significantly improve its properties.[2] Trifluoromethylated pyrazoles, in particular, are important motifs in biologically active compounds.[3] Examples of marketed drugs that contain trifluoromethylpyrazole cores include the anti-inflammatory celecoxib[4a] and mavacoxib[4b] and the anticoagulant razaxaban[4c] (Scheme 1).

Compared to the better known 3-(trifluoromethyl)pyrazoles, synthetic methods that allow access to *4-(trifluoromethyl)-pyrazoles* are severely limited,[5] which has hampered the biomedical application of this class of compounds.[3a] Typical approaches for preparing 4-(trifluoromethyl)pyrazoles include cycloadditions/cyclizations using CF_3-containing building blocks[6] or trifluoromethylation of prefunctionalized pyrazole cores,[7] reactions that often suffer from a tedious preparation of the substrates, harsh reaction conditions, and poor regioselectivities.

Scheme 1. Marketed Drugs Containing (Trifluoromethyl)pyrazole Cores and a Domino Synthetic Approach toward 4-(Trifluoromethyl)pyrazoles 2



We envisioned that a new method could be developed for constructing 4-(trifluoromethyl)pyrazole cores **2** in one step from readily accessible α,β-alkynic hydrazones **1**. This approach would rely on a domino cyclization pathway with concomitant introduction of a CF_3 group from a suitable CF_3 source.[8] While cyclizations of **1** can be promoted by base,[9a] iodine,[9b] copper,[9c] and gold,[9d] the incorporation of a CF_3 group at the C4 position in the domino process remained unknown. Only one recent example can be found for the synthesis of 3-(trifluoromethyl)-pyrazoles via a cyclization reaction using Togni's reagent.[10] We decided to test our hypothesis using copper as a promoter due to the prior precedents for copper-promoted trifluoromethylation of unsaturated moieties.[11] Initial studies were carried out using tosylhydrazone **1a** in DMF at room temperature to identify a suitable combination of copper and CF_3 sources (Scheme 2).

The desired 4-CF_3 pyrazole product **2a′** was produced in 30% yield according to ^{19}F NMR spectroscopy using the electrophilic Togni's reagent with CuCl. A major side product, the 4-H pyrazole **2a″** arising from the background cyclization, was also detected. Using a previously reported fluoroform-derived $CuCF_3$ reagent decreased the yield (24%).[12] However, by employing the nucleophilic $TMSCF_3$ (Ruppert–Prakash reagent)[13] in the presence of CuCl, the 4-(trifluoromethyl)pyrazole **2a** was obtained in 71% yield. To our surprise, only the detosylated product was obtained after the reaction.

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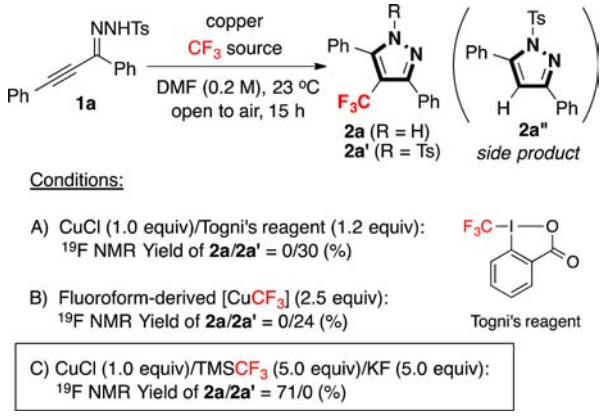
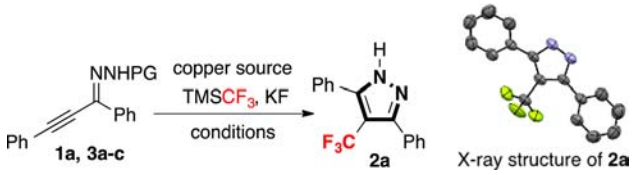
Scheme 2. Identification of Copper and CF_3 Sources



Various reaction parameters were subsequently screened to further increase the yield of **2a**.[14] The reaction was sensitive to solvents, DMF was the optimal solvent, and no product was detected in less polar solvents such as THF, CH_2Cl_2, and toluene. A strong impact from the copper source was observed (Table 1).

Table 1. Effects of Copper Sources and Protecting Groups[a]



entry	PG	copper source	yield[b] (%)
1	Ts (**1a**)	CuBr	28
2	Ts (**1a**)	CuCN	46
3	Ts (**1a**)	CuI	57
4	Ts (**1a**)	CuSCN	80
5	Ts (**1a**)	$Cu(OAc)_2$	25
6	Ts (**1a**)	$CuBr_2$	44
7	Ts (**1a**)	$CuCl_2$	72
8	**Ts (1a)**	**$Cu(OTf)_2$**	**83, 80**[c]
9[d]	Ts (**1a**)	$Cu(OTf)_2$	41
10[e]	Ts (**1a**)	$Cu(OTf)_2$	36
11[f]	Ts (**1a**)	$Cu(OTf)_2$	<5
12	C(O)4-MeC_6H_4 (**3a**)	$Cu(OTf)_2$	80[c]
13	$SO_2$4-$NO_2C_6H_4$ (**3b**)	$Cu(OTf)_2$	75[c]
14	Ph (**3c**)	$Cu(OTf)_2$	<5

[a]General conditions: copper source (1.0 equiv), **1a** or **3a–c** (0.1 mmol), $TMSCF_3$ (5.0 equiv), KF (5.0 equiv), DMF (0.2 M), open to air, at 23 °C for 15–24 h. [b]Determined by 376 MHz ^{19}F NMR analysis using benzotrifluoride as the internal standard. [c]Isolated yield. [d]At 50 °C. [e]Using 0.5 equiv of $Cu(OTf)_2$. [f]Reaction was run under argon, 46% yield of **2a′**.

Copper(I) salts such as CuBr, CuI, and CuCN afforded the product in lower yields (entries 1–3). However, copper(I) thiocyanate was high yielding (entry 4). Copper(II) salts such as $Cu(OAc)_2$ and $CuBr_2$ were effective only to a small extent (entries 5 and 6). Equally good yields were obtained using either $CuCl_2$ (entry 7) or CuCl (cf. Scheme 2). The highest yield was achieved with $Cu(OTf)_2$ where **2a** was isolated in 80% yield (entry 8). Higher reaction temperature and reducing the amount of $Cu(OTf)_2$ led to a decrease in yield (entries 9 and 10). In fact, we also observed a decrease in yield (39%) when an excess of $Cu(OTf)_2$ (1.5 equiv) was used due to an increased background cyclization to form **2a″**. Adding a ligand such as phen, 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr), *t*-Bu-bpy, or PPh_3 was less effective than without ligand. Other metal salts including $FeCl_2$, $FeCl_3$, $ZnCl_2$, and $ZnBr_2$ were ineffective in this reaction. Aerobic oxidative conditions were absolutely necessary to achieve a high yield of **2a**, since when the reaction was conducted under argon only the *N*-Ts product **2a′** was observed in 46% yield (entry 11, cf. Scheme 2).[15] The structure of **2a** and the 4-position of its CF_3 group were unambiguously confirmed by X-ray crystallography.[16]

The effects of other *N*-protecting groups (PGs) were investigated under the optimized conditions. Comparable to the tosylhydrazone **1a**, substrates bearing electron-withdrawing PGs such as carbonyl (**3a**) and nosyl (**3b**) groups also afforded **2a** in good yields (entries 12 and 13). However, impurities were formed, which caused difficulties in purification. On the other hand, the *N*-Ph substrate **3c** did not afford **2a** (entry 14) but gave the *N*-Ph 4-CF_3 pyrazole product in 37% yield (see the Supporting Information). Tosylhydrazones **1** can be conveniently prepared from commercial tosylhydrazides. They also gave cleaner reaction profiles and therefore were used subsequently in the scope studies.

Under the optimized conditions, a wide range of novel 4-(trifluoromethyl)pyrazoles **2b–y** were successfully synthesized, with the reactions displaying good functional group tolerance (Figure 1). Substituent groups (R^1 and R^2) were varied to study their electronic and steric influences on the reaction. For R^1, electron-rich aryl groups gave higher yields than electron-poor ones (**2b,c** vs **2k–m**). Halogens were also compatible (**2d–f**). Substituents at the *ortho*-position of the aromatic ring did not impede the reaction (**2h,i**). Heteroaryl and naphthyl groups (**2n–p**) were tolerated, although a lower yield was obtained from the pyridyl group. On the other hand, alkyl substituent groups gave a poor yield (**2q**). For R^2, aryl groups were higher yielding than alkyl groups (**2r–u** vs **2x,y**), with electron-rich (**2r**), electron-poor (**2s**), and *ortho*-substituents (**2t,u**) all working well. In fact, the electronic properties of the aryl groups on both the R^1 and R^2 positions could be easily tuned by choosing a suitable tosylhydrazone (**2v,w**). In all cases, only the detosylated *N*-H products **2** were obtained.

Our method has been applied to the synthesis of a 4-trifluoromethyl analogue of the anti-inflammatory drug celecoxib (Scheme 3). The 4-CF_3 pyrazole core of celecoxib (cf. Scheme 1) was constructed via the domino cyclization/trifluoromethylation/detosylation using substrate **4**. The CuSCN proved to be a more efficient promoter than $Cu(OTf)_2$ with this substrate.[14] Subsequent Cu-catalyzed *N*-arylation[17] with *N,N*-dibenzyl-4-iodobenzenesulfonamide and removal of the benzyl groups with H_2SO_4 afforded compound **5**, where the CF_3 group was at the C4 position, in 37% yield over three steps. X-ray crystallography confirmed the structure of **5** (see the Supporting Information).[16]

To probe the reaction mechanism, ^{19}F NMR studies were carried out at different time intervals to analyze the reaction mixture using tosyl hydrazone **1a** as the substrate.[14] The results revealed that the *N*-Ts pyrazole product **2a′** was formed exclusively at the beginning of the reaction, which was then completely detosylated to give the *N*-H product **2a** after 24 h. A control experiment also showed that **1a** is very prone to background cyclization (cf. Scheme 2). In the presence of 1.0 equiv of $Cu(OTf)_2$ without $TMSCF_3$ and KF under standard conditions, the background cyclization product **2a″** was isolated in 76% yield from **1a**. Based on these observations and related

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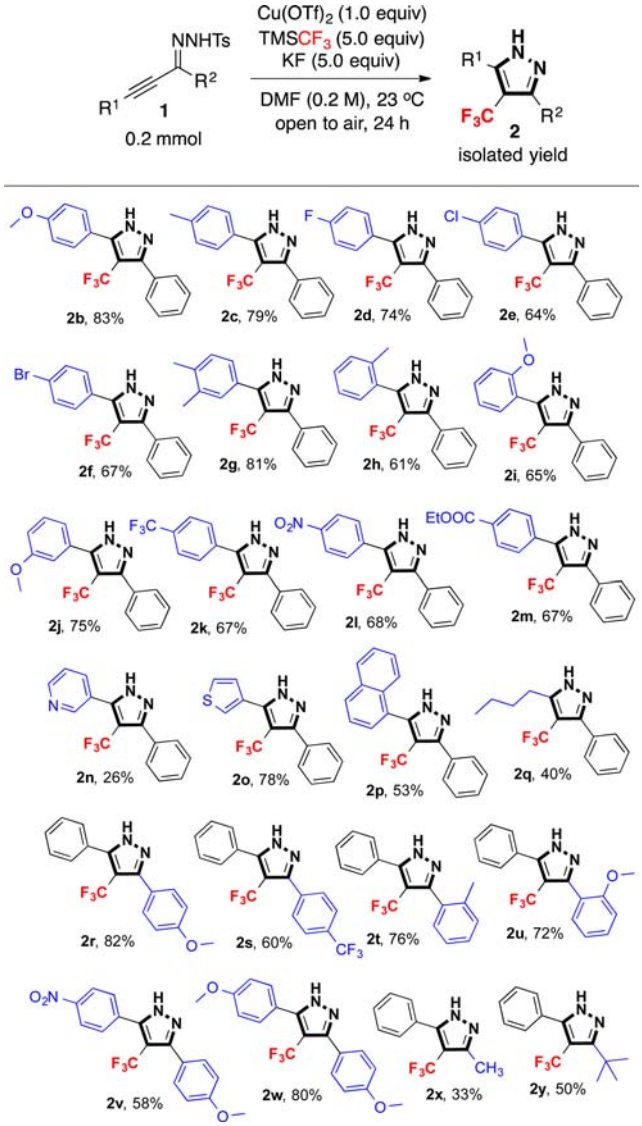
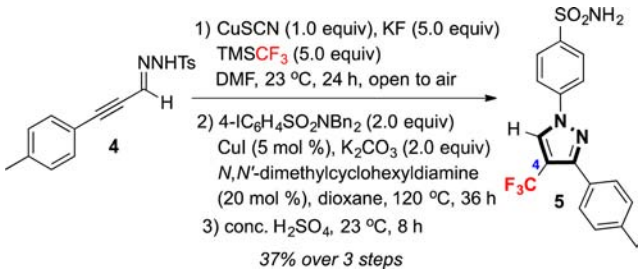


Figure 1. Scope of 4-(trifluoromethyl)pyrazoles **2**.

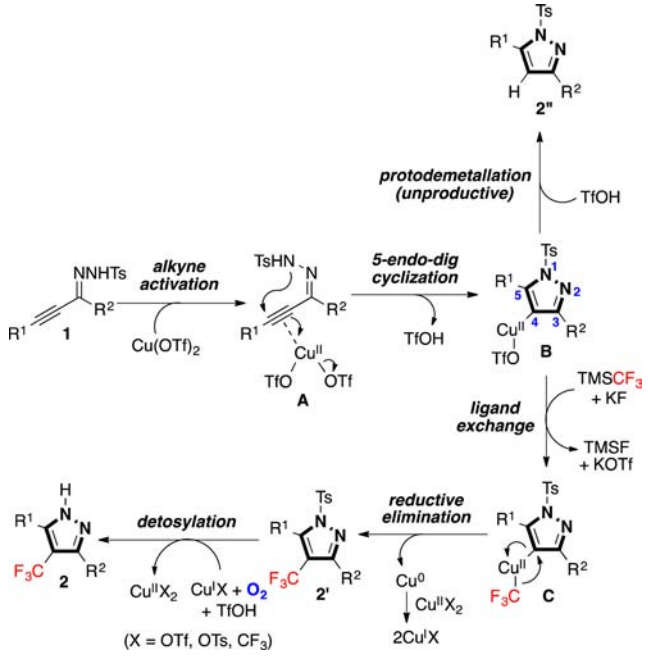
Scheme 3. Synthesis of a 4-CF_3 Analogue of Celecoxib



literature,[18] we propose the following mechanism for the domino reaction (Scheme 4).

The alkyne moiety of tosylhydrazone **1** is activated by $Cu(OTf)_2$ by forming the coordination complex **A**.[18a] The 5-*endo-dig* cyclization initiated by the nucleophilic attack of the nitrogen atom to the alkyne then furnishes the 4-copper pyrazole core **B** and eliminates TfOH. Protodemetalation of **B** with TfOH accounts for the formation of 4-H pyrazole side product **2″**, an unproductive pathway. However, in the presence of $TMSCF_3$ and KF, ligand exchange takes place to generate the

Scheme 4. Proposed Mechanism for the Domino Cyclization/Trifluoromethylation/Detosylation Process



trifluoromethylated copper species **C**. Reductive elimination at the copper center gives the 4-CF_3 product **2′**.[18b] During this step, Cu(0) is presumably generated, which is known to be oxidized by Cu(II) species to Cu(I).[18c,d] In the presence of oxygen, this Cu(I) species is further oxidized to Cu(II) during which the *N*-Ts group is cleaved via single-electron transfer mechanisms to give the final detosylated product **2**. The exact nature of the CuX and CuX_2 species is not clear at the moment. The involvement of Cu(III) species cannot be completely ruled out as the formation of $[Cu^{III}(CF_3)_4]^-$ has been described under similar conditions.[19] While copper-facilitated *N*-detosylation of heterocycles is rare, such types of reductive cleavage by dissolving metals and single-electron transfer reagents are well-precedented.[20] The oxidative conditions are crucial for the detosylation as the reactions run without oxygen afford product **2′** only (cf. Table 1, entry 11). Copper(I) salts such as CuCl were also effective in this transformation (cf. Scheme 2, Table 1). It is known that Cu(I) can facilitate the electrophilic cyclization of α,β-alkynic hydrazones and therefore would lead to a similar Cu(I) pyrazole intermediate **B**.[9c] Under oxidative conditions, the Cu(I) is likely to be oxidized to Cu(II) and follow the analogous subsequent pathway for forming product **2**.

In conclusion, we have developed a method for synthesizing a novel class of densely functionalized 4-(trifluoromethyl)-pyrazoles. These trifluoromethylated heterocycles may exhibit interesting pharmaceutical properties of values for drug discovery. The reaction utilizes a copper-mediated domino cyclization/trifluoromethylation/deprotection sequence where copper plays a distinct role in each step. The reaction is practical owing to its mild conditions (room temperature, open to air) and its reliance on the readily available CF_3 source ($TMSCF_3$). We plan to study the bioactivities of the 4-CF_3 analogue of celecoxib **5** in anti-inflammatory applications. The effects of the CF_3 group at the C4 position on the reactivity and properties of the pyrazole core will also be explored.[21] These findings as well as further mechanistic studies on the reaction pathways will be disseminated in due course.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03822.

Experimental procedures and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(14) See the Supporting Information for full details.

(15) Adding Ag_2CO_3 as an oxidant under argon also gave **2a′** exclusively (36% yield). A change in procedure such as running the reaction under an oxygen atmosphere or bubbling air through decreased the yield of **2a** to 73% and 33%, respectively. See the Supporting Information for details.

(16) CCDC 1519958 (**2a**) and CCDC 1525831 (**5**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk.

(17) Note that the *N*-arylation occurred at the *N*-2 position rather than the *N*-1 position of the initially formed unprotected pyrazole. This unexpected phenomenon was possibly due to an isomerization process under the reaction conditions followed by *N*-arylation. Further details are currently under investigation. For the procedure used in the Cu-catalyzed *N*-arylation step, see: (a) Li, F.; Nie, J.; Sun, L.; Zheng, Y.; Ma, J.-A. *Angew. Chem., Int. Ed.* **2013**, *52*, 6255. (b) Wang, Y.; Han, J.; Chen, J.; Cao, W. *Tetrahedron* **2015**, *71*, 8256.

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