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Base-catalyzed cascade 1,6-sulfur-Michael/Henry reaction of trifluoromethyl-substituted styrylisoxazoles: Diastereoselective synthesis of tetrahydrothiophenes with a trifluoromethylated quaternary center

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ABSTRACT

An effective diastereoselective [3+2] annulation of 1,4-dithiane-2,5-diol to trifluoromethyl-substituted styrylisoxazoles catalyzed by DABCO is described, giving highly functionalized tetrahydrothiophenes containing trifluoromethylated quaternary center in excellent yields and diastereoselectivities.

Sulfur-containing compounds are widely present in natural products and synthetic bioactive molecules as well as in materials.[1] In particular, tetrahydrothiophenes have attracted tremendous attention owing to their diverse bioactivities. Representative examples include the Co-enzyme Biotin **I**,[2] the various penicillins **II**,[3] the potent α-glucosidase inhibitor salacinol **III**,[4] and the nucleoside **IV** showing potent activity against human cytomegalovirus[5] (Fig. 1). Hence, the development of elegant synthetic methods to access tetrahydrothiophenes with diverse structural motifs is particularly appealing.[6]

On the other hand, trifluoromethylated organic pharmaceuticals have received increasing attention owing to the unique effect of the CF_3 group on the modification and improvement of their original biological activities.[7] Thus, the incorporation of CF_3 group into biologically important heterocyclic frameworks is ubiquitous in the field of drug discovery. Accordingly, tremendous efforts have been addressed to the development of elegant synthetic methods for the synthesis of trifluoromethylated compounds.[8] Among them, methods for the construction of trifluoromethylated all-carbon quaternary centers are still rare and extremely challenging for organic synthetic chemists. To achieve this goal, various trifluoromethylated substrates, such as CF_3-ketone,[9] CF_3-ketoimine[10] and trifluoromethylated α,β-unsaturated systems[11] were used as electrophiles to react with suitable donors via 1,2- or 1,4-addition reactions. However, the construction of trifluoromethylated all-carbon quaternary centers via 1,6-addition reactions[12] is still unexplored, and remains a great challenge in organic synthesis.

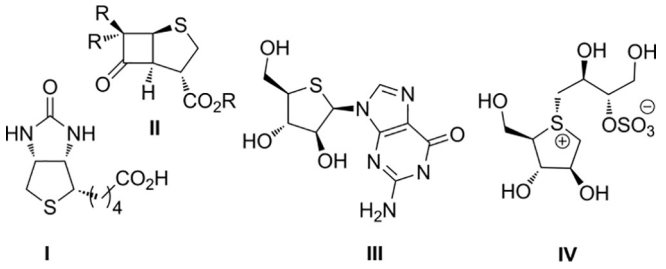

Fig. 1. Representative biologically important tetrahydrothiophenes.

Isoxazole represents as a heterocyclic privileged scaffold in pharmaceutical and natural products with a broad spectrum of interesting biological activities.[13] As part of our continuing interest in the development of efficient methods for the synthesis of various isoxazole derivatives,[14] we recently developed trifluoromethyl-substituted 3-methyl-4-nitro-5-styrylisoxazole as a novel trifluoromethylated substrate for the 1,6-Michael addition with nitromethane.[14c] Herein, we demonstrate the application of

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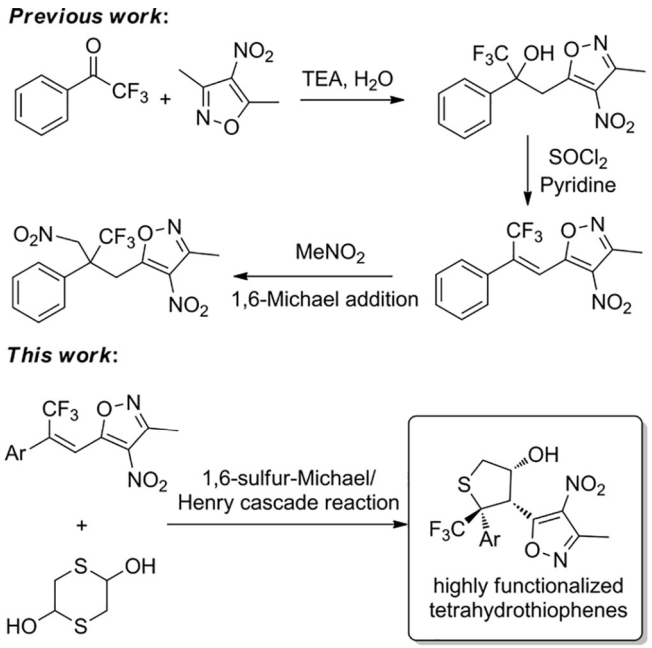
trifluoromethyl-substituted styrylisoxazoles in organocatalytic cascade reaction to afford the highly substituted tetrahydrothiophenes bearing trifluoromethylated all-carbon quaternary centers with high diastereoselectivities (Scheme 1).

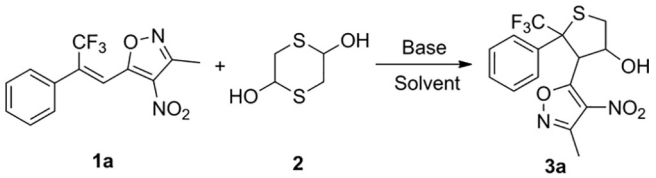
We initiated our investigation by evaluating the reaction of trifluoromethyl-substituted 3-methyl-4-nitro-5-styrylisoxazole and 1,4-dithiane-2,5-diol[15] with acetonitrile as the solvent in the presence of 20 mol% of NEt_3 at room temperature. To our gratification, this 1,6-sulfur-Michael/Henry cascade reaction proceeded efficiently with NEt_3 to provide a cyclic product in 60% isolated yield with good diastereoselectivity (90:10 dr) within 30 min (Table 1, entry 1). Encouraged by this promising result, several other bases were screened, and DABCO proved to be the most suitable catalyst in term of both reaction efficiency and selectivity (Table 1, entry 5). Subsequently, solvent effects were investigated for the reaction using DABCO as the catalyst. Although excellent diastereoselectivities were obtained with the solvents $CHCl_3$ and THF, the isolated yields were rather poor (28% and 38%) even with a prolonged reaction time (24 h). Other solvents such as CH_2Cl_2, EtOH and Toluene were screened, and no better results were achieved (entries 10–13). After further investigation on the catalyst loading and the reaction concentration, the optimum reaction conditions was established with 0.25 M of **1a** and **2** in MeCN catalyzed by 10 mol% of DABCO (97% yield and 94:6 dr, entry 16).

Having established the optimal reaction conditions, the substrate scope of this cascade reaction was explored with a wide array of trifluoromethyl-substituted styrylisoxazoles. Indeed, most of the reactions proceeded quickly to give the expected cycloadducts in high yields (up to 98%) and diastereoselectivities (up to >20:1). As shown in Table 2, this cascade reaction is considerably general and tolerates trifluoromethyl-substituted styrylisoxazoles bearing both electron-rich and electron-deficient groups on the aromatic ring. The substrates with *para*- or *meta*-substituent on



Scheme 1. Application of trifluoromethyl-substituted styrylisoxazoles: outline of previous and current studies.

Table 1
Optimization of the reaction conditions.[a]



Entry	Solvent	Catalyst	T	Yield[b] (%)	Dr[c]
1	MeCN	Et_3N	30 min	60	90:10
2	MeCN	Et_2NH	30 min	65	88:12
3	MeCN	DBU	30 min	29	87:13
4	MeCN	DMAP	30 min	87	74:26
5	MeCN	DABCO	15 min	94	81:19
6	MeCN	Na_2CO_3	5 h	87	60:40
7	MeCN	$NaHCO_3$	48 h	79	77:23
8	$CHCl_3$	DABCO	2 h	28	>20:1
9	THF	DABCO	24 h	38	>20:1
10	CH_2Cl_2	DABCO	24 h	67	88:12
11	EtOH	DABCO	24 h	50	78:22
12	EtOAc	DABCO	24 h	84	80:20
13	Toluene	DABCO	24 h	33	80:20
14[d]	MeCN	DABCO	5 h	87	91:9
15[e]	MeCN	DABCO	48 h	68	93:7
16[f]	MeCN	DABCO	20 min	97	94:6

[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.2 mmol), catalyst (0.04 mmol), solvent (1.0 mL), room temperature.
[b] Isolated yield.
[c] Determined by ^1H NMR.
[d] Catalyst: 0.02 mmol (10 mol%).
[e] Catalyst: 0.01 mmol (5 mol%).
[f] Catalyst: 0.02 mmol (10 mol%), 0.8 mL solvent.