Potassium Iodide Promoted Thiolation of Pyrazolones and Benzofurans Using Aryl Sulfonyl Chlorides as Sulfenylation Reagents

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ABSTRACT

An efficient, transition-metal-free method to synthesize pyrazolone thioethers as well as 2-aryl and 3-aryl benzofuran thioethers by employing aryl sulfonyl chlorides as sulfenylation reagents in the presence of triphenylphosphine was developed. Potassium iodide was found to facilitate the transformation for the first time by generating more reactive sulfenyl iodide *in situ* from sulfonyl chloride.

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1. Introduction

Carbon–Sulfur (C–S) bond-forming reactions play a pivotal role in the synthesis of organo-sulfur compounds of pharmaceutical and material interest.¹ Therefore, exploration of new methods for C–S bond generation has attracted much attention in recent years.² Although transition-metal-catalyzed C–S bond formation reactions could avoid harsh condition as well as toxic polar solvents with high boiling temperatures, expensive and often air-sensitive catalysts as well as foul-smelling, unstable and volatile sulfur sources limited their further application.³ Recently, sulfonyl hydrazides have emerged as a novel and environmental-friendly sulfenylation reagents because they are generally stable, readily accessible, and odor-free.⁴ To the best of our knowledge, the synthetic precursor sulfonyl chlorides have rarely been reported to be sulfenylation reagents, although they are used as sulfonylating reagents as well as arylation reagents in C–C cross coupling reactions. In 2011, You and co-workers reported an efficient thiolation of indolizines, indoles and electron-rich benzenes using aryl sulfonyl chlorides as sulfenylation reagents in combination with PPh₃ as reductant.⁵ In 2012, Zheng and coworkers reported Ru(bpy)₃Cl₂ catalyzed visible light-induced 3-sulfenylation of *N*-methylindoles with arylsulfonyl chlorides (Scheme 1).⁶ As a part of ongoing our interests in exploring new sulfenylation reagents, we have developed an iodine catalyzed thiolation of pyrazolones,⁷

benzofurans⁸ and electron-rich aromatics⁹ with sulfonyl hydrazides as the sulfur source. Herein, we would like to report a novel potassium iodide facilitated thiolation reaction of pyrazolones and benzofurans with aryl sulfonyl chlorides as sulfenylation reagents.

Scheme 1 Thiolation of indolizines and *N*-methylindoles using sulfonyl chlorides as sulfenylation reagents

2. Results and discussion

To probe the thiolation of heterocyclic compounds like pyrazolones and benzofurans, we employed the reaction of 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one **1a** and 4-methylbenzenesulfonyl chloride **2a** as the model reaction and PPh₃ as reductant. The reaction in toluene at 70 °C gave the desired thiolation product **3aa** in 49 % yield (Table 1, Entry 1). To improve the yield, a series of solvents such as 1,2-

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dichloroethane (DCE), 1,4-dioxane and *N,N*-dimethylformamide (DMF) were investigated (Table 1, Entry 2-4) and 1,4-dioxane gave the best yield. Next, temperature and additive effects were evaluated from 80 °C to 100 °C. When the reaction was carried out at 80 °C and 90 °C, the yield increased to 65% (Table 1, Entries 5 and 6). However, further increasing the reaction temperature to 100 °C led to a diminished yield (Table 1, Entry 7). Notably, when 0.2 equiv. potassium iodide (KI) was added, the yield increased dramatically to 90% yield (Table 1, Entry 8), while the classical iodide anion source tetra-*n*-butylammonium iodide (*n*Bu₄NI) decreased the yield (Table 1, Entry 9). Finally, equivalents of **2a**, PPh₃ and KI as well as the reaction concentration were investigated (Table 1, Entries 10-15). For sulfonyl chloride, 1.2 equiv. of **2a** gave the highest yield, and decreasing the amount of **2a** led to a diminished yield (Table 1, Entry 10). For reductant, 2.0 equiv. of PPh₃ were sufficient to obtain a yield of 90%, and further increasing the amount of the PPh₃ did not affect the yield (Table 1, Entry 11). For additive, 0.2 equiv. of KI gave a yield of 90% as shown above. Decreasing the KI amount to 0.15 equivalent led to a decreased yield (Table 1, Entry 12), while further increasing the amount did not affect the yield (Table 1, Entry 13). It was noteworthy that increasing or decreasing the concentration both diminished the yield (Table 1, Entries 14 and 15). Therefore, the reaction conditions were optimized to be as follows: **1a** (0.5 mmol), **2a** (0.6 mmol), PPh₃ (1.0 mmol), KI (0.1 mmol) and 1,4-dioxane (1 mL), at 80 °C.

Table 1 Optimization of the thiolation of **1a** with **2a** in the presence of PPh₃^a

Entry	KI (equiv)	T (°C)	Solvent	Volume (mL)	Yield (%)
1	-	70	Toluene	1.0	49
2	-	70	DCE	1.0	32
3	-	70	DMF	1.0	48
4	-	70	1,4-dioxane	1.0	55
5	-	80	1,4-dioxane	1.0	65
6	-	90	1,4-dioxane	1.0	65
7	-	100	1,4-dioxane	1.0	37
8	0.2	80	1,4-dioxane	1.0	90
9	0.2 ^b	80	1,4-dioxane	1.0	56
10	0.2	80	1,4-dioxane	1.0	79 ^c
11	0.2	80	1,4-dioxane	1.0	90 ^d
12	0.15	80	1,4-dioxane	1.0	78
13	0.25	80	1,4-dioxane	1.0	90
14	0.2	80	1,4-dioxane	1.5	79
15	0.2	80	1,4-dioxane	0.5	71

^a Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), PPh₃ (1.0 mmol). ^b *n*Bu₄NI was used. ^c **2a** (0.55 mmol) was used. ^d PPh₃ (1.1 mmol) was used.

The substrate scope of the sulfenylation reaction was investigated under the optimized conditions. As shown in Table 2, a series of substituted pyrazolones could be coupled with various substituted aryl sulfonyl chlorides to afford the corresponding pyrazolone thioethers in moderate to excellent yields.¹⁰ For pyrazolones, both aryl groups (**1a-1d**) and alkyl groups (**1e-1h**) on 1-position were well tolerated. Moreover, pyrazolones bearing phenyl, benzyl and methyl groups on 3-position could be readily converted to the desired products in good yields.

For aromatic sulfonyl chloride, both electron-donating and electron-withdrawing groups, as well as *ortho*-, *meta*-, and *para*-substitutions (**2a-2j**) were tolerated in the reaction. Notably, for steric effect, phenyl sulfonyl chloride with an *ortho*-methyl group provided pyrazolone thioether in a relatively low yield compared with the corresponding *para*-methyl group (**3aa** versus **3ad**, **3ea** versus **3ed**).

Table 2 Thiolation of pyrazolones with aryl sulfonyl chloride in the presence of PPh₃^a

Entry	1, R ₁ =, R ₂ =	2, Ar =	Yield (%)
1	1a , Ph, Me	2a , <i>p</i> -MeC ₆ H ₄	3aa , 90
2	1a , Ph, Me	2b , <i>p</i> -NCC ₆ H ₄	3ab , 78
3	1a , Ph, Me	2c , 3,5-Cl ₂ C ₆ H ₃	3ac , 75
4	1a , Ph, Me	2d , <i>o</i> -MeC ₆ H ₄	3ad , 50
5	1b , <i>p</i> -MeOC ₆ H ₄ , Me	2a , <i>p</i> -MeC ₆ H ₄	3ba , 55
6	1b , <i>p</i> -MeOC ₆ H ₄ , Me	2e , <i>m</i> -ClC ₆ H ₄	3be , 70
7	1b , <i>p</i> -MeOC ₆ H ₄ , Me	2f , <i>p</i> -MeOC ₆ H ₄	3bf , 65
8	1c , <i>p</i> -NCC ₆ H ₄ , Me	2a , <i>p</i> -MeC ₆ H ₄	3ca , 60
9	1c , <i>p</i> -NCC ₆ H ₄ , Me	2b , <i>p</i> -NCC ₆ H ₄	3cb , 64
10	1d , Ph, Ph	2a , <i>p</i> -MeC ₆ H ₄	3da , 80
11	1e , Me, Me	2a , <i>p</i> -MeC ₆ H ₄	3ea , 85
12	1e , Me, Me	2b , <i>p</i> -NCC ₆ H ₄	3eb , 96
13	1e , Me, Me	2c , 3,5-Cl ₂ C ₆ H ₃	3ec , 87
14	1e , Me, Me	2d , <i>o</i> -MeC ₆ H ₄	3ed , 74
15	1e , Me, Me	2e , <i>m</i> -ClC ₆ H ₄	3ee , 78
16	1e , Me, Me	2f , <i>p</i> -MeOC ₆ H ₄	3ef , 83
17	1e , Me, Me	2g , Ph	3eg , 73
18	1e , Me, Me	2h , <i>p</i> -BrC ₆ H ₄	3eh , 92
19	1e , Me, Me	2i , <i>p</i> -FC ₆ H ₄	3ei , 71
20	1e , Me, Me	2j , <i>p</i> -CF ₃ C ₆ H ₄	3ej , 96
21	1f , Me, Ph	2a , <i>p</i> -MeC ₆ H ₄	3fa , 70
22	1g , Me, Bn	2a , <i>p</i> -MeC ₆ H ₄	3ga , 68
23	1h , Bn, Me	2a , <i>p</i> -MeC ₆ H ₄	3ha , 70

^a Reaction conditions: **1a-i** (0.5 mmol), **2a-j** (0.6 mmol), PPh₃ (1.0 mmol), KI (0.1 mmol), 1,4-dioxane (1 mL), 80 °C, 12 h.

The reaction condition was then explored for the thiolation of benzofuran derivatives. Considering the relatively less nucleophilicity of benzofuran versus pyrazolone, the reaction of 2-(4-methoxyphenyl)benzofuran (**4a**) with **2a** was carried out in the presence of PPh₃ and KI at 100 °C in 1,4-dioxane, and the desired thiolation product **5aa** was obtained in 58% yield (Table 3, Entry 1). To improve the yield, varied solvents such as DCE, DMF, toluene, ethanol (EtOH) and isopropanol (*i*-PrOH) were tested (Table 3, Entry 2-6), and EtOH gave the highest yield of 80%. Reaction temperatures and KI equivalents were evaluated as well. Increasing the reaction temperature to 110 °C did not affect much on the yield (Table 3, Entry 7), while decreasing the reaction temperature to 90 °C led to an increase of the yield to 90% yield (Table 3, Entry 8). However, further decreasing the reaction temperature to 80 °C diminished the yield (Table 3, Entry 9). Decreasing KI loading to 0.15 equiv. or 0.1 equiv. led to a decrease of the yield (Table 3, Entries 10 and 11). Finally, concentration screening demonstrated that decreasing or increasing reactant concentrations led to a decrease of the yield (Table 3, Entries 12 and 13). Thus, the optimized reaction conditions for thiolation of **4a** were as follows: **4a** (0.5 mmol), **2a** (0.6 mmol), PPh₃ (1.0 mmol), KI (0.1 mmol) and EtOH (1 mL), at 90 °C.

Table 3 Optimization of the thiolation of **4a** with **2a** in the presence of PPh₃^a

Entry	KI (equiv)	T (°C)	Solvent	Volume (mL)	Yield (%)
1	0.2	100	1,4-dioxane	1.0	58
2	0.2	100	DCE	1.0	0
3	0.2	100	DMF	1.0	trace
4	0.2	100	Toluene	1.0	0
5	0.2	100	EtOH	1.0	80
6	0.2	100	<i>i</i> -PrOH	1.0	69
7	0.2	110	EtOH	1.0	79
8	0.2	90	EtOH	1.0	90
9	0.2	80	EtOH	1.0	80
10	0.15	80	EtOH	1.0	87
11	0.1	80	EtOH	1.0	86

12	0.2	80	EtOH	0.5	80
13	0.1	80	EtOH	1.5	80

^a Reaction conditions: **4a** (0.5 mmol), **2a** (0.6 mmol), PPh₃ (1.0 mmol)

Under the optimized reaction conditions for thiolation of benzofurans **4a**, a series of 2-substituted benzo[*b*]furans was coupled with varied of aryl sulfonyl chlorides in the presence of PPh₃ (Table 4). Aryl sulfonyl chlorides with electron-donating or electron-withdrawing substituents at *ortho*-, *meta*- or *para*-position were reacted with **4a**, and the reactions gave the desired products in good to excellent yields. However, the reaction of 2-phenylbenzofuran (**4b**) with **2a** yielded only 20% of the desired product **5ba**, which might be due to the electronic effect on the benzofuran. When more KI and higher reaction temperature were employed, the yield of **5ba** was improved to 34%. For substituted 2-phenylbenzofurans, the reaction of **2a** with 5-methyl-2-phenylbenzofuran (**4c**) gave better yields than the unsubstituted 2-phenylbenzofuran (**4b**). Notably, 2-methylbenzofuran (**4d**) could couple with **2a**, **2e** and **2f** smoothly and afforded the thiolation products **5da**, **5de** and **5df** in 60%, 44% and 70% yield, respectively.

Table 4 Thiolation of 2-substituted benzofurans with aryl sulfonyl chlorides in the presence of PPh₃^a

^a Reaction conditions: **4a-4d** (0.5 mmol), **2a, 2c-2f** (0.6 mmol), PPh₃ (1.0 mmol), KI (0.1 mmol), EtOH (1.0 mL), 90 °C, 12 h. ^b The reaction was carried at 100 °C and KI (0.25 mmol) was used as additive for 24 h.

To further probe the scope of this reaction, 3-substituted benzofurans were examined under the modified optimal reaction conditions. The results are illustrated in Table 5. 3-Phenylbenzofuran (**6a**), 3-(4-methoxyphenyl)benzofuran (**6b**) and 3-methylbenzofuran (**6c**) could all be converted to the sulfenylation products smoothly with various aryl sulfonyl chlorides (**2a, 2c, 2f** and **2k**) as sulfenylating reagents.

Based on the experiments and previous reports,⁵ a plausible mechanism for these thiolation reactions is proposed (Scheme 2). Initially, aryl sulfonyl chloride **2** is reduced by PPh₃ via intermediates **A-E** to sulfenyl chloride **F**, which is attacked by iodide anion to give sulfenyl iodide **G**. Electrophilic thiolation of pyrazolone **1** as well as benzofuran **4** and **6** by sulfenylation reagent **G** gives the corresponding pyrazolone thioethers, 2-aryl and 3-aryl benzofuran thioethers respectively.

Table 5 Thiolation of 3-substituted benzofurans with aryl sulfonyl chlorides in the presence of PPh₃^a

^a Reaction conditions: **6a-6c** (0.5 mmol), **2a, 2c, 2f, 2k** (0.6 mmol), PPh₃ (1.0 mmol), KI (0.25 mmol), EtOH (1.0 mL), 100 °C, 24 h.

Scheme 2 Proposed reaction mechanism

3. Conclusion

In conclusion, we developed a novel and concise method to synthesize pyrazolone thioethers as well as 2-aryl and 3-aryl benzofuran thioethers by using aryl sulfonyl chlorides as sulfenylation reagents. Potassium iodide was demonstrated to facilitate this transformation possibly by generating more reactive sulfenyl iodide *in situ* from sulfenyl chloride. This study broadened the scope of sulfonyl chloride as novel thiolation reagents in organic synthesis.

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 10. General procedure of thiolation of pyrazolones with aryl sulfonyl chloride in the presence of PPh₃: Pyrazolones 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (**1a**) (87 mg, 0.5 mmol), 4-methylbenzenesulfonyl chloride (**2a**) (114 mg, 0.6 mmol), PPh₃ (262 mg, 1.0 mmol) and KI (17 mg, 0.1 mmol) in 1,4-dioxane (1.0 mL) were mixed in a sealed tube. The mixture was stirred at 80 °C for 12 hours. Then, the solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to afford 3-methyl-1-phenyl-4-(p-tolylthio)-1H-pyrazol-5-ol (**3aa**) (133 mg, 90%) as a white solid.

Graphical Abstract

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