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Regioselective Synthesis of 3-Trifluoromethylpyrazole by Coupling of Aldehydes, Sulfonyl Hydrazides, and 2-Bromo-3,3,3-trifluoropropene

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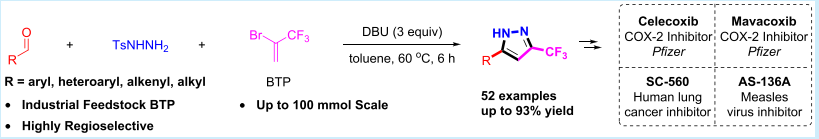

ABSTRACT: A general and practical strategy for 3-trifluoromethylpyrazole synthesis is reported that occurs by the three-component coupling of environmentally friendly and large-tonnage industrial feedstock 2-bromo-3,3,3-trifluoropropene (BTP), aldehydes, and sulfonyl hydrazides. This highly regioselective three-component reaction is metal-free, catalyst-free, and operationally simple and features mild conditions, a broad substrate scope, high yields, and valuable functional group tolerance. Remarkably, the reactions could be performed on a 100 mmol scale and smoothly afforded the key intermediates for the synthesis of celecoxib, mavacoxib, SC-560, and AS-136A. Preliminary mechanism studies indicated that a 1,3-hydrogen atom transfer process was involved in this transformation.

Trifluoromethylpyrazole, especially 3-trifluoromethylpyrazole, is a privileged core structure in many pharmaceuticals and agrochemicals (Scheme 1a),[1] such as celecoxib[2a] and mavacoxib[2b] (COX-2 inhibitors), SC-560 (human lung cancer inhibitor),[2c] DPC-602 (arterial thrombosis),[2d] AS-136A (measles virus inhibitor),[2e] razaxaban (anticoagulant),[2f] and DP-23 (insecticidal activity).[2g] Owing to the immense applications of 3-trifluoromethylpyrazole derivatives, the development of efficient methods to construct the 3-trifluoromethylpyrazole moiety has gained much attention.[3−5] Traditionally, the 3-trifluoromethylpyrazole framework could be constructed by dehydrative condensation between hydrazines and 1,3-dicarbonyl compounds or ynones via C^3−N^2 and C^5−N^1 bond formation, which often suffers from the formation of regioisomeric mixtures.[3] In 2013, Ma reported a highly regioselective [3 + 2] cycloaddition of 2,2,2-trifluorodiazoethane with alkynes[4a] or allenes[4b] for the synthesis of 3-trifluoromethylpyrazoles via C^3−C^4 and C^5−N^1 bond formation, which was promoted by superstoichiometric amounts of silver salts.[4] Later in 2017, Jamison realized the same transformation using an elegant continuous flow strategy.[5] However, owing to its gaseous and potential explosive properties, 2,2,2-trifluorodiazoethane needs to be in situ generated. In particular, these reported strategies focused on two-component coupling (Scheme 1b). Thus despite this progress, the development of more general and practical methods for the synthesis of 3-trifluoromethylpyrazole is always in high demand.

Multiple-component reactions are regarded as one of the most attractive protocols in synthetic chemistry because they enable the direct construction of useful and complex molecules from simple and readily available raw materials.[6] 2-Bromo-3,3,3-trifluoropropene (BTP) is a stable liquid at room temperature and is an environmentally friendly and large-tonnage industrial feedstock that is not classified as an ozone depletion compound and is thought to be an ideal alternative to Halon fire suppressant.[7] Thus we envision constructing 3-trifluoromethylpyrazole from BTP by a multiple-component reaction. The logical following retrosynthetic analysis shows that the coupling of BTP with a C1 synthon and a N2 moiety via C^3−N^2, C^4−C^5, and C^5−N^1 bond formation is the most promising strategy to construct this 3-trifluoromethylpyrazole core; however, to the best of our knowledge, this BTP-involved three-component strategy has never been reported before. Thus the choice of a suitable reaction system and control over the regioselectivity are the main challenges in this transformation. We herein report a highly regioselective coupling reaction of aldehydes, sulfonyl hydrazides, and BTP, delivering various useful 3-trifluoromethylpyrazole derivatives in high yield (Scheme 1c). Remarkably, this three-component reaction is metal-free, catalyst-free, scalable, and operationally simple and features mild conditions, a broad substrate scope, and valuable functional group tolerance.

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Scheme 1. 3-Trifluoromethylpyrazole

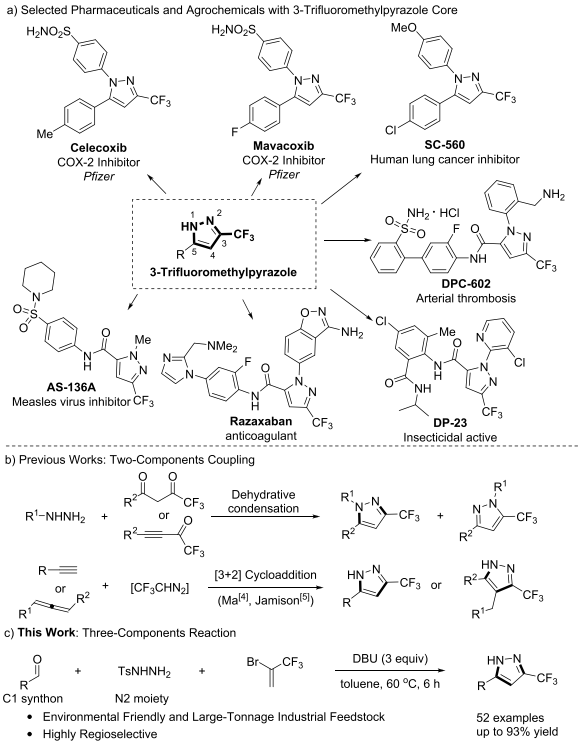
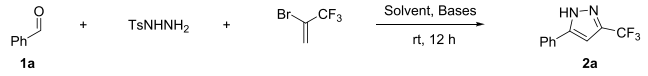


Table 1. Optimization of the Reaction Conditions[a]



entry	solvent	base	yield (%)[b]
1	toluene	Cs_2CO_3	trace
2	toluene	K_2CO_3	trace
3	toluene	Li_2CO_3	0
4	toluene	*t*-BuOK	0
5	toluene	*t*-BuOLi	24
6	toluene	MeONa	trace
7	toluene	DBU	63 (61)
8	toluene	DABCO	0
9	toluene	Et_3N	0
10	toluene		0
11	DCE	DBU	38
12	MeCN	DBU	38
13	1,4-dioxane	DBU	40
14	THF	DBU	43
15	DMF	DBU	39
16	DMSO	DBU	31
17	EtOH	DBU	58
18[c]	toluene	DBU	91 (88)
19[c,d]	toluene	DBU	91

[a]Reaction conditions: **1a** (0.5 mmol), $TsNHNH_2$ (1.2 equiv), bases (3 equiv), BTP (2 equiv), and solvent (3 mL) were stirred in a 25 mL test tube at room temperature for 12 h. [b]^{19}F NMR yields. [c]At 60 °C for 6 h. [d]Under N_2 with anhydrous toluene as the solvent. Isolated yields are presented in the parentheses.

The initial experiment of this three-component reaction for 3-trifluoromethylpyrazole synthesis was carried out with benzaldehyde **1a**, *p*-toluenesulfonyl hydrazide ($TsNHNH_2$), and BTP under the treatment of Cs_2CO_3 in toluene at room temperature (Table 1, entry 1). A trace amount of new species was detected by GC−MS with a base peak at m/z = 212.03, which has the same m/z value with respect to our desired 3-trifluoromethylpyrazole product **2a**. To identify the structure of this new species, different inorganic bases such as K_2CO_3, Li_2CO_3, *t*-BuOK, *t*-BuOLi, and MeONa and organic bases such as DBU, DABCO, and Et_3N were first examined to improve its yield (Table 1, entries 2−9). To our delight, a base of DBU gave the new species in 61% isolated yield. Thus its structure was confirmed to be our desired 3-trifluoromethylpyrazole product **2a** by nuclear magnetic resonance (NMR) analysis. Without a base, no product **2a** was detected (Table 1, entry 10). Next, different types of solvent such as 1,2-dichloroethane (DCE), MeCN, 1,4-dioxane, THF, DMF, DMSO, and EtOH were investigated to optimize the yield of **2a** (Table 1, entries 11−17); however, no superior results were obtained. Furthermore, increasing the reaction temperature to 60 °C enhanced the isolated yield of **2a** to 88% in 6 h (Table 1, entry 18). In addition, performing the reaction under anhydrous toluene and a N_2 atmosphere did not increase the yield of **2a**, indicating that this three-component reaction was not air- or moisture-sensitive (Table 1, entry 19). In particular, this three-component coupling reaction is highly regioselective, and no other regioisomers were detected.

With the optimized reaction conditions in hand, we then turned our attention to the generality of this three-component reaction with a variety of aldehydes, and the results are outlined in Scheme 2. In general, electron-neutral aromatic aldehyde derivatives such as benzaldehyde, [1,1′-biphenyl]-carbaldehyde, naphthaldehyde, anthracene-9-carbaldehyde, and pyrene-1-carbaldehyde gave the desired 3-trifluoromethylpyrazole products **2a**−**g** in high yield. Benzaldehyde derivatives with electron-donating substituents such as alkyl, alkoxy, hydroxy, amino, morpholinyl, and methylthio and electron-withdrawing substituents such as fluoro, chloro, bromo, iodo, cyano, trifluoromethyl, formic ester, sulfonyl, nitro, and ethynyl groups on the phenyl ring all smoothly afforded the corresponding products **2h**−**al**. Symmetric 3-trifluoromethylpyrazole products **2am**−**an** derived from the corresponding symmetric aldehydes were obtained in high yield. It is noteworthy that this reaction was not sensitive to steric hindrance (**2c**, **2e**, **2k**, **2o**, **2af**, and **2am**), and acid-free O−H and N−H bonds could also be tolerated under the standard reaction conditions (**2q** and **2r**). *α*,*β*-Unsaturated aldehydes such as (*S*)-perillaldehyde and (*E*)-tigladehyde also gave **2ao**−**ap** in high yield. Furthermore, different heteroaromatic aldehydes, such as furanyl-, thienyl-, pyridyl-, and quinolyl-bearing aldehydes, were also found to be good substrates, and the desired products **2aq**−**ax** were isolated in high yield. In addition, aliphatic aldehydes such as cyclohexanaldehyde and lilialdehyde were also tested under the standard reaction conditions, and the corresponding products **2ay** and **2az** were obtained in reasonable yield.

Next, four different 100 mmol scale experiments were performed under the standard reaction conditions. By simple extraction and recrystallization, products **2h**, **2v**, and **2aa** were obtained in high yield, which were independently key intermediates for colecoxib, mavacoxib, and SC-560 (Scheme 3a).[8] Importantly, product **2ar** derived from biomass derivative 2-furaldehyde was also obtained in 78% yield (15.76 g).[9] Further N−H methylation of **2ar** gave product **3** in 70% yield, which was used for the preparation of AS-136A (Scheme 3b).[2e,3g,4] It is noteworthy that these 100 mmol scale

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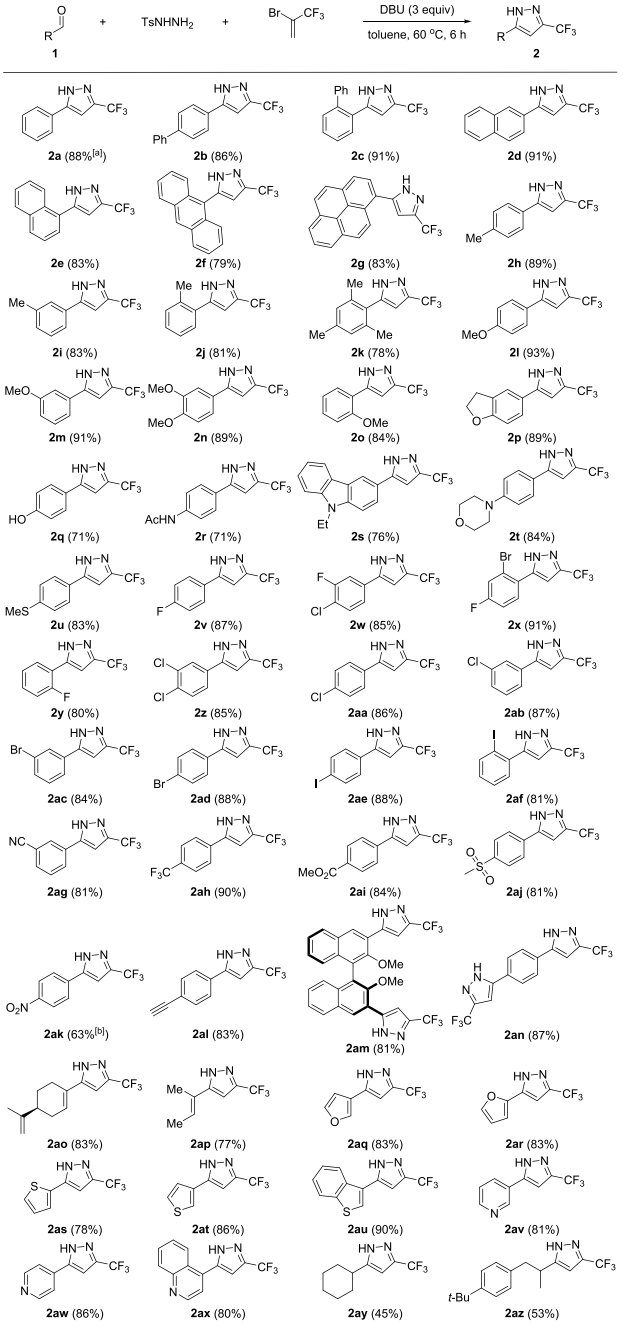
Scheme 2. Scope of Aldehydes[a]

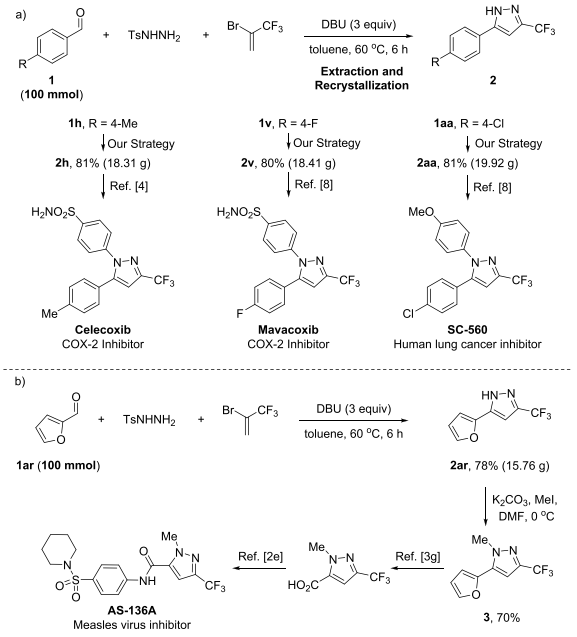


[a]Reaction conditions: **1a** (1 mmol), $TsNHNH_2$ (1.2 equiv), BTP (2 equiv), DBU (3 equiv), and toluene (6 mL) were stirred at 60 °C for 6 h. [b]Isolated yields. [c]*p*-Nitrobenzaldehyde (1 mmol), $TsNHNH_2$ (1.2 equiv), toluene (6 mL), 60 °C, 30 min, then DBU (3 equiv), BTP (2 equiv).

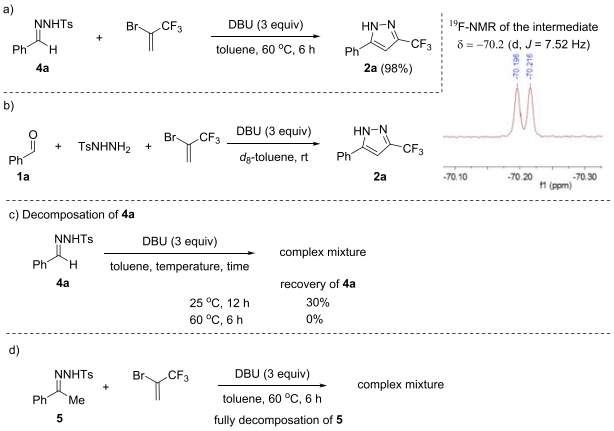
experiments were almost not exothermic, providing ample potential for the larger scale synthesis of 3-trifluoromethylpyrazoles.

The condensation of aldehydes with $TsNHNH_2$ would afford the corresponding *N*-tosylhydrazones.[10] Thus *N*-tosylhydrazone **4a** derived from benzaldehyde was tested under the standard reaction conditions and provided the desired product **2a** in 98% yield (Scheme 4a). Interestingly, although carbonyl compounds and $TsNHNH_2$ could be used instead of the corresponding *N*-tosylhydrazones in some

Scheme 3. Scale Experiments and Synthetic Applications



Scheme 4. Control Experiments



previously reported reactions, a two-step protocol is necessary for these transformations because *N*-tosylhydrazones first need to be in situ generated to ensure the efficiency of these reactions.[11] Furthermore, an intermediate featuring $\delta = -70.2$ (d, J = 7.52 Hz) was detected by a ^{19}F NMR analysis experiment to monitor the reaction (Scheme 4b), indicating that a proton was transferred to the α-position of the CF_3 group during the reaction. (For details, see the Supporting Information.) *N*-Tosylhydrazone **4a** derived from benzaldehyde could be slowly decomposed at room temperature and fully decomposed at 60 °C under the treatment of DBU for 6 h (Scheme 4c). Additionally, when *N*-tosylhydrazone **5** derived from acetophenone was treated with BTP under the standard reaction conditions, *N*-tosylhydrazone **5** decomposed completely, and a complex mixture was obtained (Scheme 4d).

The proposed reaction mechanism is illustrated in Scheme 5. The condensation of benzaldehyde **1a** with *p*-toluenesulfonyl hydrazide in-situ-generated *N*-tosylhydrazone **4a**, which then decomposed to diazo compound **A** in the presence of bases.[12] The regioselective [3 + 2] cycloaddition of dizao compound **A** with BTP afforded intermediate **B**,[13] which

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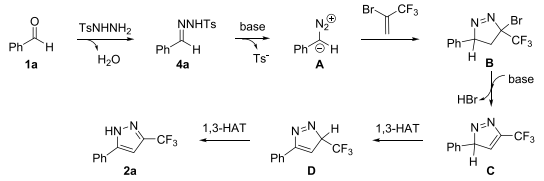
Scheme 5. Proposed Mechanism



further converted to trifluoromethylated diazo intermediate **C** via the elimination of HBr in the presence of base. The subsequent facile and chemoselective 1,3-hydrogen atom transfer (1,3-HAT) of trifluoromethylated diazo intermediate **C** provided diazo intermediate **D**, which featured a proton at the α-position of the CF_3 group.[14] Finally, the 1,3-HAT of intermediate **D** afforded the desired product **2a**.[4a]

In summary, we have reported a general and practical strategy for 3-trifluoromethylpyrazole synthesis by coupling environmentally friendly and large-tonnage industrial feedstock BTP with aldehydes and sulfonyl hydrazides. This highly regioselective three-component coupling reaction is metal-free, catalyst-free, and operationally simple and features mild conditions, a broad substrate scope, high yields, and valuable functional group tolerance. Remarkably, the reactions could be performed on a 100 mmol scale and smoothly afforded the key intermediates for the synthesis of celecoxib, mavacoxib, SC-560, and AS-136A. Preliminary mechanism studies indicated that a 1,3-HAT process was involved in this transformation. An investigation of the mechanistic details and an exploration of other potential applications of BTP are currently underway in our laboratory, the results of which will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04228.

Typical experimental procedures and characterization for all products (PDF)

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Notes

The authors declare no competing financial interest.

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