



Accepted Article

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To be cited as: Adv. Synth. Catal. 10.1002/adsc.201800630

Link to VoR: http://dx.doi.org/10.1002/adsc.201800630

COMMUNICATION

Rhodium-catalyzed Synthesis of Dialkyl(heteroaryl)phosphine Sulfides by Phosphinylation of Heteroaryl Sulfides

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Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201#######.((Please delete if not appropriate))

Abstract. Dialkyl(heteroaryl)phosphine sulfides were synthesized by the rhodium-catalyzed exchange reaction of heteroaryl aryl sulfides and tetraalkyldiphosphine disulfides. The reaction has a broad applicability, giving diverse dialkyl(heteroaryl)phosphine sulfides containing five- and six-membered heteroaryl groups. Various dialkyl(heteroaryl)phosphines were obtained by desulfurization.

Keywords: dialkyl(heteroaryl)phosphine sulfides; tetraalkyldiphosphine disulfides; phosphinylation; desulfurization; Rh catalysis

Aryl- and alkylphosphines are organophosphorus compounds used as ligands of metal-catalysis and reagents for organic synthesis,^[1] and their phosphonium salts are used as ionic liquids, antibacterial agents, and catalysts.^[2] It is therefore critical to develop a versatile method to synthesize a diversity of phosphines and phosphonium salts to improve properties and to develop novel functions. In particular, phosphines possessing heteroaryl groups are attractive, because such compounds have additional heteroatoms located in the vicinity of the phosphorus atom.

number of heteroarylphosphines, A limited known. Reported methods however. are of synthesizing of heteroaryl diarylphosphines employed diphenylphosphine oxides $Ph_2P(=O)H$ as the phosphinyl reagents, and were generally conducted by either 1) transition-metal-catalyzed substitution electron-deficient six-membered reactions of heteroaryl halides, mostly pyridines and quinolines,^[3] or 2) radical reactions of five-membered heteroaryl compounds possessing structures capable of stabilizing radical intermediates. mostly benzothiazoles.^[4] These conventional methods suffer from the limited scope of the heteroaryl moiety. Method to synthesize dialkyl derivatives of heteroarylphosphines are still rare^[5] and use dialkylphosphine oxides $R_2P(=O)H$, which are not easy to prepare and handle. The development of a versatile synthesis method for heteroarylphosphines is desired.

Described here is a rhodium-catalyzed synthesis of dialkyl(heteroaryl)phosphines from heteroarvl sulfides and tetraalkyldiphosphine disulfides (Scheme 1). Diverse dialkyl(heteroaryl)phosphine sulfides containing five- and six-membered heteroaryl groups were obtained by employing stable tetraalkyldiphosphine disulfides as the phosphinyl reagents. Dialkyl(heteroaryl)phosphine sulfides were desulfurized with tributylphosphine giving dialkyl(heteroaryl)phosphines.

HetAr -
$$\frac{S}{P}$$
 - SAr + R₂P - PR₂
HetAr - $\frac{S}{P}$ - R₂ + R₂P - SAr
↓ - S
HetAr - PR₂

Scheme 1. Rhodium-catalyzed synthesis of dialkyl(heteroaryl)phosphine sulfides by phosphinylation of heteroaryl sulfides.

Synthesis of aryldialkylphosphine sulfides was initially examined by the reaction of diaryl sulfides and tetraethyldiphosphine disulfide^[6] which was accompanied by aryl diethyldithiophosphinates. When equimolar amounts of 2-[(4-tolyl)thio]-5trifluoromethylbenzonitrile 1a and tetraethyldiphosphine disulfide 2 were reacted in refluxing THF for 3 h in the presence of RhH(PPh₃)₄ (5 mol%) and 1,2-bis[di(4methoxyphenyl)phosphino]ethane (dmppe, 10 mol%), 2-diethylphosphinothioyl-5trifluoromethylbenzonitrile 3a and aryl diethyldithiophosphinate 4a were obtained in 90% and 81% yields, respectively (Scheme 2). No reaction occurred in the absence of the rhodium complex or dmppe. The use of several bidentate ligands revealed

the high efficiency of dmppe for the reaction of 1 and 2: 1,2-bis(diphenylphosphino)ethane (yields of 3a and 55% 37%). **4a**: and 1,2-bis[di(4methoxyphenyl)phosphino]benzene (24% and 43%), 1,2-bis(diphenylphosphino)benzene (both in amounts 1,3-bis(diphenylphosphino)propane trace). (not detected), and 1,4-bis(diphenylphosphino)butane (not detected). The monodentate ligands tris(4methoxyphenyl)phosphine and tris(cyclohexyl)phosphine were ineffective. These results showed that the bidentate phosphine ligands with diarylphosphino groups separated by two carbon atoms are essential, and that the yield increased using dmppe possessing 4-methoxyphenyl groups.

Aryl 4-tolyl sulfides possessing two electronwithdrawing groups gave the corresponding aryldiethylphosphine sulfides **3a–3c**, although no reaction occurred with 4-[(4-tolyl)thio]benzonitrile. The leaving arylthio moiety, can possess either 4electron-donating or 4-electron-withdrawing groups, both of which provided **3a** in high yields. It was also noted that the octylthio derivative **1d** was phosphinylated in 90% yield. The Ar–S bonds of diaryl and aryl alkyl sulfides were cleaved and converted to the Ar–P bonds through rhodium catalysis.



Scheme 2. Rhodium-catalyzed synthesis of aryldialkylphosphine sulfides by phosphinylation of aryl sulfides.

Various dialkyl(heteroaryl)phosphine sulfides 6a-60 were synthesized by the reaction of five-membered heteroaryl 4-chlorophenyl sulfides in high yields, which involved 1,3-benzothiazolyl, 1,3-benzoxazolyl, 1,3-oxyazolyl, and 2-furyl derivatives (Table 1). When equimolar amount of 5-chloro-2-(4an chlorophenyl)thiobenzothiazole 5a and 2 were reacted in refluxing THF for 3 h in the presence of RhH(PPh₃)₄ (5 mol%) and dmppe (10 mol%), 6a and 4c were obtained in 99% and 91% yields, respectively. 6a and 4a were also obtained in 92% and 84% yields, respectively, by the reaction of 4-tolyl sulfide. Diphosphine disulfides such as tetramethyl, tetraethyl, teterabutyl, 1,2-dipropyl-1,2tetrapropyl, and diphenyldiphosphine disulfides, as well as tetraphenyldiphosphine disulfide reacted efficiently.

Six-membered heteroaryl 4-chlorophenyl sulfides containing 2-triazyl, 4-quinazolyl, and pyrimidyl groups were also converted to the heteroaryldiethylphosphine sulfides 6p-6v. For the six-membered heteroaryl derivatives, the use of 4chloroaryl sulfides 5u and 5v improved the yields of 6u and 6v to 65% and 83% compared with the use of 4-tolyl sulfides which provided **6u** and **6v** in 35% and respectively. 10% yields, Various dialkyl(heteroaryl)phosphine sulfides were effectively by dialkylthiophosphinylation synthesized of heteroaryl sulfides using tetraalkyldiphosphine disulfides. All the dialkyl(heteroaryl)phosphines shown here are new compounds except for **6f**,^[7] which has not been reported before.

Table1.Rhodium-catalyzedsynthesisofdialkyl(heteroaryl)phosphinesulfidesfromheteroarylsulfides.



^{a)} Heteroaryl 4-tolyl sulfide was used. ^{b)} Rh cat. (15 mol%) and dmppe (30 mol%) were used. ^{c)} Rh cat. (50 mol%) and dmppe (100 mol%) were used. ^{d)} *o*-Dichlorobenzene reflux using Rh cat. (5 mol%) and dmppe (10 mol%), 3 h.

A possible mechanism of the reaction is provided in Scheme 3. The phosphine ligand in RhH(PPh₃)₄ is exchanged with dmppe, and the reaction of diphosphine sulfide provides rhodium(I) phosphide intermediate **A**. Then, the oxidative addition of tetraalkyldiphosphine disulfide provides the bis(dialkylphosphinyl)rhodium(III) intermediate **B**. The intermediate **B** undergoes a heteroaryl exchange reaction with a heteroaryl aryl sulfide, forming HetAr'-Rh(III)-P(S)R₂ complex **C** and an aryl dialkyldithiophosphinate,

dialkyl(heteroaryl)phosphine sulfide is liberated by reductive elimination with the regeneration of rhodium catalyst. The rhodium(I) phosphide complex (X = $P(S)R_2$) may be formed as an active species.^[8]

and



Scheme 3. Proposed reaction mechanism.

Dialkyl(heteroaryl)phosphine sulfides were desulfurized using tributylphosphine (Table 2).^[9] 2-(dibutylphosphinothioyl)-5-When chlorobenzothiazole 6c was reacted with tributylphosphine (1.2 eq.) in refluxing 0dichlorobenzene for 10 h, the corresponding 2-(dibutylphosphinyl)-5-chlorobenzothiazole 8a was obtained in 99% yield. Thus. various dialkyl(heteroaryl)phosphines with six- and fivemembered heteroarenes 8a-8g were synthesized, all of which are new compounds except for 8d.^[3d]

Table 2. Synthesis of dialkyl(heteroaryl)phosphines.



8a 99%

8c X = Ph, R = Et 84% 8d X = H, R = Ph 95%



It was noted that the HetAr-P bonds in the dialkyl(heteroaryl)phosphine sulfides were cleaved under the rhodium-catalyzed conditions, and the heteroaryl exchange of heteroarylphosphine sulfides occurred in the presence of diphosphine disulfides. When 2-(dimethylthiophosphino)benzothiazole 6e was reacted with tetraethyldiphosphine disulfide (3 equiv) in the presence of RhH(PPh₃)₄ (5 mol%) and dmppe (10 mol%) in refluxing THF for 9 h, 2-(diethylphosphinothioyl)benzothiazole 6f was obtained in 63% yield (Scheme 4). The heteroaryl group can be transferred from the dimethylphosphinothioyl group to dibutylphosphinothioyl and 1-butyl-1phenylphosphinothioyl giving 2groups, phosphinothioylbenzothiazoles 9b. 9a and respectively.



Scheme 4. The heteroaryl exchange of heteroarylphosphine sulfides via HetAr-P bond cleavage reaction.

was also noted that the reaction It of heteroarylphosphine sulfides and disulfides provided heteroaryl sulfides, which is the reverse reaction of the dialkylphosphinylation of heteroaryl sulfides. When 2-(dimethylthiophosphinyl)-1,3-benzothiazole 6e was reacted with dioctyl disulfide 10 (1 equiv.) in refluxing chlorobenzene for 3 h in the presence of RhH(PPh₃)₄ (10 mol%) and dmppBz (20 mol%), 2-octylthio-1,3benzothiazole **11** and octyl dimethyldithiophosphinate 12 were obtined in 46% and 45% yields, respectively (Scheme 5). No reaction occurred in the absence of the rhodium complex or dmppBz. The use of dmpp decreased 11 in 25% yield. It is interesting to note that the C–P bonds in heteroarylphosphines can be cleaved and converted to C–S and P–S bonds, and that such a method can be used for the synthesis of various heteroaryl compounds.



Scheme 5. The reaction of heteroarylphosphine sulfides and disulfides.

In summary, diverse dialkyl(heteroaryl)phosphine sulfides containing fiveand six-membered heteroarenes were synthesized from heteroaryl aryl sulfides and tetraalkyldiphosphine disulfides in high yields. The dialkyl(heteroaryl)phosphine sulfides were dialkyl(heteroaryl)phosphines converted to by desulfurization. The substrates, heteroaryl aryl sulfides, can be synthesized by a conventional nucleophilic substitution reaction of heteroaryl halides and arylthiols.^[10] Alternatively, we developed a rhodium-catalyzed heteroaryl exchange reaction of heteroaryl aryl ethers and aryl thioesters^[11] and a C-H

arylthiolation reaction of heteroarenes and α -arylthioketones.^[12] Related metal-catalyzed C–H arylthiolation reactions were also reported.^[13] Novel dialkyl(heteroaryl)phosphines obtained by this method may be used to develop novel catalysts and materials.

Experimental Section

Typical procedures for synthesis of 3a

In a two-necked flask were placed RhH(PPh₃)₄ (57.6 mg, 5 mol%), dmppe (51.8 mg, 10 mol%), [2cyano-4-(trifluoromethyl)phenyl] 4-tolylsulfide (1.0 mmol, 293.0 mg), and tetraethyldiphosphine disulfide (1.0 mmol, 242.0 mg) in THF (2.0 mL) under an argon atomosphere, and the mixture was heated at reflux for 3 h. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel giving **3a** (263.1 mg, 90%) and **4a** (198.0 mg, 81%).

Typical procedures for synthesis of 6a

In a two-necked flask were placed RhH(PPh₃)₄ (28.8 mg, 5 mol%), dmppe (25.9 mg, 10 mol%), 5-chlorobenzothiazolyl 4-chlorophenyl sulfide (0.5 mmol, 155.5 mg), and tetraethyldiphosphine disulfide (0.5 mmol, 121.0 mg) in THF (1.0 mL) under an argon atomosphere, and the mixture was heated at reflux for 3 h. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel giving **6a** (142.6 mg, 99%) and **4c** (125.7 mg, 95%).

Acknowledgements

This research was supported by the Platform Project for Supporting Drug Discovery and Life Science Research from AMED under Grant Number JP18am0101100, JSPS KAKENHI Grant Numbers 17K19112, 15H00911, Tohoku University Center for Gender Equality Promotion (TUMUG), and Morinomiyako Project for Empowering Women in Research.

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Adv. Synth. Catal. Year, Volume, Page – Page

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