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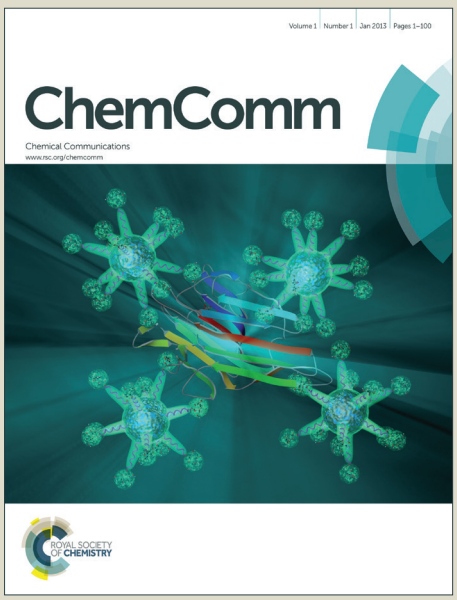

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Cite this: DOI: 10.1039/c0xx00000x

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ARTICLE TYPE

Synthesis of 3-Trifluoromethylpyrazoles *via* Trifluoromethylation/ Cyclization of α, β-Alkynic Hydrazones Using a Hypervalent Iodine Reagent

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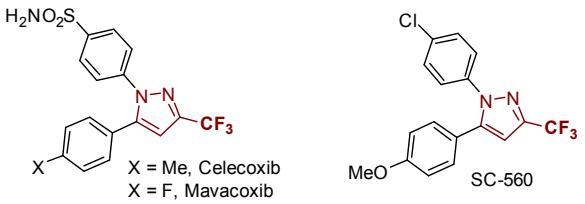
Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

A mild and efficient method for the synthesis of 3-trifluoromethylpyrazoles has been established *via* trifluoromethylation/cyclization of α, β-alkynic hydrazones with a hypervalent iodine reagent under transition-metal-free conditions.

The trifluoromethylated arenes and heteroarenes play an increasingly important role in the fields of pharmaceuticals, agrochemicals, and material sciences, because of their unique properties, including high electronegativity, lipophilicity, metabolic stability, and bioavailability.[1,2] However, the compounds bearing CF_3 groups are absent in nature. Accordingly, the scientific community exert a great effort to develop efficient methods for introducing trifluoromethyl group onto aromatic and heteroaromatic rings.[3]

The pyrazole ring is an important moiety found in many natural products and compounds with biological activities, which draw considerable attention in pharmaceutical and agrochemical research.[4] 3-Trifluoromethylpyrazole is a feature structure of many drugs, agrochemicals, and related candidates. For example, as shown in Scheme 1, Celecoxib is a nonsteroidal anti-inflammatory drug,[5a] and Mavacoxib is a veterinary drug.[5b] SC-560 shows antitumor activity.[5c]



Scheme 1 Bioactive compounds bearing 3-trifluoromethyl-pyrazole moiety.

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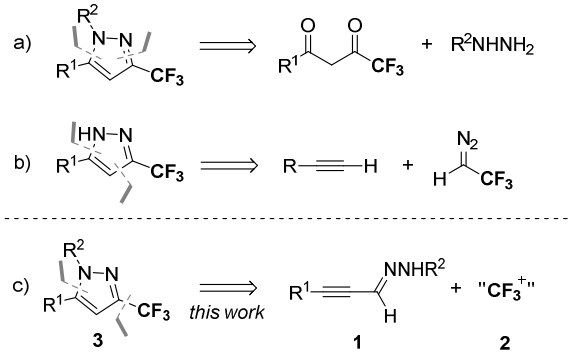
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

In general, functionalized 3-trifluoromethylpyrazoles are prepared *via* cyclocondensations of 1,3-dicarbonyl compounds with substituted hydrazines. (Scheme 2, a).[6] An alternative strategy is the use of 1,3-dipole cycloaddition of alkyne with 2,2,2-trifluorodiazoethane, generated *in situ* from 2,2,2-trifluoroethylamine hydrochloride (Scheme 2, b).[7]

Although remarkable progresses have been made in the synthesis of substituted 3-trifluoromethylpyrazoles, these methods suffer from some limitations, which include: 1) for method a, the cyclocondensation of unsymmetrical 1,3-diketone with hydrazines leads to the formation of a mixture of two regioisomers, which are often difficult to separate; 2) for method b, an excess amount of the $CF_3CH_2NH_2$·HCl and transition metal promoters are essential for the high efficiency of the 1,3-dipole cycloaddition. Consequently, it is still highly desirable to develop new method for the synthesis of 3-trifluoromethylpyrazoles.

To this end, we have conceived that deprotonation of α, β-alkynic hydrazones **1**,[8] followed by nucleophilic attack to the electrophilic trifluoromethylation reagent "CF_3^+" **2** and subsequent cyclization may lead to the formation of 3-trifluoromethylpyrazoles.[9]

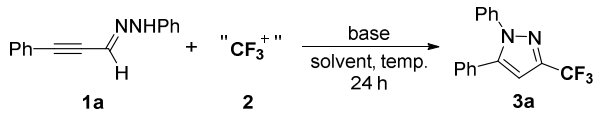


Scheme 2 Strategies for the synthesis of 3-trifluoromethyl-pyrazoles.

With this in mind, we first studied the reaction of α, β-alkynic hydrazones **1a** and Togni reagent **2a** in acetonitrile at 25 °C with a series of bases. Preliminary screening showed that Cs_2CO_3 was the suitable base for the expected conversion, while LiO*t*-Bu,

KO*t*-Bu, and Et_3N seemed to be incompatible with strong electrophilic "CF_3^+" reagent (Table 1, entries 1-5). The reaction was completely shut down without the base (Table 1 entry 6). Copper chloride catalyst, which was used for single electron reduction of Togni reagent **2a** to generate trifluoromethyl radical,[10] was less efficient for this transformation (Table 1, entry 7). Diminished yield of **3a** was observed when the reaction was conducted at elevated temperature (Table 1, entry 8). Then we turned to other electrophilic "CF_3^+" reagents. The study revealed that Togni reagent **2b** had essentially no effect (Table 1, entry 9), while Umemoto reagents **2c** and **2d** afforded the expected product **3a** in 35% and 26%, respectively (Table 1, entries 10 and 11). Further screening of different solvents showed that DCE and MeOH were inferior to MeCN (Table 1, entries 12 and 13). We have speculated that small amount of water may facilitate the proton transfer in the transformation. Indeed, a mixed solvent of MeCN/H_2O (20:1, v/v) led to further improvement of the yield (Table 1, entry 14). Finally, the optimal condition was obtained when the ratio **1a**/**2a** was maintained at 1:1.3, giving **3a** in 70% isolated yield (Table 1, entry 15).

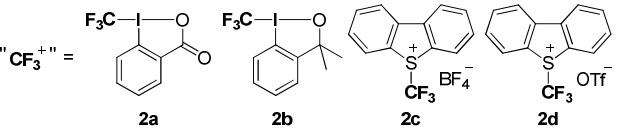
Table 1 Optimization of the conditions[a]



1a **2** **3a**

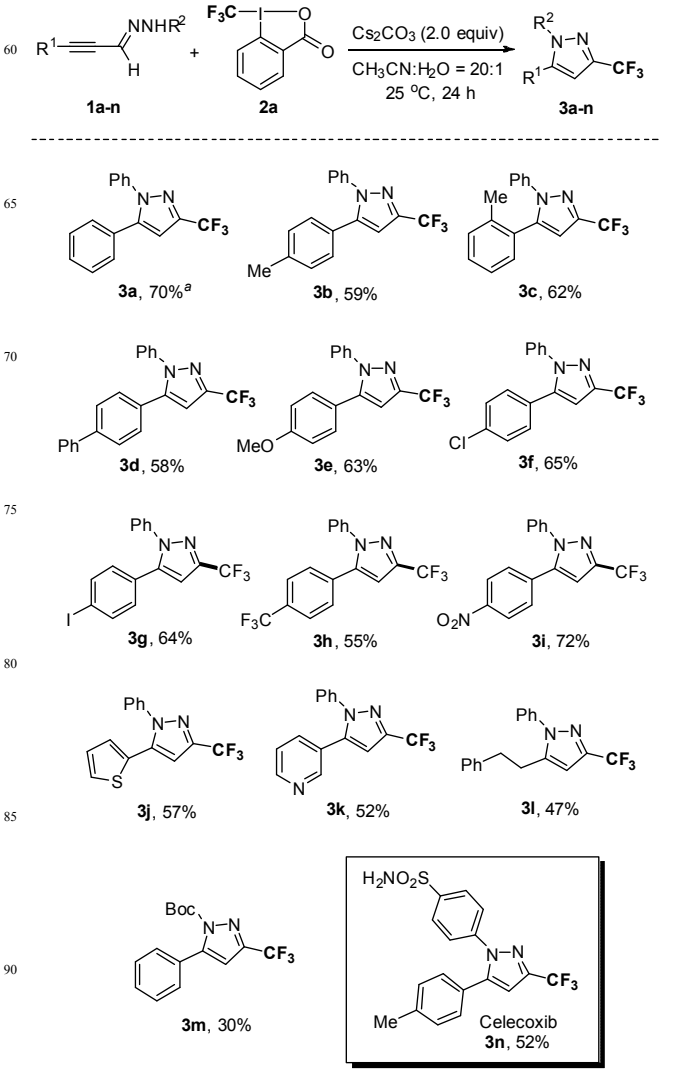
Entry	Base (equiv)	**2** "CF_3^+" (equiv)	Solvent	*T* (°C)	Yield (%)[b]
1	LiO*t*-Bu (2.0)	**2a** (1.0)	MeCN	25	16
2	KO*t*-Bu (2.0)	**2a** (1.0)	MeCN	25	14
3	Et_3N (2.0)	**2a** (1.0)	MeCN	25	14
4	K_2CO_3 (2.0)	**2a** (1.0)	MeCN	25	16
5	Cs_2CO_3 (2.0)	**2a** (1.0)	MeCN	25	39
6	none	**2a** (1.0)	MeCN	25	0
7[c]	Cs_2CO_3 (2.0)	**2a** (1.0)	MeCN	25	28
8	Cs_2CO_3 (2.0)	**2a** (1.0)	MeCN	50	23
9	Cs_2CO_3 (2.0)	**2b** (1.0)	MeCN	25	0
10	Cs_2CO_3 (2.0)	**2c** (1.0)	MeCN	25	35
11	Cs_2CO_3 (2.0)	**2d** (1.0)	MeCN	25	26
12	Cs_2CO_3 (2.0)	**2a** (1.0)	DCE	25	22
13	Cs_2CO_3 (2.0)	**2a** (1.0)	MeOH	25	14
14	Cs_2CO_3 (2.0)	**2a** (1.0)	MeCN:H_2O (20:1)	25	46
15[d]	**Cs_2CO_3 (2.0)**	**2a (1.3)**	**MeCN:H_2O (20:1)**	**25**	**68 (70)**

[a] Reaction conditions: **1a** (0.20 mmol), **2**, solvent (1 mL), 24 h, under N_2 atmosphere. [b] Unless otherwise noted, the yields are based on ^{19}F NMR with *p*-$CF_3OC_6H_4OCH_3$ as internal standard. [c] CuCl (20 mol%) was used. [d] Value in parentheses refers to isolated yield.



2a **2b** **2c** **2d**

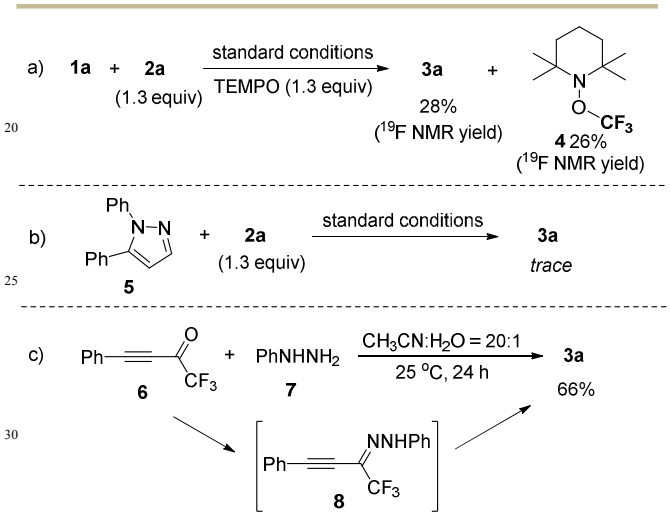
The scope of α, β-alkynic hydrazones for this trifluoromethylation/cyclization transformation is summarised in Scheme **3**. The reaction exhibits good functional group tolerance in general. The transformation of electron-neutral phenyl α, β-alkynic hydrazones **1a** and aryl α, β-alkynic hydrazones with electron-donating substituents on aromatic ring provides the corresponding 3-trifluoromethylpyrazoles in moderate to good yields (**3b-e**). Chloro- and iodo-substituted aryl alkynic hydrazones **1f** and **1g**, which are valuable for further functionalization, undergo smooth conversion. The strong electron-withdrawing group -CF_3 and -NO_2 are also compatible with the reaction conditions, giving **3h** and **3i** in 55% and 72% isolated yield, respectively. To our delight, for the substrates bearing thiophene and pyridine moiety, the transformation affords moderate yield of **3j** and **3k**. Besides, the alkyl-substitutedα, β-alkynic hydrazone **1l** is successfully converted into 3-trifluoromethylpyrazole **3l** in 47% yield. The *N*-Boc protected pyrazole **3m**, which can be used as starting material for further



Scheme 3 Trifluoromethylation/cyclization of α, β-alkynic hydrazones using a hypervalent iodine reagent **2a**. Reaction conditions: **1a** (0.20 mmol, 1.0 equiv), **2a** (0.26 mmol, 1.3 equiv), Cs_2CO_3 (0.40 mmol, 2.0 equiv), CH_3CN/H_2O (20:1, v/v, 1 mL), 25 °C, 24 h, under N_2 atmosphere. [a] Isolated yield.

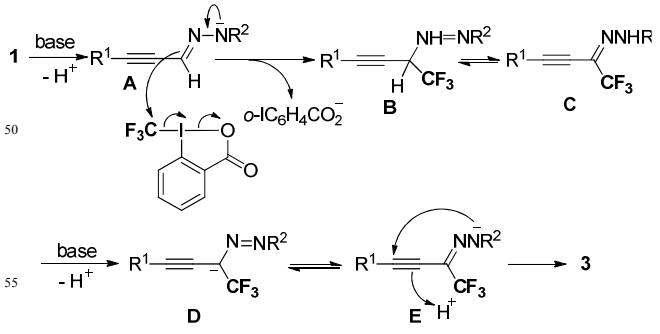
transformations, can also be obtained by this method. Finally, this novel method has been successfully applied for the synthesis of the antiarthritic drug Celecoxib **3n**.

Several experiments have been carried out in order to gain insights into the reaction mechanism. First, 1.3 equiv of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was introduced as the free radical trapping agent in the standard reaction. The yield of **3a** was dropped to 28%, while TEMPO-CF_3 adduct **4** was produced in 26% (Scheme 4, a). These observations do not support a pure trifluoromethyl radical pathway. Next, direct C-H trifluoromethylation of pyrazole **5** with **2a** under the standard conditions does not give **3a** (Scheme 4, b). Finally, condensation of alkynyl trifluoromethyl ketone **6** with phenylhydrazine **7** in the absence of base affords **3a** directly, instead of α, β-alkynic hydrazone **8** (Scheme 4, c).



Scheme 4 Preliminary mechanistic studies.

Based on these experiments, a plausible reaction mechanism is proposed as shown in Scheme 5. The reaction is initialized with deprotonation of α, β-alkynic hydrazones **1** with base to form the anionic intermediate **A**, which reacts with highly electrophilic Togni reagent to form C-CF_3 bond, affording azo intermediate **B** or α, β-alkynic hydrazone **C**. Species **B** or **C** undergoes deprotonation/cyclization/pronation sequence to give products **3**. However, since trifluoromethyl radical has been trapped by TEMPO in this reaction, a radical mechanism cannot be strictly removed. Further studies are needed to firmly establish the reaction mechanism.



Scheme 5 Proposed mechanism.

In conclusion, a novel strategy for the synthesis of 3-trifluoromethylpyrazole derivatives through transition-metal-free trifluoromethylation/cyclization of α, β-alkynic hydrazones has been developed. Further work will be focused on in-depth mechanistic studies of this reaction and the exploration of other functionalization of pyrazoles through coupling/cyclization sequence.

The project was supported by 973 Program (No. 2012CB821600) and NSFC (Grant 21172005, 21272010 and 21332002).

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