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Communication

Direct construction of sulfenylated pyrazoles catalyzed by I₂ at room temperature

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ABSTRACT

An iodine-catalyzed sulfenylation of pyrazoles at room temperature is described, in which a variety of pyrazoles were well tolerated and the desired products were obtained in good to excellent yields.

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Sulfur-containing compounds are crucial for the synthesis of diverse molecules in organic synthesis, the pharmaceutical industry, and materials science [1–9]. In the last few decades, much effort has been devoted to developing new methods for C–S bond construction. Among these approaches, transition-metal catalyzed cross coupling reactions are among the most powerful tools for C–S bond formation [10–18]. However, some of these methods require expensive and air-sensitive metal catalysts, and are not environmentally benign. Therefore, direct sulfenylation reactions under metal free conditions have received increasing interest recently [19–32]. For example, in 2016, an iodine catalyzed regioselective sulfenylation of imidazoheterocycles using dimethyl sulfoxide as both oxidant and solvent was reported by Prabhu *et al.* [33]. An efficient method using an ionic liquid as solvent was developed by Zhang *et al.* for the synthesis of 3-sulfonyl imidazo[1,2-a]pyridines in the

presence of Cs₂CO₃ [34]. In 2016, Lu *et al.* showed that aryl sulfonyl chlorides were good reagents for the sulfenylation of pyrazolones and benzofurans [35]. In 2016, another system consisting of KIO₃ and air was disclosed by Wan *et al.* for the α -sulfenylation of enaminones and related enamines [36]. Furthermore, Wang *et al.* reported that the direct arylthiation of substituted anilines was realized in the presence of I₂ and di-*tert*-butyl peroxide [37]. In 2017, Song *et al.* described an electrolytic C–H thiolation reaction catalyzed by (2,2,6,6-tetramethyl-piperidin-1-yl)oxyl (TEMPO) for the synthesis of benzothiazoles and thiazolopyridines [38]. However, new versatile and practical methods for C–S bond synthesis remain desirable. As part of our continuing efforts toward iodine-catalyzed reactions [39,40], we now disclose a new strategy for the convenient and highly efficient iodine-catalyzed synthesis of sulfenylated pyrazoles at room temperature.

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The reaction of 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (**1a**) with disulfide (**2a**) in the presence of H₂O₂ was chosen as the model reaction to optimize conditions. Initially, various catalysts were screened, with the highest yield (88%) obtained using I₂ as catalyst (Table 1, entry 5). Using *N*-bromobutanamide (NBS) as the catalyst, desired product **3a** was obtained in only 43% yield (Table 1, entry 1). In contrast, *N*-chlorosuccinimide (NCS), *N*-iodosuccinimide (NIS), and NH₄I did not successfully catalyze the model reaction (Table 1, entries 2–4). We next investigated the effect of solvent on the model reaction, and found that 1,4-dioxane was superior to the other solvents. No desired product was generated when water was used as the solvent (Table 1, entry 10), while other solvents, such as DMF, dichloroethane (DCE), 1,2-dimethoxyethane (DME), and EtOH, generated the corresponding products in (39–67)% yields (Table 1, entries 6–9). Furthermore, when the amount of H₂O₂ was decreased from 2 to 1 equiv., a slightly lower yield of 60% was obtained (Table 1, entry 11).

Having obtained optimized reaction conditions, the scope of this reaction was evaluated for a variety of pyrazoles with different substituted disulfides. As shown in Scheme 1, substituted pyrazoles with either electron-donating or electron-withdrawing groups were well tolerated in this system (**3a–3d**). Chlorine-substituted pyrazoles reacted with a series of disulfides smoothly, affording the desired product in (75–93)% yields (**3e–3k**). Furthermore, methyl-substituted pyrazoles afforded the desired products in (77–97)% yields (**3d**, **3l–3o**). For substituted disulfides, the electronic effects of the substituent groups had no significant effect on the catalytic efficiency (**3p–3s**). To our delight, when 1,2-di(pyridin-2-yl)disulfane was used, the corresponding products were obtained in moderate to high yields (**3t–3v**).

To demonstrate the synthetic utility of this transformation, a scaled up experiment (6 mmol) was carried out (Scheme 2). When 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (**1a**) and 1,2-

Table 1
Iodine-catalyzed sulfenylation of pyrazoles ^a.

Entry	Catalyst (mol%)	Solvent	Yield ^b (%)
1	NBS (10)	1,4-dioxane	43
2	NCS (10)	1,4-dioxane	0
3	NIS (10)	1,4-dioxane	0
4	NH ₄ I (10)	1,4-dioxane	0
5	I ₂ (10)	1,4-dioxane	88
6	I ₂ (10)	DMF	54
7	I ₂ (10)	DCE	51
8	I ₂ (10)	EtOH	67
9	I ₂ (10)	DME	39
10	I ₂ (10)	H ₂ O	0
11	I ₂ (10)	1,4-dioxane	60 ^c

^a Reaction conditions: **1a** (0.2 mmol), **2a** (0.11 mmol), I₂ (10 mol%), solvent (1 mL), 25 °C, 30% aq. H₂O₂ in decane (0.4 mmol), 24 h, in air.

^b Isolated yields. ^c 30% aq. H₂O₂ in decane (0.2 mmol) was used.

Scheme 1. Scope of pyrazole sulfenylation using disulfides. Reaction conditions: Pyrazole (0.2 mmol), disulfide (0.11 mmol), I₂ (10 mol%), solvent (1 mL), 25 °C, 30% aq. H₂O₂ in decane (0.4 mmol), 24 h, in air. Isolated yields are shown.

diphenyldisulfane (**2a**) were tested under the optimized conditions, product (**3a**) was obtained without a major decrease in yield. Therefore, the present method should be a robust method for the large-scale synthesis of sulfenylated pyrazoles.

To gain insight into the reaction mechanism, control experiments were performed, as shown in Scheme 3. When TEMPO was added to the reaction, the product yield was significantly decreased (Scheme 3(a)). This indicated that a radical intermediate might be involved in the reaction. When the reaction was conducted without I₂, no desired product was detected, indicating the important role of I₂ (Scheme 3(b)). Furthermore, when the reaction of **1a** with **2a** was performed without H₂O₂ (Scheme 3(c)), the yields of the desired product decreased to 48%. These results demonstrated the importance of I₂ and H₂O₂ in this reaction.

Based on these preliminary experiments and previous reports [19,41–45], a plausible reaction mechanism was proposed, as shown in Scheme 4. Firstly, homolytic cleavage of the disulfide bond occurs, forming thiyl radicals. The thiyl radicals then react with I_2 to generate electrophilic sulfenyl iodide PhSI. Finally, electrophilic PhSI reacts with pyrazoles to produce the desired product and HI, and I_2 is readily regenerated by the oxidation of HI with H_2O_2 .

Scheme 2. Gram-scale synthesis of sulfenylated pyrazoles **3a**.

Scheme 3. Controlled experiments.

Scheme 4. Proposed reaction mechanism.

In conclusion, we have developed an efficient and simple I_2 -catalyzed protocol for the synthesis of sulfonylated pyrazoles at room temperature. Under the present reaction conditions, a variety of desired products were obtained in good to excellent yields. Further investigations into the reaction scope and mechanism, and the synthetic applications of these sulfonylated pyrazoles, are now in progress.

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Graphical Abstract

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室温下碘催化直接构建硫化吡啶啉酮

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摘要: 含硫化合物在有机合成、药物化学以及材料化学等领域具有重要的作用。到目前为止, 科学家已经在C–S键的构建领域进行了很多工作。在构建C–S键的众多方法中, 金属催化的C–S键合成反应是一类很重要的反应, 但是此方法存在着催化剂对空气敏感、环境不友好等问题。因此, 发展无金属催化的C–S键构建反应受到了人们越来越多的重视。基于我们在碘催化相关反应方面的研究, 本文报道了一种碘催化的硫化吡啶啉酮类化合物的合成方法。

我们选用3-甲基-1-苯基-2-吡啶啉-5-酮与二苯二硫醚为底物进行条件筛选实验, 发现I₂(10%)为催化剂, 二氧六环为溶剂, H₂O₂为氧化剂为最优化的实验条件, 目标产物硫化吡啶啉酮最高产率为88%。在最优化的反应条件下, 我们尝试了带有不同官能团(NO₂, Cl, OH等)的吡啶啉酮与二硫醚的反应, 均能以较高产率得到目标产物。当含有杂环的二硫醚(2,2'-二硫二吡啶)作为反应底物时, 也能以中等以上的产率得到相应的目标产物。另外还进行了对比试验, 例如在反应体系中加入自由基捕获剂TEMPO, 反应产率会大大降低, 说明反应中应该有自由基中间体生成; 如果反应体系中不加碘, 则反应产率为零; 如果反应体系中不加H₂O₂, 则反应产率由88%降低至48%, 说明碘和H₂O₂在反应中都起到了重要作用。通过以上对比试验, 提出了可能的反应机理: 首先, 二硫醚发生均裂反应生成苯硫基自由基, 然后苯硫基自由基与碘反应生成亲电的PhSI活性中间体, PhSI与异构化的吡啶啉酮发生亲电取代反应, 生成目标产物硫化吡啶啉酮和HI, HI可以被H₂O₂氧化生成I₂继续参与下一轮催化反应。

以3-甲基-1-苯基-2-吡啶啉-5-酮与二苯二硫醚为底物, 我们对此反应进行了放大试验, 结果显示反应产率几乎没有降低, 这为此反应的大规模应用奠定了基础。

在此, 我们发展了一种简单高效的合成硫化吡啶啉酮的反应, 此方法无需金属催化剂, 利用常见的碘为催化剂就可以以较高的产率得到目标产物。为合成含硫化合物提供了一种新的方法。

关键词: C–S键; 碘; 室温; 二硫醚; 硫化

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