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Efficient organocatalytic α-sulfenylation of substituted piperazine-2,5-diones

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ABSTRACT

Organocatalytic α-sulfenylation of substituted piperazine-2,5-diones is reported through the use of cinchona alkaloids as Lewis bases and electrophilic sulfur transfer reagents. 1-Phenylsulfanyl[1,2,4]triazole, a novel sulfur transfer reagent, gave excellent product yields with a number of substituted piperazine-2,5-diones under mild conditions. Catalyst loading, stoichiometry of sulfur electrophile, temperature, and solvent were optimized to achieve high product yields.

Organocatalytic α-sulfenylation of carbonyl compounds is of considerable synthetic utility because it produces synthetic intermediates useful in a variety of organic transformations.[1] To date, the majority of reported organocatalytic sulfenylations utilized aldehydes,[2] ketones,[3] lactones, lactams, and β-dicarbonyl compounds[4] as substrates. Despite their simplicity and low catalyst costs such transformations, to our knowledge, have not been reported for β-amido esters or diketopiperazines. In this Letter, we report the first organocatalytic α-sulfenylation of substituted piperazine-2,5-diones.

Direct α-sulfenylation of substituted β-amido esters and diketopiperazines could facilitate synthesis of epidithiodiketopiperazines (ETPs)—an intriguing class of biologically active natural products.[5] ETPs are cytotoxic and immunomodulatory constituents produced by the filamentous fungi *Chaetomium* and *Pithomyces* sp. They contain one or two polysulfide-bridged piperazine-2,5-dione fragments and display a broad spectrum of biological activity. Recent studies have shown that two members of this diverse family, chaetocin[6] and chetomin[7] (Fig. 1), suppress neovascularization in solid tumors[8] by disrupting the expression of *VEGF* gene mediated by hypoxia-inducible factor 1α (HIF-1α).[9] All reported methods for the preparation of ETPs require multistep sequences for the introduction of sulfur.[10–13] Direct, catalytic procedure for α-sulfenylation of piperazine-2,5-diones could prove valuable in the development of a concise synthetic route to ETPs.

Organocatalytic transformation of piperazine-2,5-dione ring system is more challenging as compared to aldehydes, ketones, and esters due to its lower reactivity toward electrophilic sulfur reagents and greater steric bulk. Hence, the preliminary goal was to investigate the reactivity of the substituted piperazine-2,5-diones under typical conditions of organocatalytic α-sulfenylation with cinchona alkaloids as catalysts. Initially, 1-benzylsulfanyl[1,2,4]triazole (**2a**)[2,4] was used as the electrophilic sulfenylating reagent in attempts to convert substrates **1a–e** to products **3** (Table 1). This reagent is known to give products in high yields with the variety of aldehydes, ketones, and β-ketoesters.[4] However, with substituted piperazine-2,5-dione **1a**, only low yields of the product **3a** were obtained. Therefore, our goal was to improve the efficiency of this reaction by varying the amount of sulfenylating reagent **2a** and changing the type of catalyst **4a–d** (Fig. 2).

In order to obtain higher yields, the loading of the sulfenylating reagent **2a** was increased (Table 1). Despite using an excess of **2a**, the product **3a** was still obtained in low yields. Using precursor **1b** without substituent at the *N*-4 position resulted in significantly improved yields. Compounds **1c** and **1d** gave product **3b** in low yields, along with the removal of the substituents at the *N*-4 position. Such a removal could be the result of an attack of the formed in the trace amounts thiolate anion on acetyl or benzoyl groups of **1c–d**. The small quantities of the newly formed **1b** could then be sulfenylated by **2a**, producing compound **3b**. No product formation could be observed with substrate **1e**. It is believed that the low reactivity of the *N*-4 substituted piperazine-2,5-diones is attributable to the steric clash between the approaching sulfenylating reagent and the substrate, because only the compound lacking

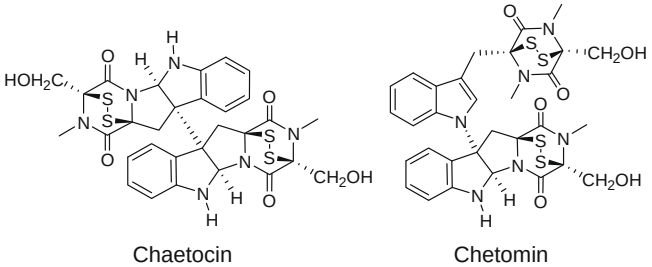

Figure 1. Epidithiodiketopiperazine fungal metabolites.

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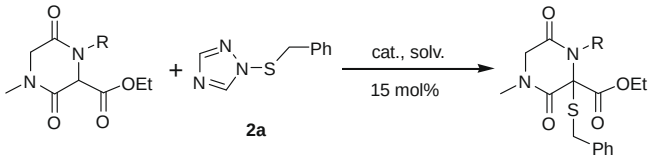
Table 1
Organocatalytic α-sulfenylation of **1a–e** with 1-benzylsulfanyl[1,2,4]triazole **2a** and Lewis bases **4a–d**



1a: R = Me
1b: R = H
1c: R = CH_3CO
1d: R = PhCO
1e: R = Ts

3a: R = Me
3b: R = H

High substrate	Solvent	Temp. (°C)	Time (h)	Catalyst	Equiv of **2a**	Yield[a] (%)
1a	CH_2Cl_2	rt	120	**4a**	5.0	46
1a	Toluene	rt	120	**4a**	5.0	44
1a	CH_2Cl_2	rt	120	**4d**	10.0	55
1b	CH_2Cl_2	rt	48	**4d**	2.0	93
1b	Toluene	rt	24	**4c**	2.0	95
1b	Toluene	−10	24	**4c**	1.5	90
1b	Toluene	−78	24	**4c**	1.5	20
1b	Toluene	−10	24	**4a**	2.0	94
1b	Toluene	−10	24	**4b**	2.0	91
1c[b]	Toluene	rt	72	**4a**	2.6	10
1c[b]	Toluene	−10	72	**4a**	2.6	10
1d[b]	Toluene	rt	72	**4a**	2.6	10
1e	Toluene	rt	72	**4a**	2.6	[c]

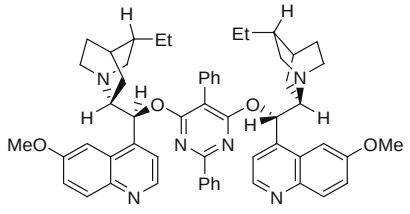
[a] Yield of purified product after chromatographic separation.
[b] Compound **3b** was obtained as the product.
[c] No product was formed, as observed by ^1H NMR.

N-4 substituent, **1b,** gave yields with **2a**. This limits the scope of **2a** as an electrophile in sulfenylation of substituted piperazine-2,5-diones.

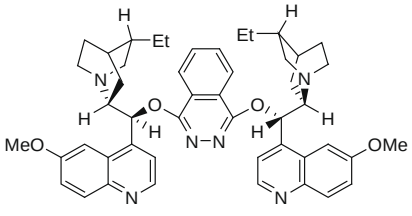
In an attempt to improve the substrate scope, we also synthesized 1-(*p*-methoxybenzyl)sulfanyl[1,2,4]triazole and 1-(*p*-nitrobenzyl)sulfanyl[1,2,4]triazole. These reagents, prepared in a manner similar to **2a**, were found to be too unstable for practical application.

To improve yields, a new sulfenylating reagent 1-phenylsulfanyl[1,2,4]triazole (**2b**) was tested. This reagent gave excellent product yield with substrate **1a** and was chosen for subsequent reaction optimizations. First, we screened the reaction conditions needed to efficiently carry out the α-sulfenylation with compound **2b**. Catalysts, solvents, temperature as well as amounts of sulfenylating reagent **2b** were varied in order to improve yields (Table 2). The sterically bulky compound **1g** was selected because its lower reactivity made it an ideal substrate for screening of sulfenylation conditions.

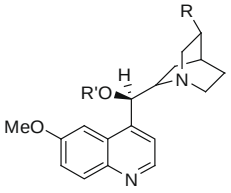
Gratifyingly, sulfenylating reagent **2b** gave considerably higher yields than **2a** in all reactions with lower amounts of **2b** required for efficient sulfenylation (Table 2). Different catalysts were screened, to find the most suitable candidate. The readily accessi-



4a: $(DHQD)_2PYR$



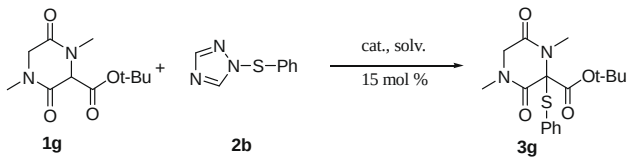
4b: $(DHQD)_2PHAL$



4c: R = CH_2=CH, R' = H, Quinine
4d: R = Et, R' = H, Dihydroquinine

Figure 2. Cinchona alkaloids used as catalysts.

Table 2
Optimization of reaction conditions of sulfenylation of **1g** with 1-phenylsulfanyl[1,2,4]triazole **2b**



1g **2b** **3g**

Entry	Solvent	Temp (°C)	Catalyst	Equiv of **2b**	Yield[a] (%)
1	CH_2Cl_2	rt	**4c**	2.0	79
2	Toluene	rt	**4a**	2.0	60
3	Toluene	rt	**4b**	2.0	65
4	Toluene	rt	**4c**	2.0	91
5	Toluene	0	**4c**	3.0	97
6	PhH/PhMe (3:1)	−10	**4c**	3.0	96

[a] Yield of purified product after chromatographic separation.

ble quinine (**4c**) was found to be superior to catalysts $(DHQD)_2PYR$ (**4a**) and $(DHQD)_2PHAL$ (**4b**). This is probably due to the fact that the tertiary amines in both $(DHQD)_2PYR$ (**4a**) and $(DHQD)_2PHAL$ (**4b**) are more sterically demanding than quinine. Toluene and benzene/toluene mixture were also found to be superior to dichloromethane for obtaining high yields. The higher stability of **2b** as compared to **2a** under sulfenylation conditions has facilitated product isolation, because lesser amount of this reagent was required to obtain high yields.

Next, to test the substrate scope, the reactivity of **2b** with other substituted piperazine-2,5-diones **1f–j** was studied. Compounds **1a** and **1f** gave excellent yields with **2b** (Table 3). Substrates **1h** and **1i** with ethyl and benzyl groups at the *N*-4 position are more sterically demanding than substrates with a methyl group at that position. Compounds **1h** and **1i** were sulfenylated using **2b** in high yields. This shows that 1-phenylsulfanyl[1,2,4]triazole (**2b**) is able to efficiently sulfenylate piperazine-2,5-dione substrates under different reaction conditions. Compound **1j** which has a benzyl substituent at the *N*-4 position and a *t*-butyl ester at the α-position, is the most sterically hindered substrate used in this study. It showed moderate yield with **2b** and quinine **4c** as the catalyst. When $(DHQD)_2PYR$ **4a** and $(DHQD)_2PHAL$ **4b** were used, low product yield was observed. Presumably the greater steric bulk of **4a** and **4b** played a major role in reducing the reaction rate when these catalysts were used with the bulky substrates. Because quinine is the least expensive organocatalyst among all tested cinchona alkaloids, its use in combination with the readily prepared **2b**, provides an economical route to α-sulfenylated piperazine-2,5-diones.

Crystallization of product **3g** from ethanol at room temperature provided single crystals suitable for X-ray diffraction analysis.[14] The molecular structure of **3g** is shown in Figure 3. The compound **3g** has crystallized in the centrosymmetric orthorhombic space group *Pbca* and the crystal packing shows efficient stacking of the phenyl and diketopiperazine rings in the solid state. It is hypothesized that this stacking may provide additional stabilization in the transition state of the sulfenylation reaction.

In summary, direct and efficient organocatalytic α-sulfenylation of substituted piperazine-2,5-diones has been developed. Various substrates, solvents, and sulfur transfer reagents have been screened, resulting in high product yields under optimized reaction conditions. This methodology may be of value for future construction of the epidithiodiketopiperazine ring system in a rapid and efficient manner. We continue structural modifications of electrophilic sulfur transfer reagents in order to expand their scope to sterically bulky substrates. Further exploration of the mechanism of organocatalytic α-sulfenylation and development of its enantioselective variant are currently under investigation.

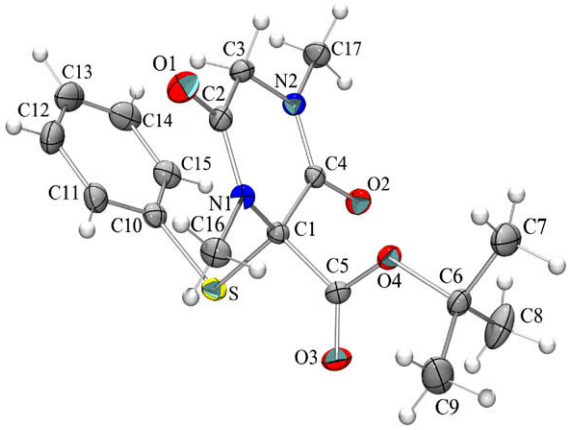


Figure 3. The molecular structure of **3g** with anisotropic displacement parameters at 30% probability level.

Acknowledgments

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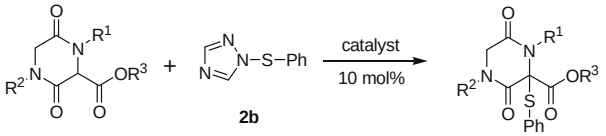
Supplementary data

Synthetic procedures, characterization, and NMR spectra of compounds **1, 2b** and **3** are available. Crystallographic data for **3g** have been deposited into the Cambridge Crystallographic Data Centre (CCDC accession number 721744). These data can be obtained free of charge from http://www.ccdc.cam.ac.uk/data_request/cif. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.05.031.

Table 3
Scope of α-sulfenylation of trisubstituted piperazine-2,5-diones with reagent **2b** and 10 mol % of cinchona alkaloids **4a–c**



Entry	Substrate	R^1	R^2	R^3	Solvent	Temp (°C)	Catalyst	Equiv of **2b**	Time (h)	Product	Yield[a] (%)
1	**1f**	Me	Me	Me	PhH/PhMe (3:1)	−10	**4c**	3.0	18	**3f**	99
2	**1a**	Me	Me	Et	PhH/PhMe (3:1)	−10	**4c**	3.0	30	**3k**	99
3	**1g**	Me	Me	*t*-Bu	PhH/PhMe (3:1)	−10	**4c**	3.0	48	**3g**	96
4	**1h**	Et	Et	Et	Toluene	rt	**4c**	3.0	60	**3h**	77
5	**1h**	Et	Et	Et	Toluene	rt	**4c**[b]	8.0	48	**3h**	94
6	**1i**	Bn	Bn	Et	Toluene	rt	**4c**	3.0	60	**3i**	75
7	**1i**	Bn	Bn	Et	Toluene	rt	**4c**[b]	8.0	48	**3i**	95
8	**1b**	H	Me	Et	Toluene	rt	**4c**	3.0	16	**3l**	81
9	**1j**	Bn	Bn	*t*-Bu	Toluene	rt	**4c**[b]	10.0	72	**3j**	52
10	**1j**	Bn	Bn	*t*-Bu	Toluene	rt	**4a**	2.0	60	**3j**	5
11	**1j**	Bn	Bn	*t*-Bu	Toluene	rt	**4b**	2.0	60	**3j**	5

[a] Yield of purified product after chromatographic separation.
[b] 20 mol % catalyst used.

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14. *Crystal data for* ***3g***: $C_{17}H_{22}N_2O_4S$, 350.43 g mol^{-1}, colorless crystal $0.72 \times 0.47 \times 0.33$ mm^3, 220(2) K, Bruker SMART 1000 CCD diffractometer with a graphite monochromator (thin-slice ω scans, θ range from 2.2° to 27.1°), MoK$_\alpha$ $\lambda = 0.71073$ Å, $a = 11.4784(15)$ Å, $b = 16.628(2)$ Å, $c = 18.778(2)$ Å, $V = 3584.1(8)$ Å^3, $Z = 8$, $\rho_{calc} = 1.299$ g cm^{-3}, μ 0.203 mm^{-1}, $2\theta_{max} = 27.1°$ 99.9% complete, reflections collected/unique = 28,216/3954 ($R_{int} = 0.0321$), $R_1 = 0.0399$, $wR_2 = 0.0928$ for 2960 reflections with $I > 2\sigma(I)$. See Supplementary data for complete X-ray crystallographic information.