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HBr-PROMOTED SULFENYLATION OF PYRAZOLONES AND 4-HYDROXYCOUMARINS WITH *N*-(ORGANOTHIO)SUCCINIMIDES

Hongai Jin, Wangyang Wang, Zhaohua Yan,* Rongxing Zhang, Mingchuang He, and Sen Lin*

College of Chemistry, Nanchang University, Nanchang, Jiangxi Province 330031, P. R. China. Email: yanzh@ncu.edu.cn

Abstract – A convenient, effective and metal-free method for the synthesis of C-4 sulfenylated pyrazolones via HBr-promoted sulfenylation of pyrazolones with *N*-(organothio)succinimides as sulfur sources was developed. The method can be extended to apply for substrates 4-hydroxycoumarins. A series of C-4 sulfenylated pyrazolones and C-3 sulfenylated 4-hydroxycoumarins were smoothly synthesized in good to excellent yields.

The construction of C-S bond was crucial for organic synthesis because sulfides are widely spread in pharmaceutical industry,[1] pesticide[2] and material science.[3] The traditional methods for the synthesis of organosulfides used metal catalysts, environmentally malign reagents and complex conditions.[4] Therefore, seeking simple, effective and environmentally benign strategies for the synthesis of sulfur-containing compounds has always been a highly challengable task for organic chemists.[5]

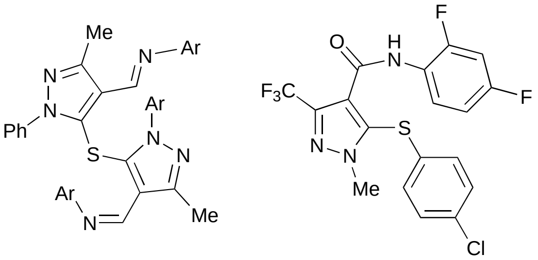
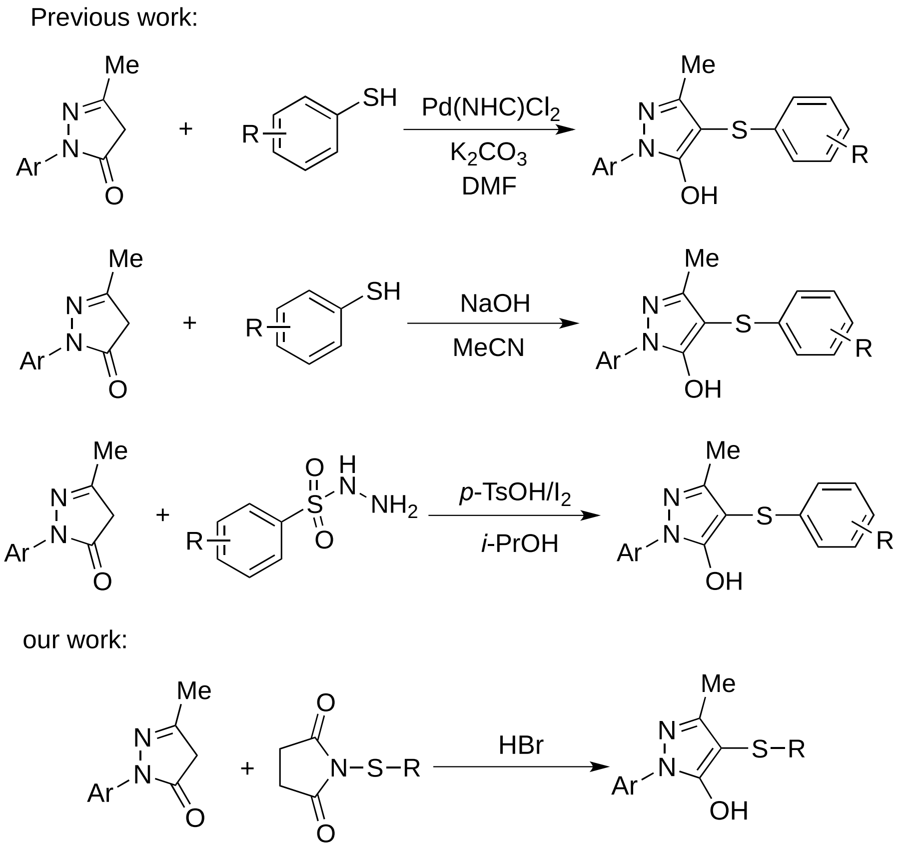


Figure 1. Bioactive pyrazolone thioethers

Pyrazolone compounds have been widely used in the fields of medicine and pesticide because of their structural variability and their high biological activities. Pyrazolone thioether derivatives have excellent bactericidal activity,[6] and they also can be used as herbicides to control some weeds in crops (Figure 1).

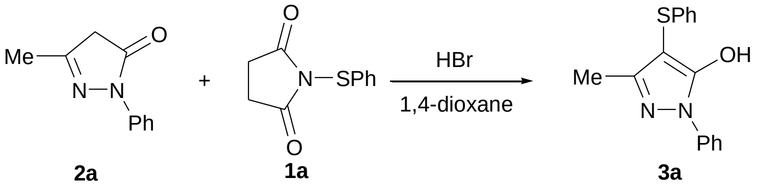
Some methodologies for the synthesis of pyrazolone thioethers have been published (Scheme 1). Purohit described a Pd/N-heterocyclic carbene-catalyzed sulfenylation of 1-aryl-3-methyl-1*H*-pyrazol-5(4*H*)-ones with aryl thiols as sulfenylating reagents.[7] Zhao et al. developed an acid-promoted and I_2-catalyzed sulfenylation of pyrazolones with arylsulphonyl hydrazides.[8] Lu disclosed a similiar reaction with *p*-toluenesulfonic acid/I_2 system.[9] However, the use of expensive, sensitive and toxic reagents and metal catalysts involved in these methods might limit their extensive applications.[10]



Scheme 1. Methods for sulfenylation of pyrazolones

1-(Organolthio)pyrrolidine-2,5-dione [also named *N*-(organothio)succinimide] is a kind of important thiolating reagent due to its environmental friendliness, ready availability and stability.[11] 1-(Organolthio)pyrrolidine-2,5-dione has found wide applications as versatile sulfur source in the synthesis of thiosulfonates,[12] the sulfenylation of diverse electron-rich arenes and heteroarenes,[13] and in the difunctionization of alkenes leading to β-acetamido sulfides and β-alkoxy sulfides.[14] However, to the best of our knowledge, the reactions of pyrazolones and 4-hydroxycoumarins with 1-(organothio)pyrrolidine-2,5-diones have not been investigated yet. Herein, we describe a simple, efficient and novel strategy for sulfenylation of pyrazolones and 4-hydroxycoumarins promoted by HBr with *N*-(organothio)succinimides as sulfur reagents under mild conditions.

Table 1. Opitimization of reaction conditions[a]



Entry	Acids	Solvents	Temp. (°C)	Yield [b] (%)
1	HCl	MeCN	50	66
2	HBr	MeCN	50	72
3	*P*-TsOH	MeCN	50	61
4	HBr	$CHCl_3$	50	56
5	HBr	THF	50	68
6	HBr	DMF	50	65
7	HBr	DMSO	50	61
8	HBr	DME	50	63
9	HBr	DCE	50	71
10	HBr	toluene	50	76
11	HBr	H_2O	50	N.R.
12	HBr	EtOH	50	69
13	HBr	1,4-dioxane	50	79
14	HBr	1,4-dioxane	80	84
15	HBr	1,4-dioxane	100	86
16	HBr	1,4-dioxane	100	88[c]
17	HBr	1,4-dioxane	100	92[d]
18	-	1,4-dioxane	100	N.R.

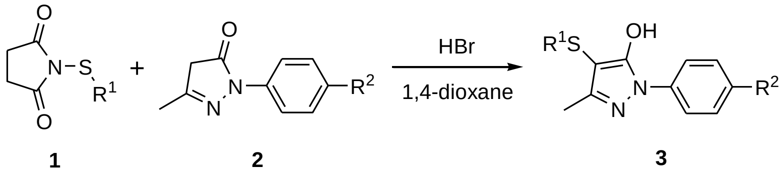
[a] Reaction conditions: **1a** (0.6 mmol), **2a** (0.3 mmol), acid (0.3 mmol), solvent (2 mL), 50-100 °C, air, 2 h. [b] Isolated yields. [c] HBr (0.45 mmol). [d] HBr (0.60 mmol).

We initially optimized the reaction of 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**2a**) with 1-(phenylthio)pyrrolidine-2,5-dione (**1a**) in the presence of various acids in solvent at 50 °C for 2 h. Among the several acids screened, HBr (40% wt aqueous solution was used) provided the best result and the corresponding product **3a** was generated in 72% yield (Table 1, entries 1-3). Subsequently, we tested the effects of solvents on the sulfenylation. We found that the yield of **3a** reached to 79% when

1,4-dioxane was used as solvent (Table 1, entries 4-13). Next, we explored the effect of temperature, and the results revealed that the best yield of **3a** was obtained when reaction temperature was increased to 100 °C (Table 1, entries 13-15). When the amount of HBr was increased up to 2.0 molar equivalents, **3a** was obtained in 92% yield (Table 1, entries 16-18). Finally, no desired product was detected in the absence of HBr. Thus, the optimized reaction conditions were chosen to study the scope of the reaction: pyrazolone (1.0 equiv), *N*-(organothio)succinimide (2.0 equiv), HBr (2.0 equiv) as acid and 1,4-dioxane (2 mL) as solvent at 100 °C in air for 2 h.

A variety of pyrazolones were employed as substrates to undergo sulfenylation with *N*-(organothio)succinimides. The results were summarized in Table 2. Pyrazolones (**2a**) and *N*-(organothio)succinimides (**1a**-**1d**) with electron-donating (Me) or electron-withdrawing groups (Cl, Br) at the *para* position on phenyl ring were employed and the corresponding products were obtained in good to excellent yields (Table 2, **3a**-**3d**). Notably, when *N*-(butylthio)succinimides (**1e**) was subjected to sulfenylation of **2a**, the corresponding product **3e** was formed in a good yield of 73%. Similarly, the aryl(alkyl)thiolation of pyrazolones **2b** and **2c** all worked smoothly to give sulfenylated products (Table 2, **3f**-**3o**) in good to excellent yields.

Table 2. HBr-Promoted sulfenylation of pyrazolones[a]



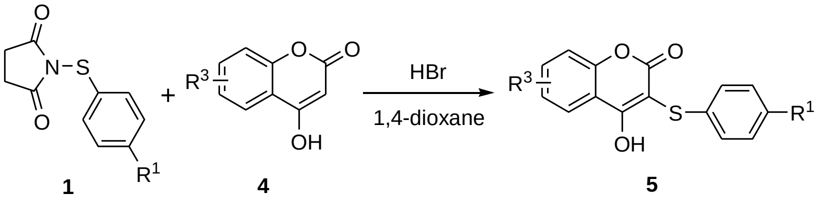
Entry	1	2	3	Yield[b] (%)
1	**1a** (R^1=Ph)	**2a** (R^2=H)	**3a**	92
2	**1b** [R^1=*p*-(Me)C_6H_4]	**2a**	**3b**	92
3	**1c** [R^1=*p*-(Cl)C_6H_4]	**2a**	**3c**	85
4	**1d** [R^1=*p*-(Br)C_6H_4]	**2a**	**3d**	82
5	**1e** (R^1=C_4H_9)	**2a**	**3e**	73
6	**1a**	**2b** (R^2=Me)	**3f**	90
7	**1b**	**2b**	**3g**	90
8	**1c**	**2b**	**3h**	86
9	**1d**	**2b**	**3i**	85
10	**1e**	**2b**	**3j**	76

11	**1a**	**2c** (R^2=Cl)	**3k**	85
12	**1b**	**2c**	**3l**	88
13	**1c**	**2c**	**3m**	85
14	**1d**	**2c**	**3n**	81
15	**1e**	**2c**	**3o**	70

[a]Reaction conditions: **1** (0.6 mmol), **2** (0.3 mmol), HBr (0.6 mmol), solvent (2 mL), 100 °C, air, 2 h. [b]Isolated yields.

Next, in order to expand the substrate scope of this reaction, the sulfenylation of 4-hydroxycoumarins **4** with *N*-(organothio)succinimides **1** were investigated and results were shown in Table 3. Among the tested four sulfenylation reactions, the corresponding C-3 sulfenylated 4-hydroxycoumarins were all obtained in excellent yields (Table 3, **5a-5d**).

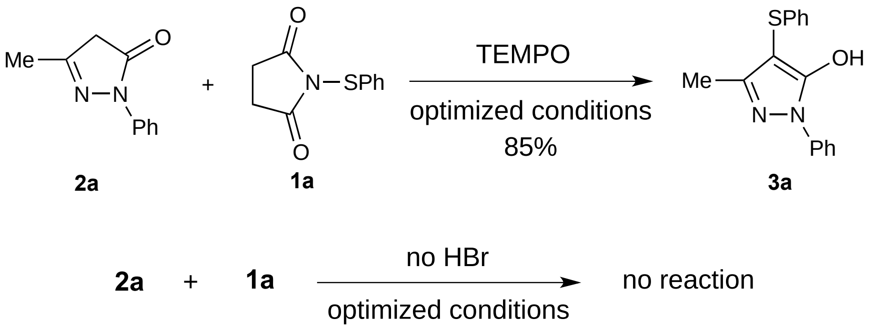
Table 3. HBr-Promoted sulfenylation of 4-hydroxylcoumarins[a]



Entry	**1**	**4**	**5**	**Yield[b] (%)**
1	**1b**	**4a** (R^3=H)	**5a** (R^1=Me)	89
2	**1d**	**4a**	**5b** (R^1=Cl)	87
3	**1e**	**4a**	**5c** (R^1=Br)	84
4	**1b**	**4b** (R^3=Me)	**5d** (R^1=Me)	91

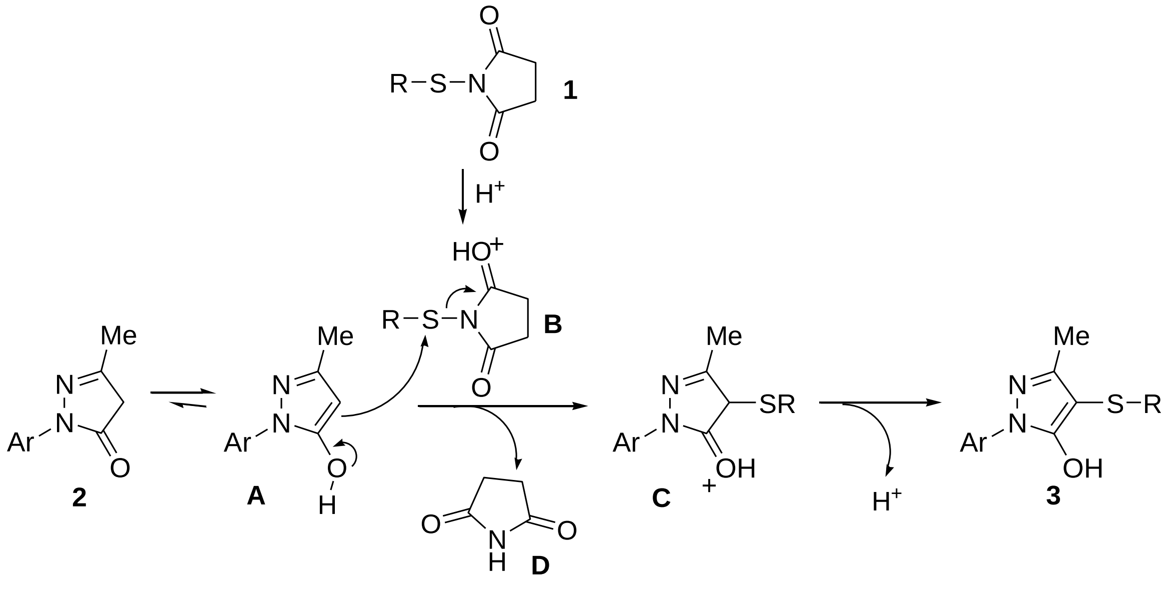
[a]Reaction conditions: **1** (0.6 mmol), **4** (0.3 mmol), HBr (0.6 mmol), solvent (2 mL), 100 °C, air, 2 h. [b]Isolated yields.

To gain further insight into the mechanism, several control experiments were carried out under optimized conditions. The desired product **3a** was not detected when 1-(phenylthio)pyrrolidine-2,5-dione (**1a**) and 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**2a**) were subjected to the sulfenylation reaction in the absence of HBr. After the addition of TEMPO (free radical scavenger), target product **3a** was still generated to a considerable extent indicating that this is not a free radical process (Scheme 2).



Scheme 2. Control experiments

On the basis of the control experiments and previous reports,[15] a plausible mechanism was thus proposed as illustrated in Scheme 3. Initially, the tautomerization of pyrazolone **2** would produce enol species **A**. Meantime, species **B** resulted from the reaction of HBr with *N*-(organothio)succinimide **1**. Subsequently, **B** was attacked by **A** to produce the expected sulfenylated species **C** and succinimide **D** as the byproduct. Finally, the rapid deprotonation of **C** liberated the desired product **3**.



Scheme 3. Plausible reaction mechanism

In summary, a convenient and effective method has been developed for the synthesis of C-4-sulfenylated pyrazolones and C-3 sulfenylated 4-hydroxycoumarins via HBr-promoted direct sulfenylation of pyrazolones and 4-hydrocoumarins with *N*-(organothio)succinimides as sulfur sources. High yields, operational simplicity and the use of stable, environmentally benign and readily available sulfur reagents are advantages to this methodology.

EXPERIMENTAL

General methods

^{1}H and ^{13}C NMR spectra were recorded on Bruker Ascend™ 400 (400 MHz) using tetramethylsilane as an internal reference. NMR multiplicities are abbreviated as follows: s = singlet, d = doublet, m = multiplet, br = broad signal. Chemical shifts (δ) and coupling constants (J) were expressed in ppm and Hz. HRMS date were obtained by ESI on a TOF mass analyser. The rest of chemicals were purchased from the Sinopharm Chemical Reagent Co., Adamas, Aladdin and TCI used as received.

General Procedure for 3

HBr (40% wt HBr aqueous solution, 84 μL, 0.6 mmol) and *N*-(organothio)succinimide (**1**, 0.6 mmol) were added to a solution of 1,4-dioxane containing pyrazolone (**2**, 0.3 mmol). The reaction mixture was stirred in a sealed tube at 100 °C for 2 h. After completion of the reaction, the reaction mixture was diluted with EtOAc, and extracted three times with EtOAc (3×10 mL). The organic layer was washed with water and dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo, and the residue was subjected to column chromatography using EtOAc in petroleum ether as the eluent to afford the pure target product **3**.

General Procedure for 5

HBr (40% wt HBr aqueous solution, 84 μL, 0.6 mmol) and *N*-(organothio)succinimide (**1**, 0.6 mmol) were added to a solution of 1,4-dioxane containing 4-hydroxycoumarins (**4**, 0.3 mmol). The reaction mixture was stirred at 100 °C for 2 h. After completion of the reaction, the reaction mixture was diluted with EtOAc, and extracted three times with EtOAc (3×10 mL). The organic layer was washed with water and dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo, and the residue was subjected to column chromatography using EtOAc in petroleum ether as the eluent to afford the pure target product **5**.

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