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Synthesis of Trifluoromethylated Isoxazolidines: 1,3-Dipolar Cycloaddition of Nitrosoarenes, (Trifluoromethyl)diazomethane, and Alkenes

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ABSTRACT

Isoxazolidines have proven to be important substrates in synthetic organic chemistry. Limited examples in the literature that provide trifluoromethylated versions of these compounds have prompted us to investigate a 1,3-dipolar cycloaddition route providing access to N-functionalized isoxazolidines containing a trifluoromethyl group. Thus, a 1,3-dipolar cycloaddition of nitrosoarenes, (trifluoromethyl)diazomethane, and alkenes was developed. The starting materials can be synthesized from easy to handle and accessible reagents. The reaction proved to be tolerant of a variety of electron-deficient alkenes and nitrosoarenes.

Isoxazolidines are important building blocks in organic synthesis.[1] Their valuable nitrogen–oxygen bond provides easy access to 1,3-amino alcohols and lactams. The most common method to access these structures is the 1,3-dipolar cycloaddition of nitrones and alkenes.[2] Although an effort has been made to improve reaction conditions and substrate scope,[3] the synthesis of diverse *N*-functionalized nitrones remains a challenge, and multistep synthetic operations are often required. Zhong and coworkers developed an alternative to the use of nitrones by using diazo reagents and nitrosobenzene in the acid catalyzed 1,3-dipolar cycloaddition with electron-deficient alkenes.[4] The method proved to be efficient for a variety of alkenes. However, the scope of the nitrosoarenes was limited to a few aryl systems. Moreover, although many isoxazolidines have proven to be of biological importance, the availability of the trifluoromethylated version of these compounds remains somewhat limited.[5] Trifluoromethylated molecules figure prominently among pharmacologically active compounds.[6] The trifluoromethyl group

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[1] (a) *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*; Torssell, K. G. B., Ed.; Wiley-VCH: Weinheim, Germany, 1998. (b) Gothelf, K. V.; Jørgensen, K. A. *Chem. Commun.* **2000**, 1449. (c) Wilson, M. S.; Padwa, A. *J. Org. Chem.* **2008**, *73*, 9601. (d) Akai, S.; Tanimoto, K.; Kanao, Y.; Omura, S.; Kita, Y. *Chem. Commun.* **2005**, 2369. (e) Gallos, J. K.; Stathakis, C. I.; Kotoulas, S. S.; Koumbis, A. E. *J. Org. Chem.* **2005**, *70*, 6884. (f) Tamura, O.; Iyama, N.; Ishibashi, H. *J. Org. Chem.* **2004**, *69*, 1475.

[2] For reviews, see: (a) *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Ed.; Wiley: Hoboken, NJ, 2003. (b) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863.

[3] For selected examples, see: (a) Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874. (b) Jensen, K.; Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1997**, *62*, 2471. (c) Rios, R.; Ibrahem, I.; Vesely, J.; Zhao, G.-L.; Cordova, A. *Tetrahedron Lett.* **2007**, *48*, 5701. (d) Kano, T.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 11926.

[4] Xu, Z.-J.; Zhu, D.; Zeng, X.; Wang, F.; Tan, B.; Hou, Y.; Lv, Y.; Zhong, G. *Chem. Commun.* **2010**, *46*, 2504.

[5] Tanaka, K.; Sugimoto, Y.; Okafuji, Y.; Tachikawa, M.; Mitsuhashi, K. *J. Heterocycl. Chem.* **1989**, *26*, 381.

[6] For reviews, see: (a) *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*; Kirsch, P., Ed.; Wiley-VCH: Weinheim, 2004. (b) Schlosser, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5432. (c) Isanbor, C.; Hagan, D. O. *J. Fluorine Chem.* **2006**, *127*, 303. (d) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 188. (e) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320.

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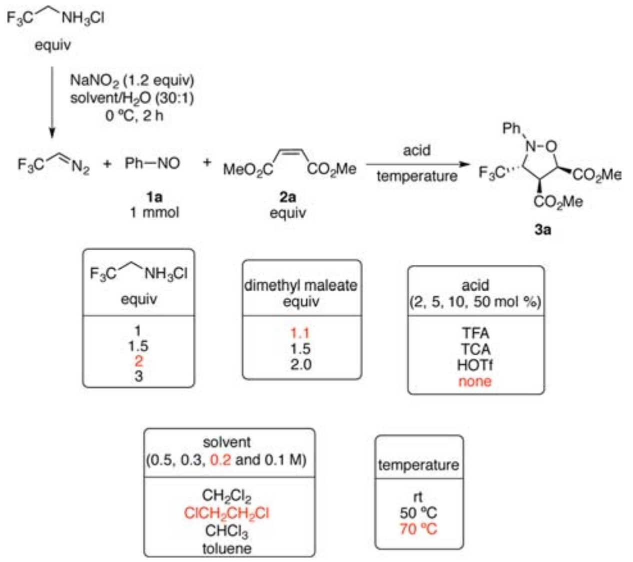
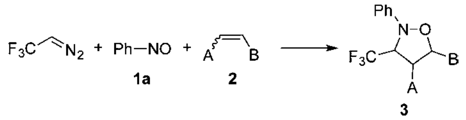
adds, among other features, stability and lipophilicity to a molecule. Thus, the need for the development of methods to afford compounds containing a CF_3 group has increased. Recently, Carreira and co-workers reported a simple and effective method to access trifluoroethyl-substituted ketones.[7] In this elegant protocol they were able to generate 2-diazo-1,1,1-trifluoroethane *in situ* by reacting inexpensive and widely available 2,2,2-trifluoroethylamine hydrochloride with sodium nitrite in a mixture of dichloromethane and water. Inspired by this work, in combination with our previously developed method to access aryl and heteroaryl nitrosoarenes from organotrifluoroborates,[8] we became interested in a three-component 1,3-dipolar cycloaddition of nitrosoarenes, (trifluoromethyl)-diazomethane, and alkenes to afford trifluoromethylated isoxazolidines.

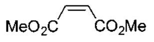
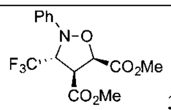
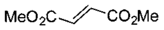
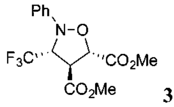
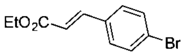
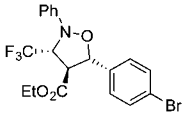
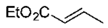
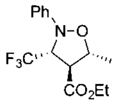
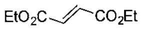
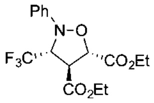
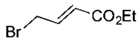
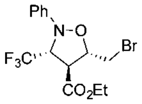
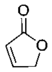
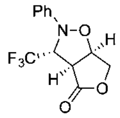
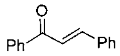
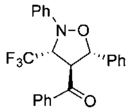
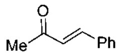
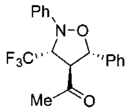
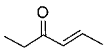
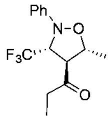
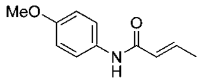
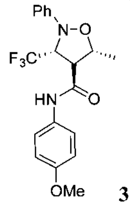
Scheme 1. Optimization of Reaction Conditions



We began the optimization of the reaction conditions by combining the procedures developed separately by Carreira and Zhong. Thus, to a solution of *in situ* formed (trifluoromethyl)diazomethane were added nitrosobenzene, dimethyl maleate, and triflic acid in dichloromethane/H_2O at room temperature. Although some isoxazolidine was observed, the reaction afforded azoxybenzene and dimethyl 3-(trifluoromethyl)cyclopropane-1,2-dicarboxylate as major side products. Therefore, further optimization of the reaction conditions (Scheme 1) was necessary. The use of other acids did not improve the selectivity of the reaction, and azoxybenzene was obtained as the major product. When the reaction was performed without an acid additive, total conversion was obtained and the formation of azoxybenzene was suppressed. Increasing the equivalents of 2,2,2-trifluoroethylamine hydrochloride yielded 3-(trifluoromethyl)cyclopropane-1,2-dicarboxylate as the major product. The same undesired product was

Table 1. Scope of Electron-Deficient Alkenes[a]



entry	alkene	product	yield (%)
1	 2a	 3a	91[b]
2	 2b	 3b	80[c]
3	 2c	 3c	78
4	 2d	 3d	85
5	 2e	 3e	75[c]
6	 2f	 3f	81
7	 2g	 3g	78
8	 2h	 3h	55
9	 2i	 3i	62[c]
10	 2j	 3j	80
11	 2k	 3k	71

[a] Conditions: 2,2,2-Trifluoroethylamine hydrochloride (2 equiv), $NaNO_2$ (2.4 equiv), dichloroethane/H_2O (30:1, 0.2 M), 2 h at 0 °C, then **1a** (1 mmol) and alkene (1.1 equiv), 16 h at 70 °C. [b] 1 g scale. [c] Along with a small amount of side product impurity.

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(7) Morandi, B.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 9085.

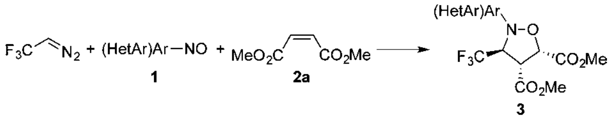
(8) Molander, G. A.; Cavalcanti, L. N. *J. Org. Chem.* **2012**, *77*, 4402.

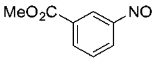
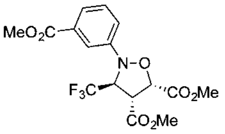
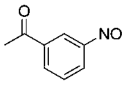
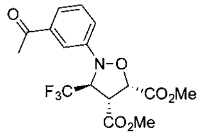
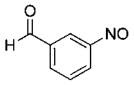
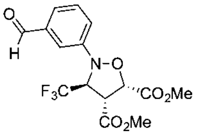
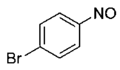
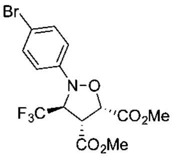
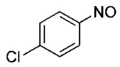
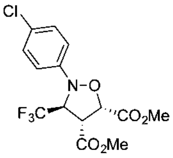
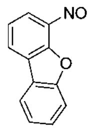
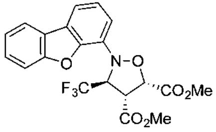
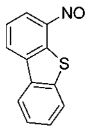
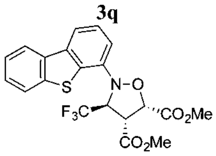
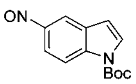
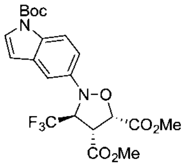
observed when more than 1.1 equiv of dimethyl maleate were utilized. Dichloromethane and dichloroethane were both efficient, affording the desired isoxazolidine as the major component in the crude product mixture. However, because the amounts of side product were reduced by running the reaction at higher temperatures, dichloroethane was the selected solvent. Therefore, after extensive screening, it was determined that nitrosobenzene reacts with 2 equiv of 2,2,2-trifluoroethylamine hydrochloride and 1.1 equiv of dimethyl maleate in dichloroethane/H_2O at 70 °C to afford the desired trifluoromethylated isoxazolidine **3a** in 94% isolated yield. The reaction proved to be diastereoselective, providing **3a** in a diastereomeric ratio higher than 30:1 as determined by crude NMR, with verification of the stereochemistry by single crystal X-ray structural analysis.

With optimal conditions in hand, we further investigated the scope of the reaction for diverse alkenes (Table 1). Dipolarophiles containing esters, ketones, and amides were efficiently reacted, providing the desired trifluoromethylated isoxazolidines in moderate to excellent yields. As previously reported,[4,5] the reaction proceeded with transfer of the dipolarophile geometry to the product. For example, when *cis*-alkenes, such as **2a**, were used, the 4,5-*cis* isoxazolidine products were observed. The same trend was noticed with *trans*-alkenes, such as **2h**, wherein the 4,5-*trans* cycloadduct **3h** was obtained in a diastereomeric ratio higher than 30:1 as determined by crude NMR, with the stereochemistry of the structure again being confirmed by X-ray structural analysis. Lactone **2g** was also utilized, providing access to the bicyclic trifluoromethylated isoxazolone **3g** in 78% yield. The reactions using dimethyl and diethyl fumarate (**2b** and **2e**) afforded the isoxazolidine products along with cyclopropanation side products.[9] Of note, the reaction of alkene **2a** was performed on a gram scale open to the atmosphere to yield trifluoromethylated product **3a** in 91% yield.

Next, we were interested in expanding the scope of the reaction with diverse nitrosoarenes. As previously mentioned, our recently developed method to synthesize nitroso compounds from organotrifluoroborates provides easy access to a variety of aryl and heteroaryl nitroso reagents.[8] As illustrated in Table 2, transformations utilizing nitrosoarenes containing ester, ketone, aldehyde, and halide functional groups were successful, affording the desired trifluoromethylated 1,3-dipolar cycloaddition product in excellent yields. Importantly, heteroarylnitroso species were also utilized, and the isoxazolidines containing trifluoromethyl and heteroaryl functional units were obtained in good yields. None of the isoxazolidines generated by this protocol have been previously reported.

Table 2. Scope of Aryl and Heteroaryl Nitroso Compounds[a]



entry	(HetAr)Ar—NO	product	yield (%)
1	 **1b**	 **3l**	94
2	 **1c**	 **3m**	90
3	 **1c**	 **3n**	85
4	 **1d**	 **3o**	96
5	 **1e**	 **3p**	91
6	 **1f**	 **3q**	81
7	 **1g**	 **3r**	71
8	 **1h**	 **3s**	76

[a] Conditions: 2,2,2-Trifluoroethylamine hydrochloride (2 equiv), $NaNO_2$ (2.4 equiv), dichloroethane/H_2O (30:1, 0.2 M), 2 h at 0 °C, then **1** (1 mmol) and **2a** (1.1 equiv), 16 h at 70 °C.

To illustrate the utility of the isoxazolidines herein obtained, we subjected product **3a** to a reductive ring-opening reaction using zinc powder in acetic acid[10] (Scheme 2). Interestingly, when **3a** reacts with zinc for only 10 min

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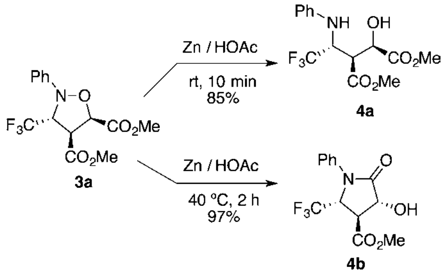
(9) For reactions to obtain this product, see: (a) Morandi, B.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 938. (b) Morandi, B.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 4294. (c) Morandi, B.; Mariampillai, B.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 1101. (d) Morandi, B.; Cheang, J.; Carreira, E. M. *Org. Lett.* **2011**, *13*, 3080.

(10) Schmidt, V. A.; Alexanian, E. J. *J. Am. Chem. Soc.* **2011**, *133*, 11402.

Scheme 2. Reductive Cleavage of the N−O Bond

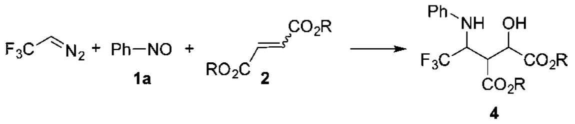


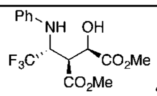
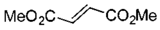
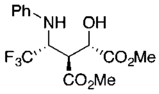
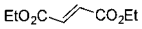
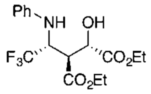
at room temperature, the desired trifluoromethylated 1,3-amino alcohols **4a** is obtained, while heating the reaction at 40 °C for 2 h provides the trifluoromethylated lactam.

Because alkenes such as dimethyl and diethyl fumarate (**2b** and **2e**) provided a mixture of products that could not be further purified, we turned our attention to a one-pot/two-step 1,3-dipolar cycloaddition followed by reductive ring cleavage to provide direct access to the amino alcohol. Thus, alkenes **2a**, **2b**, and **2c** were tested on this sequential process, and the desired trifluoromethylated 1,3-amino alcohols were obtained as pure products after column chromatography in good yields (Table 3).

In conclusion, *in situ* formed (trifluoromethyl)diazomethane was successfully used in a 1,3-dipolar cycloaddition with nitrosoarenes and alkenes. A broad range of electron-deficient alkenes can be used in conjunction with a variety of aryl and heteroaryl nitroso substrates, providing access to very unique, previously unreported structures. The cycloadduct products could be reduced to yield trifluoromethylated hydroxyamines or lactams.

Table 3. One-pot 1,3-Dipolar Cycloaddition/Reductive Ring Cleavage[a]



entry	alkene	product	yield (%)
1	 **2a**	 **4a**	80
2	 **2b**	 **4c**	82
3	 **2e**	 **4d**	78

[a] Conditions: 2,2,2-Trifluoroethylamine hydrochloride (2 equiv), $NaNO_2$ (2.4 equiv), dichloroethane/H_2O (30:1, 0.2 M), 2 h at 0 °C, then **1** (1 mmol) and **2a** (1.1 equiv), 16 h at 70 °C. After reaction time, Zn (10 equiv) and HOAc (1 mL) were added at rt for 10 min.

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Supporting Information Available. Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.