Nucleophilic Addition

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Trifluoromethylation of Aromatic Isoxazoles: Regio- and Diastereoselective Route to 5-Trifluoromethyl-2-isoxazolines**

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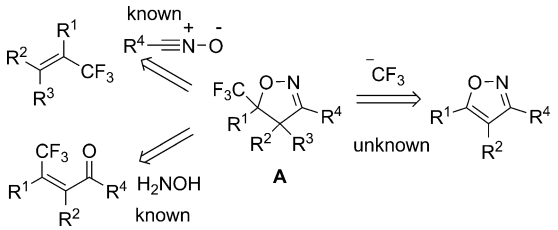
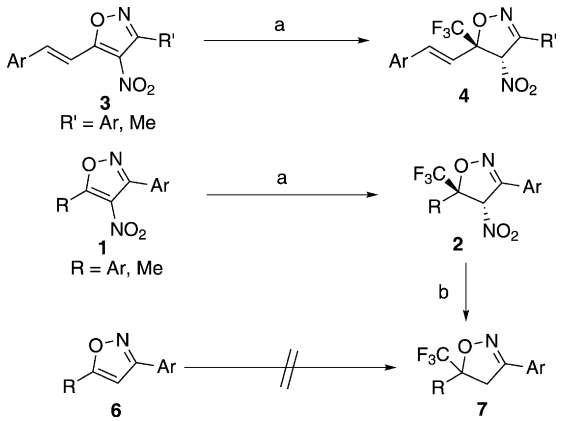
5-Trifluoromethyl-2-isoxazolines with a quaternary carbon center bearing a CF_3 group are part of an important class of heterocyclic compounds with remarkable biological activities, which make them promising synthetic targets in the fields of medicinal chemistry and agrochemistry.[1] Particularly since the discovery of the structurally unique 3,5-diaryl-5-(trifluoromethyl)-2-isoxazoline derivatives **A** (Scheme 1; $R^1 = R^4 =$ Ar) as pest-control agents in 2004,[2a] the search for new agrochemicals and veterinary medicines has focused largely on this skeleton.[2] Thus far, more than 20000 compounds have been synthesized and patented over the past 6 years (the result of a substructure search for **A** using the SciFinder database), and many potential drug candidates have been disclosed, including an antiparasitic. There are two principal strategies for the construction of the 5-trifluoromethyl-2-isoxazoline framework: 1) a building-block approach, which includes the 1,3-dipolar cycloaddition of trifluoromethylated styrenes and nitrile oxides,[2a–d] and a hydroxylamine/enone cascade reaction consisting of the conjugated addition/cyclization/dehydration reactions,[2e–h,3] and 2) the direct nucleophilic addition of a CF_3 group to an isoxazole (Scheme 2).



Scheme 1. Synthetic strategies for 5-trifluoromethyl 2-isoxazolines.



Scheme 2. Synthesis of 5-trifluoromethyl 2-isoxazolines **2**, **4**, and **7** by regio- and diastereoselective trifluoromethylation of 4-nitroisoxazoles **1** and **3** by nucleophilic addition. Reaction conditions: a) Me_3SiCF_3 (2.0 equiv), NaOAc (1.5 equiv), $[CH_3(CH_2)_{15}N(CH_3)_3]Br$ (30 mol%), DMF, RT; b) nBu_3SnH (1.5 equiv), AIBN (0.5 equiv).

However, only building-block methods have been reported and no examples of the trifluoromethylation of isoxazoles by direct nucleophilic addition have appeared, despite the clear advantage of a direct method over the building-block approach. This issue is apparently a consequence of the fundamental aromatic character of isoxazoles,[4] that is, the preference to retain the aromaticity rather than become a nonconjugated system, particularly in the case of the conjugated 3,5-diarylisoxazoles. Indeed, the addition of nucleophiles at the 5-position of an isoxazole is a challenge.[5] To realize the previously unknown trifluoromethylation of aromatic 3,5-diarylisoxazoles by nucleophilic addition, we came up with the idea of introducing a strong electron-withdrawing nitro group at the 4-position of the isoxazole ring; this group should alter the aromaticity of the isoxazoles to activate the 5-position.[6] As part of our ongoing research programs, which are directed towards the development of novel methods of trifluoromethylation,[7] we disclose herein an expeditious synthesis of biologically important 5-(trifluoromethyl)-2-isoxazoline derivatives **A** in high yields and with complete diastereoselectivity by a novel trifluoromethylation of 4-nitroisoxazoles using the Ruppert–Prakash reagent (trifluoromethyltrimethylsilane) in the presence of NaOAc and a phase-transfer catalyst. Regio- and diastereoselective trifluoromethylation by nucleophilic addition was even also achieved in high to excellent yields without giving any 1,6-adducts in the reaction of 1,6-conjugated styryl-4-nitroisoxazoles **3** with Me_3SiCF_3 under the same reaction conditions (Scheme 2). Despite the ever-increasing repertoire of trifluoromethylation reactions of carbonyls,[8] imines,[9] alkenes,[10] aromatic rings,[11] and other groups[8] with Me_3SiCF_3, this is the first example of the trifluoromethylation of an aromatic isoxazole by nucleophilic addition. Since the nitro group in the products can be easily removed under radical reaction conditions, the process not only constitutes a

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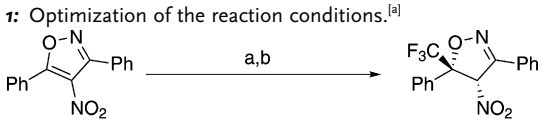
rare example of the trifluoromethylation of aromatic compounds by nucleophilic addition, but also provides a new synthetic route to the agrochemically important 5-trifluoromethyl-2-isoxazolines.

We first examined the reaction of 4-nitro-3,5-diphenylisoxazole (**1a**), as a model substrate, with Me_3SiCF_3 in the presence of a stoichiometric amount of tetrabutylammonium fluoride (nBu$_4$NF) in DMF at ambient temperature. Substrate **1a** completely disappeared during the reaction, as monitored by TLC analysis, but the trifluoromethylated adduct **2a** was not obtained (Table 1, entry 1). The reaction was next

Table 1: Optimization of the reaction conditions.[a]



1a **2a**

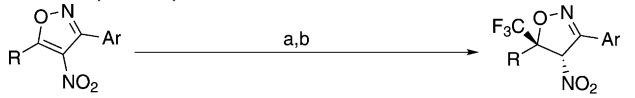
Entry	Additive	Solvent	Yield [%][b]
1	nBu$_4$NF·H$_2$O	DMF	–
2	K_2CO_3	DMF	28
3	KOH	DMF	44
4	tBuOK	DMF	57
5	KF	DMF	59
6	CsF	DMF	57
7	LiOAc	DMF	67
8	NaOAc	DMF	80
9	KOAc	DMF	78
10	NaOAc	CH_2Cl_2	–
11	NaOAc	THF	–
12	NaOAc	toluene	–
13[c]	NaOAc	DMF	95

[a] Reaction conditions: a) Me_3SiCF_3 (2.0 equiv), base (1.5 equiv), solvent, RT, 6–10 h; b) 1 M HCl aq, RT. [b] The yield of the isolated product. [c] The reaction was performed in the presence of [$CH_3(CH_2)_{15}N(CH_3)_3$]Br. DMF = *N*,*N*′-dimethylformamide.

attempted using K_2CO_3 instead of nBu$_4$NF, which gave the desired **2a** in 28% yield as a single diastereoisomer (entry 2). This preliminary result encouraged us to further investigate the reaction conditions (entries 3–13). After screening several bases (entries 3–9), the yield of **2a** was increased to 80% when the reaction was carried out using NaOAc (entry 8). The choice of solvent is important to the conversion, as the reaction did not proceed at all in CH_2Cl_2, THF, and toluene (entries 10–12). The best result was obtained by treating **1a** with Me_3SiCF_3 (2.0 equiv) at room temperature in DMF in the presence of cetyltrimethylammonium bromide ([$CH_3(CH_2)_{15}N(CH_3)_3$]Br; 30 mol%) and NaOAc (1.5 equiv), which led to the isolation of **2a** in 95% yield (entry 13).

With the optimized conditions to hand, the scope of the trifluoromethylation of 4-nitro-3,5-diarylisoxazole **1** by nucleophilic addition was explored with a variety of substrates, which were selected to establish the generality of the process by using this strategy. A range of 4-nitro-3,5-diarylisoxazoles (**1a**–**h**) were converted into the corresponding trifluoromethylated adducts (**2a**–**h**), which were isolated as single isomers in excellent yields of 85–99%; the yields were not affected by the functional groups on the aromatic ring (Table 2, entries 1–8). Interestingly, for 4-nitro-5-methyl-3-

Table 2: Stereoselective trifluoromethylation of 4-nitro-3,5-diarylisoxazole **1a**–**f** by nucleophilic addition.[a]



1a–j **2a–j**

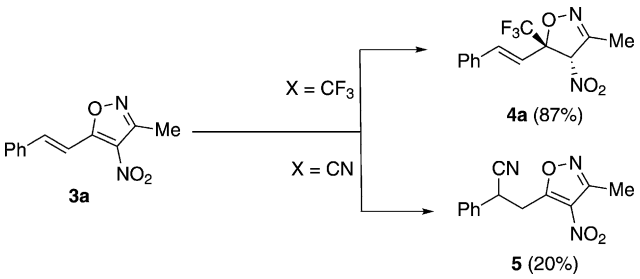
R = Ar, Me

Entry	**1**	R	Ar	**2**	Yield [%][b]
1	**1a**	Ph	Ph	**2a**	95
2	**1b**	Ph	4-MeC_6H_4	**2b**	85
3	**1c**	Ph	4-ClC_6H_4	**2c**	90
4	**1d**	3-MeC_6H_4	Ph	**2d**	90
5	**1e**	4-ClC_6H_4	Ph	**2e**	99
6	**1f**	4-BrC_6H_4	Ph	**2f**	92
7	**1g**	2-naphthyl	Ph	**2g**	90
8	**1h**	3-ClC_6H_4	4-BrC_6H_4	**2h**	97
9	**1i**	Me	Ph	**2i**	72
10	**1j**	Me	4-MeC_6H_4	**2j**	67

[a] Reaction conditions: a) Me_3SiCF_3 (2.0 equiv), NaOAc (1.5 equiv), [$CH_3(CH_2)_{15}N(CH_3)_3$]Br (30 mol%), DMF, RT; b) 1 M HCl aq, RT. [b] The yield of the isolated product.

arylisoxazoles **1i** and **1j**, which have enolizable protons, the nucleophilic addition proceeded nicely to provide the corresponding trifluoromethylated adducts **2i** and **2j** in good yields (entries 9 and 10).

We were next interested in the trifluoromethylation of 4-nitro-5-styrylisoxazoles **3**; these compounds are flexible building blocks that bear a number of different functionalities.[12] Principally, 4-nitro-5-styrylisoxazoles **3** have two electrophilic centers, both of which could be attacked by nucleophiles. In a previous report, **3** selectively reacted with nucleophiles by a 1,6-addition to yield conjugated Michael adducts in good yields,[5e,f,12g–k,m,p] although the addition of carbon nucleophiles at the 4-position of **3** is rare.[5e,f] To our delight, the reaction of 3-methyl-4-nitro-5-styrylisoxazole (**3a**) with Me_3SiCF_3 under the optimized reaction conditions exclusively afforded the trifluoromethylation product **4a** in 87% yield as a single isomer. Interestingly, when the reaction of **3a** was carried out under the same reaction conditions but using Me_3SiCN instead of Me_3SiCF_3, the 1,6-adduct **5** was selectively furnished in 20% yield (Scheme 3). These results indicated that addition at the 5-position of an aromatic isoxazole ring is specific to the trifluoromethylation reaction. Nucleophilic trifluoromethylation to conjugated alkenes

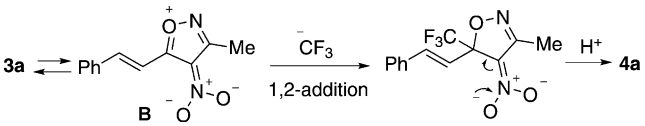


3a **4a** (87%) **5** (20%)

Scheme 3. Addition of trimethylsilyl carbon nucleophiles to 3-methyl-4-nitro-5-styrylisoxazole **3a**. Reaction conditions: Me_3SiX (2.0 equiv), NaOAc (1.5 equiv), [$CH_3(CH_2)_{15}N(CH_3)_3$]Br (30 mol%), DMF, RT; 1 M HCl aq.

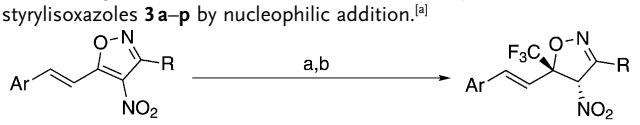
fundamentally occurs exclusively by a 1,2-addition, not a 1,4-addition,[8] except for several specific examples in which the 1,4-addition of a CF_3 anion has been reported.[10] Indeed, no example of a 1,4-addition to nitroalkanes is known. In this context, the phenomena could be explained by the nucleophilic 1,2-type addition of a CF_3 anion to a reactive species **B**, which is a tautomer of **3a** and should be included in the reaction mechanism, to provide **4a** (Scheme 4). The same mechanistic pathway is also suggested for the trifluoromethylation of **1** by nucleophilic addition to give **2** (Table 2).

The regio- and diastereoselective trifluoromethylation of 5-styrylisoxazoles **3** was found to be quite general in terms of the substrates (Table 3). The 3-methyl-5-trifluoromethyl-5-styrylisoxazoles **4a–l** were obtained in high to excellent yields and as single isomers, irrespective of the electronic nature of the aryl groups, which included naphthyl and furanyl groups, on substrates **3** (entries 1–12). 3-Aryl-4-nitro-5-styrylisoxazoles **3m–p** were also suitable substrates for the trifluoromethylation and gave the products in excellent yields of 90–96% (entries 13—16). The relative stereochemistry of (4*S**,5*S**)-**4i** was clearly determined by X-ray crystallographic analysis (Figure S1 in Supporting Information),[13] and the stereochemistry of all the other products (**2** and **4**) were tentatively assigned by the comparison of their ^{1}H and



Scheme 4. A possible reaction pathway for the regioselective trifluoromethylation of **3a** to **4a** by nucleophilic addition.

Table 3: Regio- and diastereoselective trifluoromethylation of 4-nitro-5-styrylisoxazoles **3a–p** by nucleophilic addition.[a]



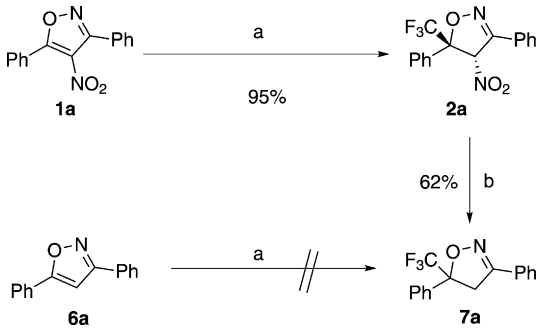
3a–p **4a–p**

Entry	3	Ar	R	4	Yield [%][b]
1	**3a**	Ph	Me	**4a**	87
2	**3b**	4-MeC_6H_4	Me	**4b**	84
3	**3c**	4-MeOC_6H_4	Me	**4c**	82
4	**3d**	2-ClC_6H_4	Me	**4d**	87
5	**3e**	3-ClC_6H_4	Me	**4e**	89
6	**3f**	4-ClC_6H_4	Me	**4f**	96
7	**3g**	4-BrC_6H_4	Me	**4g**	80
8	**3h**	4-$NO_2C_6H_4$	Me	**4h**	90
9	**3i**	2-Cl-4-$NO_2C_6H_3$	Me	**4i**	67
10	**3j**	1-naphthyl	Me	**4j**	86
11	**3k**	2-naphthyl	Me	**4k**	85
12[c]	**3l**	2-furyl	Me	**4l**	93
13	**3m**	Ph	Ph	**4m**	90
14	**3n**	Ph	4-MeC_6H_4	**4n**	95
15	**3o**	4-MeC_6H_4	Ph	**4o**	90
16	**3p**	4-ClC_6H_4	Ph	**4p**	96

[a] Reaction conditions: a) Me_3SiCF_3 (2.0 equiv), NaOAc (1.5 equiv), $[CH_3(CH_2)_{15}N(CH_3)_3]Br$ (30 mol%), DMF, RT, 3–8 h; b) 1 M HCl aq, RT. [b] The yield of the isolated product. [c] Me_3SiCF_3 (4.0 equiv), NaOAc (3.0 equiv) and $[CH_3(CH_2)_{15}N(CH_3)_3]Br$ (50 mol%) were used.

^{19}F NMR spectra with those of **4i**. The 4*S**,5*S** stereoselectivity of **4** could result from a thermodynamically controlled protonation of an intermediate, as shown in the last step in Scheme 4. The (4*S**,5*S**)-**4** might be more thermodynamically favored than another isomer, (4*R**,5*S**)-**4**, although further investigation is required to elucidate the mechanism.

In conclusion, the activation of aromatic isoxazoles with a nitro group at the 4-position has resulted in the realization of the first diastereoselective trifluoromethylation at the 5-position of isoxazoles by nucleophilic addition using Me_3SiCF_3. This method allows easy access to agrochemically important 3,5-disubstituted-5-(trifluoromethyl)-2-isoxazoline derivatives. Regio- and diastereoselective trifluoromethylation by nucleophilic addition was also achieved in the reaction of the 1,6-conjugated styryl-4-nitroisoxazoles **3** with Me_3SiCF_3 under the same reaction conditions. The process can be applied to a broad range of 3,5-aromatic, heteroaromatic, and aliphatic substrates which contain diverse functionality. Notably the nitro group at the 4-position is essential for a successful transformation. No reaction was observed between 3,5-diphenylisoxazole **6a**, which is the non-nitro analogue of **1a**, and Me_3SiCF_3 under the same reaction conditions. The nitro group of **2a** was easily removed under the radical reduction conditions to provide **7a** in 62% yield (Scheme 5). Hence, the process not only constitutes a rare



Scheme 5. The nitro group has an important role in these chemical transformations. Reaction conditions: a) Me_3SiCF_3 (2.0 equiv), NaOAc (1.5 equiv), $[CH_3(CH_2)_{15}N(CH_3)_3]Br$ (30 mol%), DMF, RT; b) nBu$_3$SnH (1.5 equiv), AIBN (0.5 equiv), benzene, reflux, 2 h.

example of the trifluoromethylation of aromatic compounds by nucleophilic addition but also provides a new synthetic route to the agrochemically important 5-trifluoromethyl-2-isoxazolines. The biological activities of selected 5-(trifluoromethyl)-2-isoxazoline derivatives are being investigated and asymmetric variants of this method are now under consideration.

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[13] CCDC 820906 (**4i**) contains 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/data_request/cif.

