



Rhodium-catalyzed phenylthiolation reaction of heteroaromatic compounds using α -(phenylthio)isobutyrophenone

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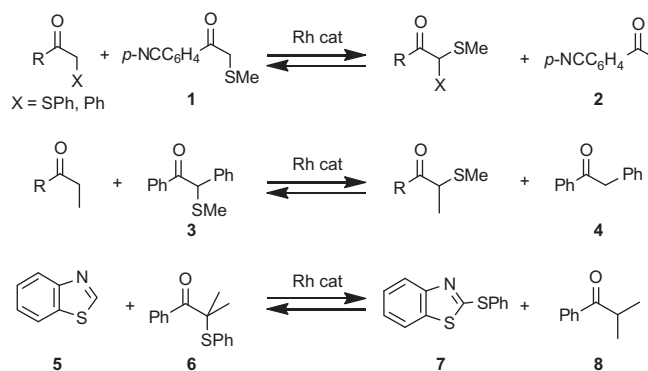
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ABSTRACT

In the presence of catalytic amounts of RhH(PPh₃)₄ and 1,2-bis(diphenylphosphino)ethane (dppe), 1,3-benzothiazoles, 1,3-benzoxazoles, and benzothiophene reacted with α -(phenylthio)isobutyrophenone giving 2-phenylthio derivatives. Reactive monocyclic heteroaromatics, 1-methyl-1,2,3,4-tetrazole and 2-cyanothiophene were also converted into the 5-phenylthio derivatives. The use of an appropriate phenylthio transfer reagent is crucial for the efficient catalyzed conversion of heteroaromatic C–H bonds into C–S bonds.

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Heteroaromatic compounds possessing organothio groups are potentially useful as drugs and materials. In general, such compounds are synthesized by the reaction of halogenated heteroaromatics and thiolate anions¹ or the reaction of heteroaromatic thiolates and organohalogen compounds.^{2,3} The direct conversion of a heteroaromatic C–H bond into a C–S bond is attractive for such synthesis, and electrophilic reactions are known for electron-rich heteroaromatic compounds, typically indoles.⁴ Recently, base-promoted reactions of 1,3-benzoxazoles, 1,3-benzothiazoles, and related heteroarenes have been reported.^{5,6} The use of transition metal catalysis for such transformation is interesting, because the method has the advantage of not employing an acid or base and can also exhibit different reactivities from conventional methods. The fact that the catalyzed method, however, was not known was ascribed to the lack of methodology and/or concepts to develop the chemical process. The reaction should proceed via C–H activation, activation of the sulfur reagent, and C–S bond formation. The series of effective activations results in low total activation energy of the reaction, which makes the overall reaction reversible and under equilibrium. The relative thermodynamic stability of substrates and products must then be considered. Development of a methodology for controlling both kinetic and



Scheme 1.

thermodynamic properties of heteroaromatic C–H functionalization is a challenge.

During our investigations on the development of transition-metal-catalyzed synthetic methods for organosulfur compounds,⁷ we reported reactions that converted the relatively acidic protons of organic compounds into sulfides. The reaction of 1-alkynes and disulfides gave 1-alkylthio-1-alkynes.⁸ The α -methylthiolation reaction of α -phenylthio ketones⁹ and α -phenyl ketones¹⁰ was conducted using α -methylthio-*p*-cyanoacetophenone **1** as the methylthio donor. In this reaction, the methylthio group was transferred

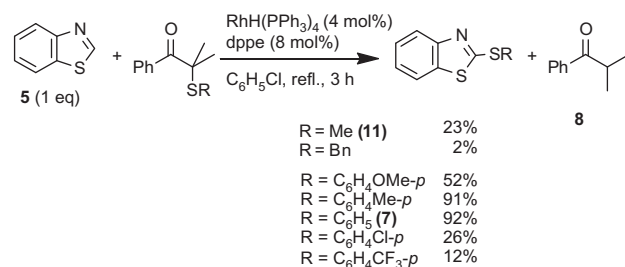
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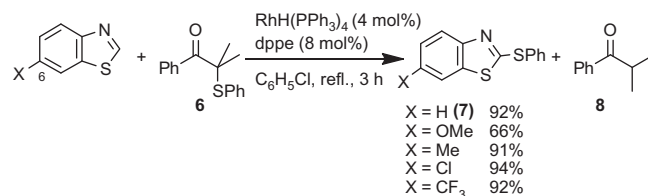
from **1** to the α -position of the ketone with the concomitant formation of *p*-cyanoacetophenone **2**. Unactivated ketones possessing less acidic α -protons were not methylthiolated by **1** but by 2-methylthio-1,2-diphenyl-1-ethanone **3**, which was converted into 1,2-diphenyl-1-ethanone **4** during the reaction (Scheme 1).¹¹ The higher efficiency of **3** than of **1** in the reaction with unactivated ketones could be ascribed to the stronger C–S bond of **3** than of **1**, which shifted the equilibrium in the desired direction. To extend this method to the functionalization of heteroaromatic C–H bonds with even less acidic protons, it was considered crucial to develop an appropriate methylthio donor. Described in this study is the use of α -(phenylthio)isobutyrophenone **6**, which effectively transferred the phenylthio group to heteroaromatic compounds such as 1,3-benzothiazole **5** giving 2-phenylthio-1,3-benzothiazole **7** with the formation of isobutyrophenone **8** (Scheme 1).

On the basis of our previous observation that **3** is a better methylthio donor than **1**, the reaction of 1,3-benzothiazole **5** and **3** was examined; however, it gave no methylthiolated product. Then, α -(methylthio)propiophenone **9**, which was considered to have a stronger C–S bond than **3** and, therefore, to be a stronger methylthio donor was reacted with **6**. When **6** (5 equiv) was treated with **9** (1 equiv) in the presence of RhH(PPh₃)₄ (4 mol %), dppe (8 mol %), and dimethyl disulfide (12 mol %) in refluxing THF for 3 h, the desired 2-methylthio-1,3-benzothiazole **11** was obtained in 13% yield based on **9** (Scheme 2).¹² The use of α -(methylthio)isobutyrophenone **10** improved the yield of **11** to 43%. The effect of the aromatic substituent on isobutyrophenone was examined, and the phenyl derivative gave a higher yield of **11** than of the derivatives with electron-donating or electron-withdrawing groups (Scheme 3). The occurrence of optimum yields with respect to electronic properties suggested the equilibrium nature of this reaction, in other words, the essential role of thermodynamics balances between substrates and products.

The reactivities of several α -(organothio)isobutyrophenones were compared. Notably, the yield of 2-organothiolated 1,3-benzothiazole increased considerably with the use of α -(phenylthio)isobutyrophenone **6**. When **5** (1 equiv) was reacted with **6** (1 equiv) in the presence of RhH(PPh₃)₄ (4 mol %), and dppe (8 mol %) in refluxing chlorobenzene for 3 h, 2-phenylthio-1,3-benzothiazole **7** was obtained in 92% yield, which was accompanied by **8** in 94% yield (Scheme 4). It was confirmed that **7** was not formed in the absence



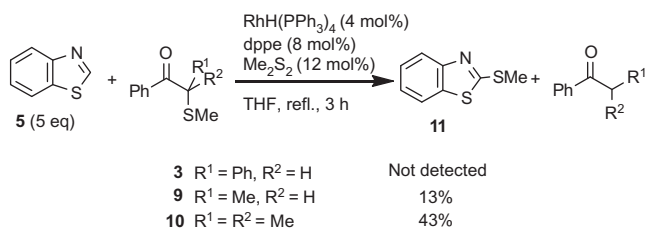
Scheme 4.



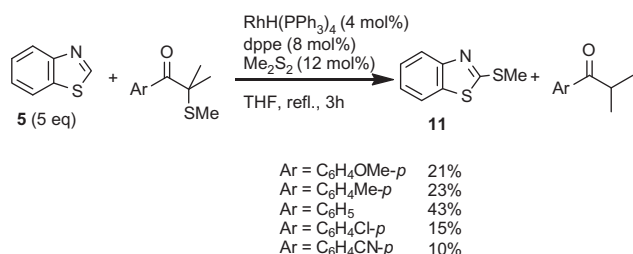
Scheme 5.

of either RhH(PPh₃)₄ or dppe. The reaction of **5** and **10** under the same conditions gave **11** only in 23% yield, and a similar result was obtained with the benzylthio derivative. The higher yield of the phenylthio derivative **7** than of the methylthio **11** may be related to the dependence of the reaction on the relative C–S bond energies of the substrate and product. A study of the *p*-substituent effect at the arylthio moiety revealed phenyl or *p*-tolyl derivatives to be more favorable than the *p*-methoxy, *p*-chloro, and *p*-trifluoromethyl. The reaction of several 6-substituted 1,3-benzothiazoles was conducted under the same conditions, and the corresponding 2-phenylthio-1,3-benzothiazoles were obtained in high yields. Exceptions were those with electron-withdrawing groups, 6-nitro- and 6-methoxycarbonyl-1,3-benzoxazoles, which gave the product in <5% yield (Scheme 5).

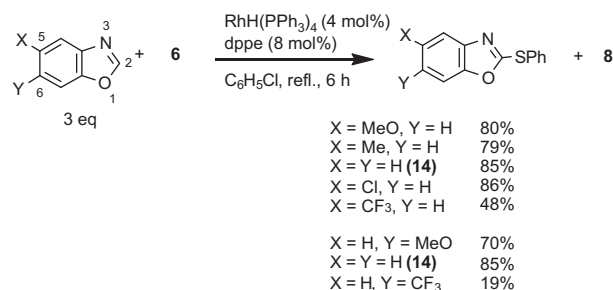
1,3-Benzoxazole **14** (3 equiv) and its 5- and 6-substituted derivatives were also reacted with **6** in the presence of the rhodium catalyst (Scheme 6). The 5- and 6-derivatives with methoxy, methyl, hydrogen, and chloro groups gave the 2-phenylthiolated products in high yields. However, the 6-trifluoromethyl derivative gave only 19% yield of the product, and 5-cyano and 5-methoxycarbonyl result in essentially no product. The significantly reduced reactivity of the substrates with electron-withdrawing groups suggested an important role of the basicity of 1-oxygen and/or 3-nitrogen in the reaction rather than the acidity at the 2-position. The reaction of 3-cyanobenzothiophene gave the 2-phenylthio derivative in 80% yield (Scheme 7). Benzothiophene itself was inert, and the presence of the cyano activating group was essential for this transformation.



Scheme 2.



Scheme 3.



Scheme 6.

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