



Potassium iodide promoted thiolation of pyrazolones and benzofurans using aryl sulfonyl chlorides as sulfenylation reagents



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ARTICLE INFO

Article history:

Received 6 September 2016

Revised 14 October 2016

Accepted 17 October 2016

Available online 18 October 2016

Keywords:

Thiolation

Pyrazolone

Benzofuran

Sulfonyl chloride

Potassium iodide

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 sulfenyl chloride.

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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 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 a reductant.⁵ In 2012, Zheng and coworkers reported Ru(bpy)₃Cl₂ catalyzed visible light-induced 3-sulfenylation of *N*-methylindoles with

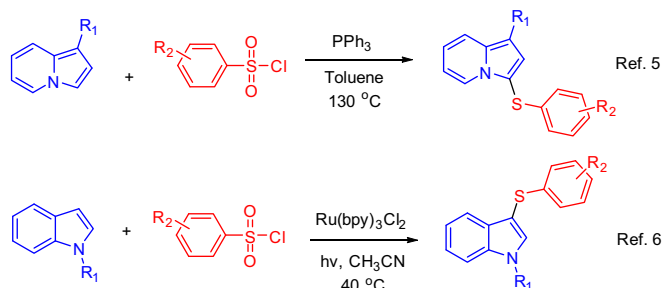
arylsulfonyl chlorides (Scheme 1).⁶ As a part of ongoing our interests in exploring new sulfenylation reagents, we have developed an iodine catalyzed thiolation of pyrazolones,⁷ benzofurans,⁸ and electron-rich aromatics⁹ with sulfonyl hydrazides as the sulfur source. Herein, we would like to report a novel potassium iodide facilitated thiolation reaction of pyrazolones and benzofurans with aryl sulfonyl chlorides as sulfenylation reagents.

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 a 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-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

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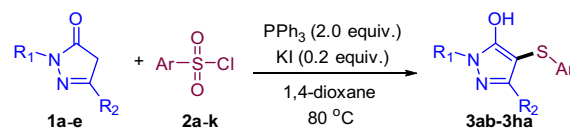
Scheme 1. Thiolation of indolizines and *N*-methylindoles using sulfonyl chlorides as sulfonylation reagents.

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 equiv 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.

The substrate scope of the sulfonylation 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

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

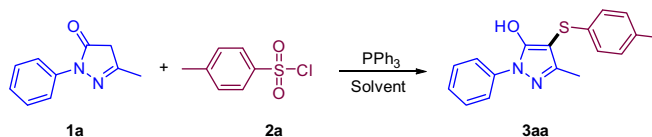
^a Reaction conditions: **1a–i** (0.5 mmol), **2a–j** (0.6 mmol), PPh₃ (1.0 mmol), KI (0.1 mmol), 1,4-dioxane (1 mL), 80 °C, 12 h.

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

Table 1

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



Entry	KI (equiv)	<i>T</i> (°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.

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