SHORT COMMUNICATION

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Enantioselective Synthesis of 5-Trifluoromethyl-2-isoxazolines and Their *N*-Oxides by [Hydroxy(tosyloxy)iodo]benzene-Mediated Oxidative N–O Coupling

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Biologically attractive trifluoromethyl-2-isoxazoline *N*-oxides were synthesized in good yields for the first time by the [hydroxy(tosyloxy)iodo]benzene-mediated oxidative N–O coupling of β-trifluoromethyl β-hydroxy ketoximes generated from trifluoromethyl β-keto alcohols. The present method allows the synthesis of previously unknown 5-trifluoromethyl-2-isoxazoline *N*-oxides and also provides an alternative for the enantioselective synthesis of antiparasitic 5-trifluoromethyl-2-isoxazolines by sequential reduction.

Introduction

Since the discovery in 2004 that 3,5-diaryl-5-(trifluoromethyl)-2-isoxazoline derivatives **1** exhibit potent antiparasitic activity against cat fleas and dog ticks,[1] the exploration for novel veterinary medicines and agrochemicals has attracted much attention to this small five-membered trifluoromethylated heterocycle.[2] More than 27000 compounds having this skeleton are registered in SciFinder®, and most of them are patented by several chemical companies.[3] Moreover, carbon and nitrogen variants of **1**, that is, trifluoromethylated pyrrolines **2** (about 7700 compounds)[4] and pyrazolines **3** (about 7400 compounds),[3e,4d,5] have also been designed and synthesized for the same purposes, and their impressive biological activities have been revealed. On the basis of this background, we were interested in trifluoromethylated isoxazoline *N*-oxides **4** as future candidates for pharmaceuticals and agrochemicals. Isoxazoline *N*-oxides and their derivatives are structurally unique heterocycles, and they have been applied in the synthesis of biologically active compounds.[6] However, there is no report on the synthesis of trifluoromethylated 3,5-diarylisoxazoline *N*-oxides **4**, despite their potential as veterinary drugs and agrochemicals (Figure 1).

In recent years, we reported the synthesis of 3,5-diaryl-5-(trifluoromethyl)-2-isoxazolines **1** by means of direct trifluoromethylation of aromatic isoxazoles as well as an enantioselective hydroxylamine–enone cascade reaction consisting of a conjugate addition/cyclization/dehydration sequence.[7] As part of our ongoing research program directed at the development of efficient methodologies for the preparation of trifluoromethylated isoxazoline and related heterocycles,[8] we disclose herein the asymmetric synthesis of 5-trifluoromethyl-2-isoxazoline *N*-oxides **4** mediated by [hydroxy(tosyloxy)iodo]benzene (HTIB). The oxidatively N–O-coupled β-trifluoromethylhydroxy β-ketoximes **5** are derived from trifluoromethyl β-keto alcohols **6** and hydroxylamine. This method provides the first synthesis of **4** and also provides an alternative approach for the enantioselective synthesis of antiparasitic medicines **1** by successive reduction (Scheme 1).

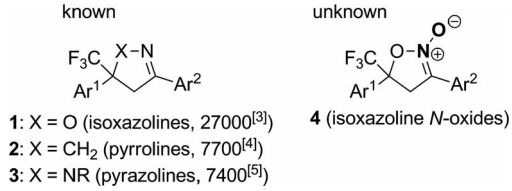
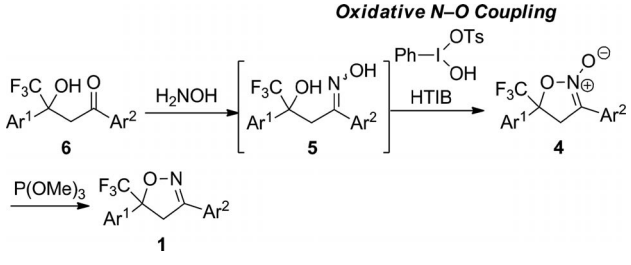


Figure 1. Structures of agrochemically important **1**, **2**, and **3**,[3–5] and previously unknown **4**.



Scheme 1. Novel approaches to 5-trifluoromethyl-2-isoxazolines **1** and unknown *N*-oxides **4** by HTIB-mediated oxidative N–O coupling; Ts = *para*-tolylsulfonyl.

Results and Discussion

Inspired by the report of Yao and co-workers on the HTIB-mediated oxidative N–O coupling of ketoximes bear-

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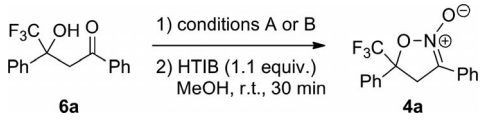
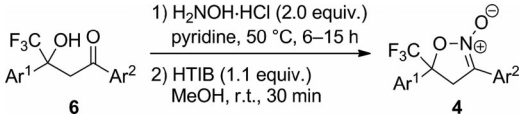
ing a secondary alcohol at the β-position to provide isoxazoline *N*-oxides,[9] we envisioned the synthesis of **4** from ketoximes **5** derived from readily available trifluoromethylated tertiary alcohols **6**.[10] We initiated our investigation with the oxime formation of **6** by using hydroxylamine ($H_2NOH{\cdot}HCl$), followed by the HTIB-mediated oxidative N–O coupling of crude β-trifluoromethyl β-hydroxy ketoximes **5** in MeOH. We first attempted oxime formation of **6a** with $H_2NOH{\cdot}HCl$ (2.0 equiv.) in EtOH under reflux conditions, followed by N–O coupling (Scheme 2, conditions A: $H_2NOH{\cdot}HCl$, EtOH, reflux). Gratifyingly, desired 5-trifluoromethyl-2-isoxazoline *N*-oxide **4a** was obtained in moderate yield (59%). We next examined the same reaction in pyridine in the presence of $H_2NOH{\cdot}HCl$ (2.0 equiv.), which afforded **4a** in a better yield of 70% (Scheme 2, conditions B: $H_2NOH{\cdot}HCl$, pyridine, 50 °C).



Scheme 2. Synthesis of **4a** under two different conditions. Conditions A: $NH_2OH{\cdot}H_2O$ (2.0 equiv.), EtOH, reflux, 14 h, 59%; conditions B: $NH_2OH{\cdot}H_2O$ (2.0 equiv.), pyridine, 50 °C, 6 h, 70%.

With suitable conditions in hand, the scope of the oxime formation of **6**, followed by the HTIB-mediated oxidative N–O coupling, was explored with a variety of substrates **6**, which were selected to establish the generality of the process by using this strategy; all of the substrates afforded the products in moderate to good yields (Table 1). Substrates with substituents derived from trifluoromethyl ketone, such as methyl, methoxy, and chloro, at the aromatic ring (Ar^1) as well as a sterically demanding naphthyl substrate were nicely converted into 5-trifluoromethyl-2-isoxazoline *N*-oxides **4b**–**e** in good yields (50–63%; Table 1, entries 2–5). We next examined the substrate scope by changing the nature of the aryl substituents (Ar^2) derived from ketones under the same reaction conditions. A series of trifluoromethyl β-keto alcohols **6f**–**j** were nicely converted into 5-trifluoromethyl-2-isoxazoline *N*-oxides **4f**–**j** in 51–64% yield; the yield was almost independent of the functional group (e.g., methyl, chloro, bromo, and nitro) on the aromatic ring of Ar^2, and a sterically demanding naphthyl substrate was also tolerated (Table 1, entries 6–10).

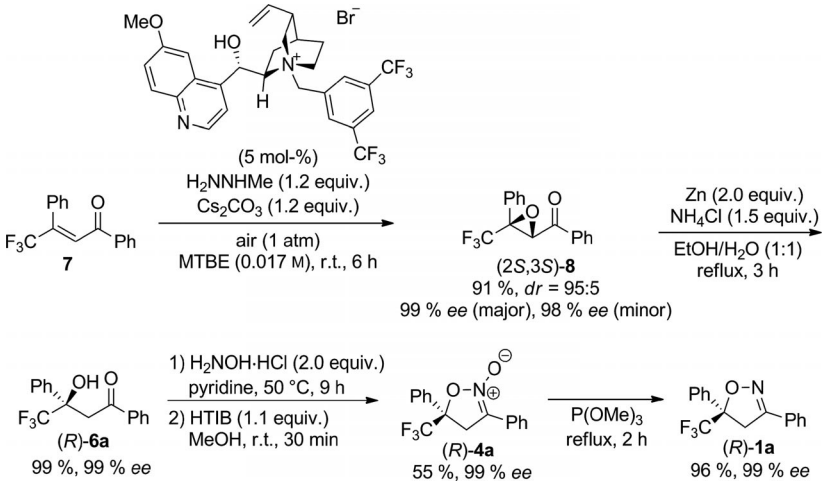
Table 1. Synthesis of 5-trifluoromethyl-2-isoxazoline *N*-oxides **4**.



Entry	6	Ar^1	Ar^2	4	Yield [%][a]
1	**6a**	Ph	Ph	**4a**	70
2	**6b**	4-MeC_6H_4	Ph	**4b**	60
3	**6c**	4-$MeOC_6H_4$	Ph	**4c**	60
4	**6d**	4-ClC_6H_4	Ph	**4d**	63
5	**6e**	2-naphthyl	Ph	**4e**	50
6	**6f**	Ph	4-MeC_6H_4	**4f**	63
7	**6g**	Ph	4-ClC_6H_4	**4g**	64
8	**6h**	Ph	4-BrC_6H_4	**4h**	61
9	**6i**	Ph	4-$NO_2C_6H_4$	**4i**	51
10	**6j**	Ph	2-naphthyl	**4j**	57

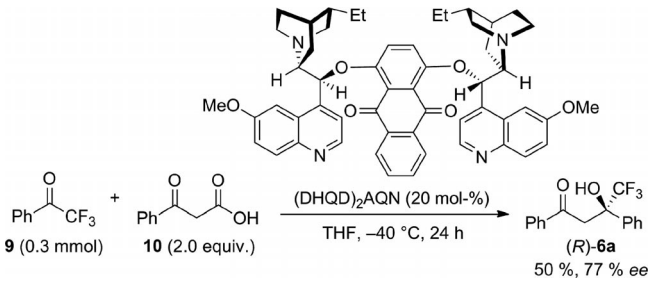
[a] Yield of isolated product calculated on the basis of **6**.

We finally attempted the asymmetric synthesis of *N*-oxides **4**. Enantioenriched tertiary alcohol **6a** was easily prepared with 99%*ee* by methylhydrazine-induced non-metallic aerobic catalytic enantioselective epoxidation of β-trifluoromethyl β,β-disubstituted enone **7** to afford epoxide **8**[11] followed by chemoselective reduction in the presence of zinc/ammonium chloride according to a reported method.[10e,12] Alcohol (*R*)-**6a** was converted efficiently into (*R*)-**4a** under the same reaction conditions without any loss of enantiomeric purity (55% yield, 99%*ee*). 5-Trifluoromethyl-2-isoxazoline *N*-oxides **4** would not only be promising candidates as pharmaceuticals and agrochemicals, but they would also be useful precursors for remarkable biologically active compounds **1**.[7b] Indeed, deoxygenation of



Scheme 3. Asymmetric synthesis of *N*-oxide **4a** from epoxide **8** and access to 5-trifluoromethyl-2-isoxazoline **1a**; MTBE = methyl *tert*-butyl ether.

(*R*)-**4a** in $P(OMe)_3$ provided (*R*)-**1a**[7b] in a good yield of 96% without any loss of enantiopurity (Scheme 3). The series of enantioenriched tertiary alcohols **6** can also be accessed by a catalytic enantioselective decarboxylative aldol reaction of β-keto acids with trifluoromethyl ketones by employing the bis-cinchona alkaloid $(DHQD)_2AQN$ (Scheme 4).[10d] Target **1a**[7b] was synthesized according to the same sequential procedure consisting of oxime formation, N–O coupling (68% yield, 78%*ee*), and reduction (80% yield, 78%*ee*).



Scheme 4. Asymmetric synthesis of *N*-oxide **4a** from trifluoromethyl ketone **9** and β-keto acid **10**.

Conclusions

We disclosed the first synthesis of 5-trifluoromethyl-2-isoxazoline *N*-oxides **4** through the HTIB-mediated oxidative N–O coupling of β-trifluoromethyl β-hydroxy ketoximes **5** derived from trifluoromethyl β-keto alcohols **6** and hydroxylamine. Our protocol provides a wide range of 5-trifluoromethyl-2-isoxazoline *N*-oxides **4**, which are potentially important and widely applicable for the syntheses of pharmaceuticals and agrochemicals as well as important precursors of veterinary medicines **1**. The organocatalyzed enantioselective synthesis of **4** and **1** was also achieved. The use of HTIB for the synthesis of biologically active compounds is another interest in the chemistry of hypervalent iodine reagents.[13]

Supporting Information (see footnote on the first page of this article): General procedures, characterization data, and copies of the ^1H, ^{13}C, and ^{19}F NMR spectra and HPLC charts.

Acknowledgments

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