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

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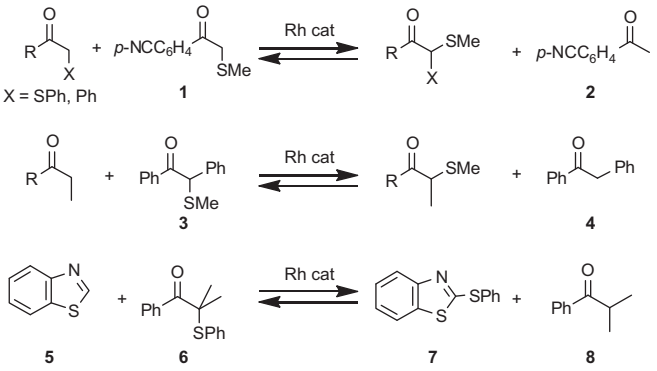
ABSTRACT

In the presence of catalytic amounts of $RhH(PPh_3)_4$ 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.

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 anions[1] 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 thermodynamic properties of heteroaromatic C–H functionalization is a challenge.



Scheme 1.

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 ketones[9] and α-phenyl ketones[10] was conducted using α-methylthio-*p*-cyanoacetophenone **1** as the methylthio donor. In this reaction, the methylthio group was transferred

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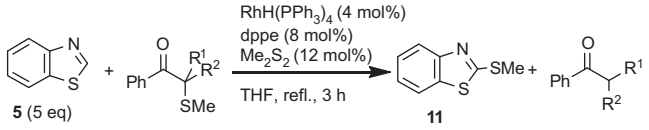
from **1** to the α-position of the ketone with the concomitant formation of *p*-cyanoacetophenone **2**. Unactivated ketones possessing less acidic α-protons were not methylthiolated by **1** but by 2-methylthio-1,2-diphenyl-1-ethanone **3**, which was converted into 1,2-diphenyl-1-ethanone **4** during 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).

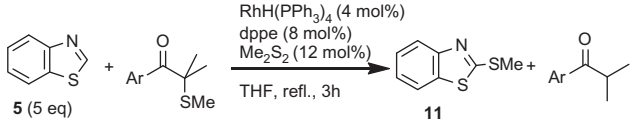
On the basis of our previous observation that **3** is a better methylthio donor than **1**, the reaction of 1,3-benzothiazole **5** and **3** was examined; however, it gave no methylthiolated product. Then, α-(methylthio)propiophenone **9**, which was considered to have a stronger C–S bond than **3** 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 $RhH(PPh_3)_4$ (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 $RhH(PPh_3)_4$ (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



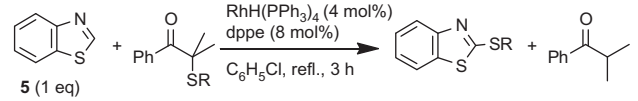
3	R^1 = Ph, R^2 = H	Not detected
9	R^1 = Me, R^2 = H	13%
10	R^1 = R^2 = Me	43%

Scheme 2.



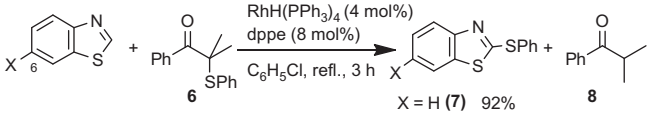
Ar = C_6H_4OMe-*p*	21%
Ar = C_6H_4Me-*p*	23%
Ar = C_6H_5	43%
Ar = C_6H_4Cl-*p*	15%
Ar = C_6H_4CN-*p*	10%

Scheme 3.



R = Me (**11**)	23%
R = Bn	2%
R = C_6H_4OMe-*p*	52%
R = C_6H_4Me-*p*	91%
R = C_6H_5 (**7**)	92%
R = C_6H_4Cl-*p*	26%
R = $C_6H_4CF_3$-*p*	12%

Scheme 4.

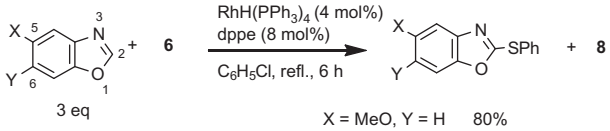


X = H (**7**)	92%
X = OMe	66%
X = Me	91%
X = Cl	94%
X = CF_3	92%

Scheme 5.

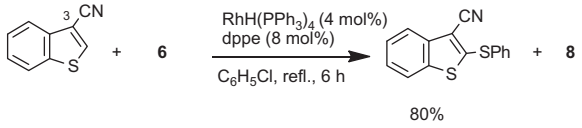
of either $RhH(PPh_3)_4$ or dppe. The reaction of **5** and **10** under the same conditions gave **11** only in 23% yield, and a similar result was obtained with the benzylthio derivative. The higher yield of the phenylthio derivative **7** than of the methylthio **11** may be related to the dependence 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.

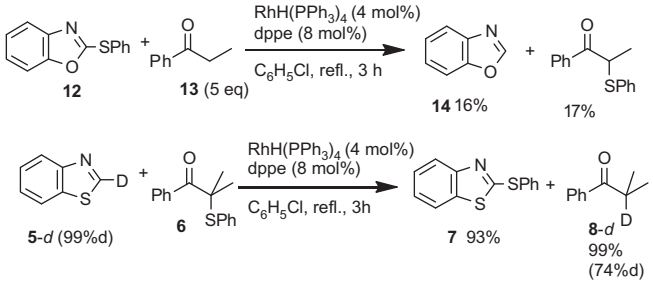


X = MeO, Y = H	80%
X = Me, Y = H	79%
X = Y = H (**14**)	85%
X = Cl, Y = H	86%
X = CF_3, Y = H	48%
X = H, Y = MeO	70%
X = Y = H (**14**)	85%
X = H, Y = CF_3	19%

Scheme 6.



Scheme 7.

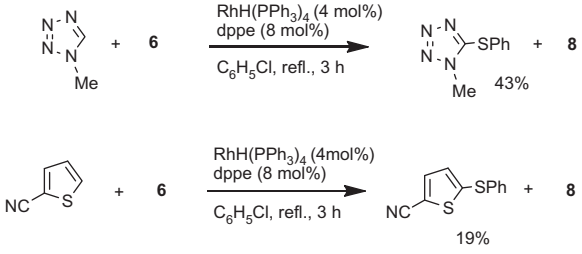


Scheme 8.

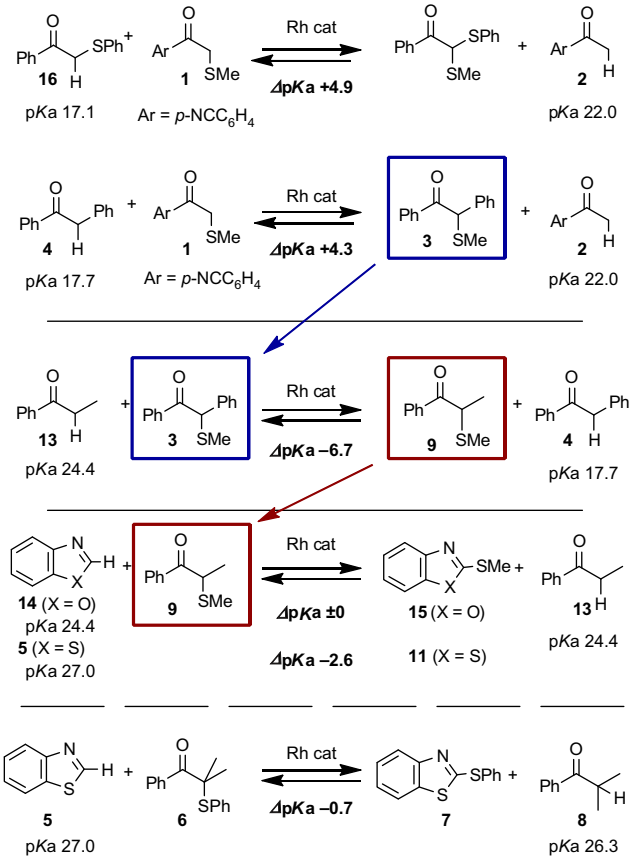
The reversibility of the methyl transfer reaction was confirmed (Scheme 8). The treatment of 2-phenylthio-1,3-benzoxazole **12** and propiophenone **13** (5 equiv) with the catalyst in refluxing chlorobenzene for 3 h gave **14** (16%) and α-(phenylthio)propiophenone (17%), which were accompanied by the recovery of **12** in 62% yield. The treatment of **12** with isobutyrophenone gave a very low yield of the product, which again showed the importance of the combination of a substrate and a methylthio donor. The metathesis of the phenylthio C–S bond and heteroaromatic C–H bond was confirmed by an experiment using deuterated **5**-*d*.

1-Methyl-1,2,3,4-tetrazole underwent the reaction giving 1-methyl-5-phenylthio-1,2,3,4-tetrazole in 43% yield (Scheme 9). 2-Cyanothiophene was phenylthiolated giving 2-cyano-5-(phenylthio)thiophene in 19% yield using **6**, whereas thiophene itself was inert under the same conditions; monocyclic 1,3-thiazole and 1,3-oxazole were also inert. An activated heteroaromatic system was required for this reaction, probably because of the higher acidity of the protons.

Our study of the rhodium-catalyzed organothiolation reaction was conducted by changing the substrates from acidic to less acidic, α-phenylthio ketones, α-phenyl ketones, unactivated ketones, and 1,3-benzoxazoles/1,3-benzothiazoles. The idea was to find an appropriate organothio donor for each substrate to control the equilibrium. Initially, the methylthiolation of α-(phenylthio)acetophenone **16** was conducted with α-methylthio-*p*-cyanoacetophenone **1** with the formation of *p*-cyanoacetophenone **2** (Scheme 10). The pK_a values of **16** and **2** are 17.1[13] and 22.0[14], respectively, which provided a pK_a difference of ΔpK_a +4.9 between the reactant and the product. Compound **1** could also be used for the reaction of α-(phenyl)acetophenone **4**. The pK_a values of **4** and **2** are 17.7[13] and 22.0, respectively, and ΔpK_a +4.3. The results indicated that these magnitudes of pK_a differences could



Scheme 9.



Scheme 10.

be overcome in the organothiolating reaction, because the relative thermodynamic stabilities of reactant and product are governed by the C–S bond energy as well as by the C–H bond energy. The reaction of less acidic propiophenone **13** (pK_a 24.4[15]), which proceeded with 1-methylthio-1,2-diphenyl-2-ethanone **3**, was examined next. The pK_a of 1,2-diphenyl-2-ethanone **4** is 17.7, and ΔpK_a is –6.7 for this reaction. As indicated in this work, 1,3-benzoxazole **14**[12] (pK_a 24.4[13]) and 1,3-benzothiazole **5** (pK_a 27.0[13]) were methylthiolated with **9** giving the 2-methylthio derivatives **15** and **11** with the formation of propiophenone **13**; the ΔpK_a values are ±0 and –2.6 for these reactions, respectively. The yield increased in the reaction of **5** using α-(phenylthio)isobutyrophenone **6** giving 2-phenylthio-1,3-benzothiazole **7**; ΔpK_a is –0.7 for this reaction. The higher efficiency of **6** than that of **9** may be the result of a fine adjustment in the balance between the reactants and the products at equilibrium.

A notable aspect of this series of equilibrium reactions is that product **3** obtained in the reaction of **1** and **4** was effectively employed in the reaction of less acidic **13**. Analogously, **9** obtained in the reaction of **3** and **13** was used in the reaction of the even less acidic **5** and **14**. It was also noted that **1** was not effective for the reaction of **13** and **5**; **3** was not effective for **5**. This method of correlating reactants and products can be useful for the control of equilibrium reactions involving C–H activation.

Typical experimental procedures

In a two-necked flask equipped with a reflux condenser were placed $RhH(PPh_3)_4$ (4 mol %, 11.5 mg), dppe (8 mol %, 8.0 mg), 1,3-benzothiazole **5** (0.25 mmol, 27.3 μL), and (α-phenylthio)isobutyrophenone **6** (0.25 mmol, 64.0 mg) in chlorobenzene (0.25 mL) under an argon atmosphere, and the solution was heated

at reflux for 3 h. The mixture was purified by flash column chromatography on silica gel giving **7** (55.8 mg, 92%) and isobutyrophenone **8** (34.3 mg, 93%) with the recovery of **5** (3.5 mg, 10%) and **6** (0.8 mg, 1%).

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.02.077.

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