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Synthesis of Isoxazole Triflones

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The first practical synthesis of isoxazole triflones **3** (4-trifluoromethanesulfonylisoxazoles, 4-triflylisoxazoles) has been achieved by an operationally simple procedure consisting of the reaction between readily available α-triflyl ketones **4** and imidoyl chlorides **5** in the presence of triethylamine. The present method provides the biologically attractive isoxazoles featuring a triflyl group at the 4-position with a wide substrate scope in good to high yield in all cases.

Introduction

The trifluoromethanesulfonyl (SO_2CF_3, triflyl, Tf) group is one of the strongest electron-withdrawing groups and this functionality has been actively used in the form of structural units in bioactive compounds,[1] chiral catalysts,[2] and advanced functional materials.[3] In particular, much attention has been paid to aryl trifluoromethyl sulfones **1** (aryl triflones, $ArSO_2CF_3$; Figure 1), and a number of methodologies were developed thus far, including oxidation of aryl trifluoromethyl sulfides,[4] trifluoromethylation of aryl sulfonyl fluorides or aryl sulfonates,[5] thia-Fries rearrangement of aryl trifluoromethanesulfonates,[6] and direct trifluoromethanesulfonylation of aromatic compounds.[7] Recently, Taguchi and co-workers reported a unique regioselective synthesis of polysubstituted aryl triflones through a self-promoting three-component reaction.[8] Although tremendous progress has been achieved in the synthesis of aryl triflones,[4–8] the preparation of heteroaryl triflones has been considerably less studied. Our research group has recently developed a convenient synthesis of indole triflones **2** by direct trifluoromethanesulfonylation of indoles with the Tf_2O/TTBP (2,4,6-tri-*tert*-butylpyridine) system.[9] As part of our ongoing research programs directed at the development of efficient methodologies for the preparation of fluorinated heterocycles,[10] we really required isoxazole triflones **3** (4-trifluoromethanesulfonylisoxazoles, 4-triflylisoxazoles) as the key core unit for novel agrochemicals, particularly, triflones **3** having aromatic groups at the 3- and 5-positions (R^1 and R^2 = Ar^1 and Ar^2, Figure 1).[11]

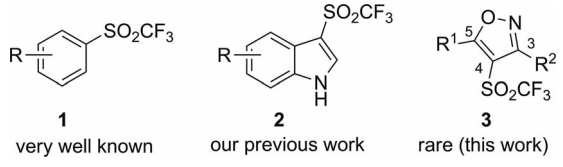
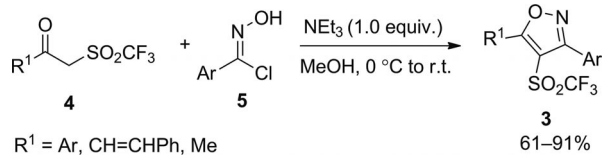


Figure 1. Aryl triflones **1**, indole triflones **2**, and isoxazole triflones **3**.

Isoxazoles are a major class of five-membered nitrogen heterocycles, are important core components in natural products, and are valuable molecules of medicinal interest.[12] Therefore numerous synthetic approaches for the construction of the isoxazole framework have been actively reported, for example, a [3+2] cycloaddition reaction between alkynes and nitrile oxides, a cycloaddition reaction with internal alkynes, and a gold-catalyzed cyclization of *O*-methyl alkynyl oxime ethers.[13] On the other hand, to date, few reports have appeared on the synthesis of isoxazole triflones[14,15] despite their clear potential usefulness and wide applicability for the syntheses of pharmaceuticals and agrochemicals.[1] We disclose herein the first practical synthesis of isoxazole 4-triflones by a tandem addition–cyclization reaction between readily available materials, α-triflyl ketones **4**,[16] and aryl imidoyl chlorides **5**,[17] in high yields and with a wide scope (Scheme 1).



Scheme 1. First synthesis of 4-triflylisoxazoles **3** (isoxazole triflones).

Results and Discussion

We initiated our investigation with the cyclization of **4** and **5** in the presence of bases. Starting substrates **4** and **5** are readily available from the corresponding ketones and aldehydes. We first attempted the reaction of **4a** and **5a** in

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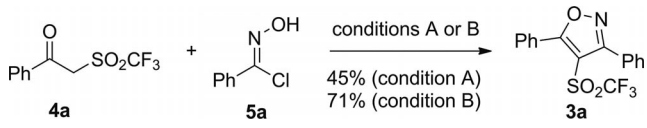
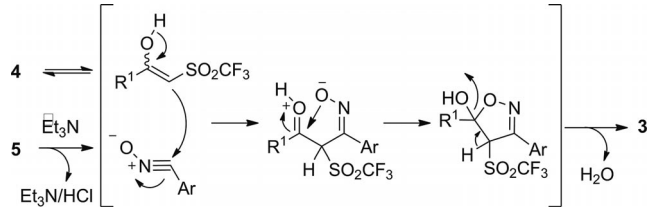
EtOH in the presence of a stoichiometric amount of Na at ambient temperature (conditions A; Na, EtOH, r.t., 10 h). However, desired isoxazole triflone **3a** was obtained in moderate yield (45%). We next examined the same reaction in MeOH in the presence of NEt_3 (1 equiv.) to afford isoxazole triflone **3a** with good yield, that is, 71% (conditions B; NEt_3, MeOH, 0 °C to r.t., 4 h; Scheme 2).



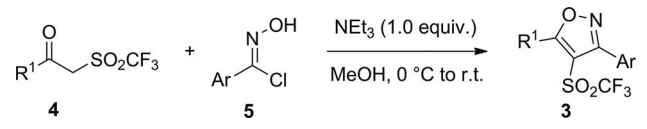
Scheme 2. Synthesis of **3a** under two different conditions.

With suitable conditions in hand, the scope of the tandem cyclization reaction was explored with a variety of substrates selected to establish the generality of the process using this strategy, all affording good to excellent yields (Table 1). A series of α-triflyl ketones **4b**–**4f** with a variety of substituents at their aromatic rings (R^1), such as methyl, methoxy, bromo, chloro, and nitro, were nicely converted into corresponding isoxazole triflones **3b**–**3f** in high yields (70%–91%; Table 1, Entries 2–6). For other aromatic analogues bearing bulky naphthyl groups (i.e., **4g**) and a heteroaryl group (i.e., **4h**), we also obtained the desired isoxazole triflones **3g** and **3h** in 84 and 80% yield, respectively (Table 1, Entries 7 and 8). Cinnamyl-substituted α-trifluoromethanesulfonyl ketone **4i** is also a suitable substrate for this transformation (Table 1, Entry 9). Moreover, enolizable aliphatic substrate **4j** was also compatible with the same reaction conditions affording product **3j** in good yield (76%), although a longer reaction time was required (Table 1, Entry 10). We next examined the substrate scope differing in the nature of the aryl substituents of imidoyl chlorides under the same reaction conditions. A series of imidoyl chlorides **5b**–**5g** were nicely converted into isoxazole triflones **3k**–**3p** in 70–83% yield, these being almost independent of the functional groups on the aromatic ring of **5** such as methyl, methoxy chloro, bromo, and nitro as well as a sterically demanding naphthyl substrate (Table 1, Entries 11–16). Imidoyl chlorides with alkyl substituents were not examined due to their instability.[17] No regioisomer of **3** was obtained, as the cyclization proceeds through a stepwise reaction mechanism involving nucleophilic addition of **4** to nitrile oxides generated in situ from **5** delineated in Scheme 3.[13j,13o,13y,13z] The characterization and assignment of products **3** thus obtained was also ascertained by comparing the spectral characteristics with the corresponding non-triflylated isoxazoles such as 4-cyano-, 4-methylsulfonyl-, 4-methylsulfinyl-, and 4-nitroisoxazoles reported earlier through a similar reaction sequence (Scheme 3).[13j,13o,13y,13z] Isoxazole triflone **3a** could also be prepared regioselectively by a halogen–lithium exchange reaction of 4-iodoisoxazole **6** followed by direct trifluoromethanesulfonylation by using Tf_2O;[9] however, the yield of **3a** was poor at 9% (Scheme 4).



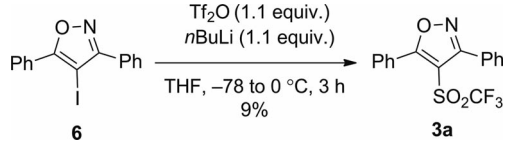
Scheme 3. Proposed reaction mechanism to **3**.

Table 1. Synthesis of 4-triflylisoxazoles **3**.[a]



Entry	4	R^1	5	Ar	3	Time [h]	Yield [%][b]
1	**4a**	Ph	**5a**	Ph	**3a**	4	71
2	**4b**	4-MeC_6H_4	**5a**	Ph	**3b**	4	78
3	**4c**	4-$MeOC_6H_4$	**5a**	Ph	**3c**	4	70
4	**4d**	4-ClC_6H_4	**5a**	Ph	**3d**	6	83
5	**4e**	4-BrC_6H_4	**5a**	Ph	**3e**	5	91
6	**4f**	4-$O_2NC_6H_4$	**5a**	Ph	**3f**	5	86
7	**4g**	2-naphthyl	**5a**	Ph	**3g**	5	84
8	**4h**	2-furanyl	**5a**	Ph	**3h**	6	80
9	**4i**	PhCH=CH	**5a**	Ph	**3i**	3	61
10	**4j**	Me	**5a**	Ph	**3j**	20	76
11	**4a**	Ph	**5b**	4-MeC_6H_4	**3k**	7	74
12	**4a**	Ph	**5c**	4-$MeOC_6H_4$	**3l**	9	70
13	**4a**	Ph	**5d**	4-ClC_6H_4	**3m**	7	83
14	**4a**	Ph	**5e**	4-BrC_6H_4	**3n**	5	81
15	**4a**	Ph	**5f**	4-$NO_2C_6H_4$	**3o**	3	74
16	**4a**	Ph	**5g**	2-naphthyl	**3p**	4	70

[a] The reaction of **4** and **5** (1.2 equiv.) was carried out in the presence of NEt_3 (1.0 equiv.) in MeOH at 0 °C to r.t. [b] Isolated yield.



Scheme 4. Preparation of **3a** by direct trifluoromethanesulfonylation of 4-iodoisoxazole **6**.

Conclusions

We disclose the first practical synthesis of isoxazole triflones **3**, which are potentially important and widely applicable for the syntheses of pharmaceuticals and agrochemicals. Our protocol provides a wide range of isoxazole triflones **3** featuring a triflyl group at the 4-position resulting from a variety of α-triflyl ketones **4** and imidoyl chlorides **5** in the presence of triethylamine. Isoxazole triflones **3** obtained here have projected utility in synthetic approaches for the production of various biologically attractive products, and biological applications will be reported in the future. The direct introduction of a triflyl group into the 4-

position of isoxazoles by trifluoromethanesulfonylation is the next challenge in this field and the subject is also under active investigation.

Experimental Section

General Procedure for Synthesis of Isoxazole Triflones 3: To a stirred solution of α-trifluoromethanesulfonyl ketone **4** (1.2 mmol) in MeOH (6.8 mL) was added NEt_3 (0.17 mL, 1.2 mmol, 1.0 equiv.) at 0 °C under a nitrogen atmosphere, and the mixture was stirred for 15 min at the same temperature. A solution of imidoyl chloride **5** (1.4 mmol, 1.2 equiv.) in MeOH (1.5 mL) was added to the reaction mixture. After stirring for 30 min at 0 °C, the reaction mixture was warmed to room temperature and left to stir for the appropriate time. After dilution with water, the whole reaction mixture was extracted with CH_2Cl_2, and the combined organic layer was washed with brine, dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by recrystallization (CH_2Cl_2/hexane) or column chromatography (*n*-hexane/ethyl acetate, 95:5) on silica gel to give isoxazole triflone **3**.

Supporting Information (see footnote on the first page of this article): Experimental procedures, characterization data, and ^1H NMR and ^{13}C NMR spectra of the prepared compounds.

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