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# A novel reductive coupling reaction between diphenylphosphine sulfide and formamides

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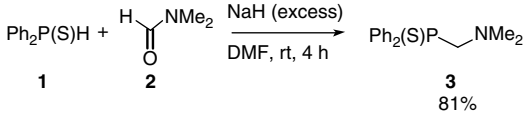
**Abstract**—The coupling reaction of diphenylphosphine sulfide with *N*,*N*-disubstituted formamides in the presence of an excess amount of sodium hydride proceeded smoothly to give the corresponding aminomethyldiphenylphosphine sulfides in good yields. This method is expected to provide a useful synthesis of P,N-containing ligands.


Phosphine sulfides are used as an effective protective group of phosphines due to their air stability.[1] However, the other properties of phosphine sulfides have received much less attention so far. We have reported that some phosphine sulfide ligands play a significant role in transition metal catalyzed reactions.[2] Since the use of phosphine sulfides has increased in the field of organic synthesis, the investigation of their properties and reactivity has become more necessary.

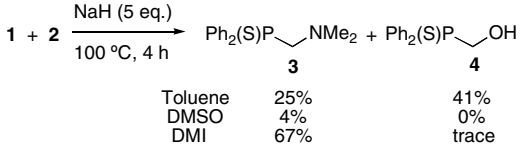
In this letter, we present a novel reaction which is useful in the synthesis of phosphorus containing ligands. We believe that the studies of the nature, scope, and mechanistic aspects of this reaction will provide valuable insights into the properties of phosphine sulfides.

The reaction comprises treatment of diphenylphosphine sulfide **1**[3] with excess NaH in dimethylformamide (DMF) **2**, resulting in the formation of (dimethylaminomethyl)diphenylphosphine sulfide **3**[4] as the main product (Eq. 1). A reductive coupling process between **1** and **2** proceeded to form a new carbon–phosphine bond. We also tested the corresponding reaction of diphenylphosphine oxide under the same conditions as Eq. 1, but the reaction gave no valuable compounds including the same type of coupling adduct. Therefore, this reaction could be characteristic for phosphine sulfide compounds.



(1)

We initially investigated whether the reaction could also proceed in other solvents. Treatment of **1** with an equimolar amount of DMF in the presence of excess NaH in toluene gave a similar product in 25% yield, however, the major product was a hydroxymethyl-derivative **4**. After having tested other solvents, it was concluded that the use of polar solvents minimized the formation of byproduct **4** and when the reaction was run in dimethylimidazolidinone (DMI), **3** was obtained in 67% yield (Eq. 2).



(2)

Next, we turned our attention to the mechanistic aspects of the reductive step. It seems that neither phosphine sulfide nor DMF is the reductant in view of the fact that the yield of **3** exceeded 50% in the equimolar reaction (Eq. 2). Further evidence is the result that **3** was obtained in 80% yield when DMF was replaced by tetramethylurea, which has no reducing ability (Eq. 3). On

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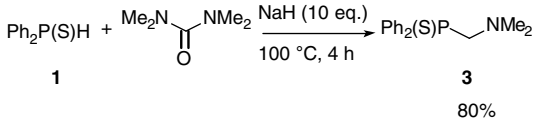
the other hand, product **3** could not be obtained on replacement of NaH with other bases such as *t*-BuOK, NaOH, $NaNH_2$, or when the amount of NaH was decreased to less than 3 M equiv. In these reactions, the product became a complicated mixture with no detectable amount of the desired compound, and furthermore the material balance between the crude mixture and starting material could not be established. From all the data in hand, it was concluded that NaH plays the role of reducing agent in the coupling reaction. Although it is known that NaH can be used in the cleavage of halogen–carbon bonds,[5] there are few reports on the use of NaH to cleave carbon–oxygen bonds. We then focused on anchimeric assistance from phosphine sulfide group.

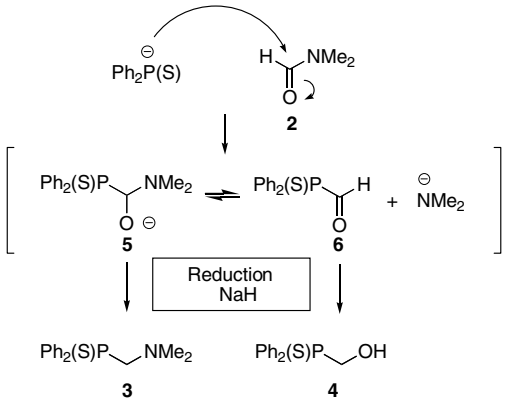



**1** **3** 80% (3)

Now, on the basis of these results and taking into account the formation of byproduct **4**, the mechanism as shown is proposed (Scheme 1). Following the nucleophilic attack on the formamide by the thiophosphinoyl anion, which is formed via deprotonation of the phosphine sulfide, tetrahedral intermediates **5**, and **6** are formed. **3** is produced from **5** via reductive carbon–oxygen bond cleavage by NaH.

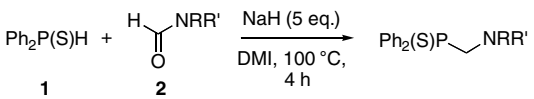
Our exploration of the scope of this coupling reaction is shown in Table 1.[6] Formamides were successfully converted to the desired products. In entry 5, the product, a thiophosphorus derivative of L-proline, contains an asymmetric center,[7] and can be expected to be a useful ligand in transition metal catalyzed asymmetric synthesis. *N*-Monosubstituted formamides (such as BnNHCHO, *t*-BuNHCHO) were not suitable for this reaction due to their acidic protons.

Finally, the product **3** was converted to the corresponding phosphine **7** via desulfurization with Raney Ni (Eq. 4).[1] Moreover phosphine oxide **8** was also obtained via air oxidation of **7** (Eq. 4). Both are known as effective ligands for a variety of hydroformylation catalysts.[8]

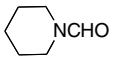
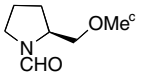



**Scheme 1.** Proposed reaction mechanism.

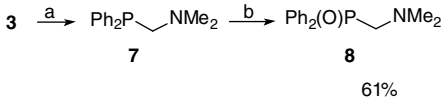
**Table 1.** Scope of the reductive coupling reaction in DMI[a]




**1** **2**

| Entry | Formamide | Yield (%) |
|---|---|---|
| 1 | $Me_2NCHO$ | 67 |
| 2 | $Et_2NCHO$ | 63 |
| 3[b] |  | 79 |
| 4[b] |  | 72 |
| 5 |  | 52 |

[a] General reaction conditions unless otherwise stated: $Ph_2P(S)H$ (1 equiv), formamide (1 equiv).
[b] 3 equiv of formamide was used.
[c] Prepared according to Ref. 7.




(4)

a. Raney Ni, EtOH, 40 °C, 90min; b. air, rt.

*N*,*N*-Disubstituted aminomethylphosphine sulfide can be synthesized by sulfurizing the corresponding phosphine[8] or by condensation of secondary phosphine sulfides with *N*-hydroxymethyldialkylamines.[9] The reductive coupling reaction, that we present here, is also expected to be a new method to prepare these compounds.

In conclusion, our results indicate that this coupling reaction between diphenylphosphine sulfide and formamides is promoted by excess sodium hydride, and that the carbon–oxygen bond is cleaved by sodium hydride. Furthermore, we hope that this reaction will be a useful methodology in the synthesis of phosphorus containing compounds.

## References and notes

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2. Hayashi, M.; Hashimoto, Y.; Yamamoto, Y.; Usuki, J.; Saigo, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 631; Hayashi, M.; Takezaki, H.; Hashimoto, Y.; Takaoki, K.; Saigo, K. *Tetrahedron Lett.* **1998**, *39*, 7529.
3. Diphenylphosphine sulfide was synthesized by sulfurizing diphenylphosphine in benzene solvent. The crude products were then purified with recrystallization from MeCN and filtration through a $CH_2Cl_2$–alumina column, according to a modified procedure reported by Semenzin, D.; Etemad-Moghadam, G.; Albouy, D.; Diallo, O.; Koenig, M. *J. Org. Chem.* **1997**, *62*, 2414.
4. An authentic sample synthesized with sulfurating (dimethylaminomethyl)diphenylphosphine was proven identical with **3** with data of GCMS, NMR, and elemental analysis. The phosphine was obtained according to Aguiar, A. M.; Hansen, A. M. *J. Org. Chem.* **1967**, *32*, 2383. (Dimethyl-

aminomethyl)diphenylphosphine sulfide **3**:[8] $^{1}$H NMR 2.29 (6H, s, Me); 3.45 (2H, d, PCHN); 7.26–7.49 (6H, m, Ph); 7.92–7.99 (4H, m, Ph); $^{31}$P NMR 35.44. Anal. Calcd for $C_{15}H_{18}NPS$: C, 65.43; H, 6.59; N, 5.09; S, 11.65. Found: C, 65.43; H, 6.67; N, 5.10; S, 11.93.

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6. General procedure for the coupling reaction in DMI: a mixture of diphenylphosphine sulfide (0.5 mmol) and formamide (0.5 mmol) was dissolved in DMI (1 mL), then sodium hydride, 60% dispension in mineral oil (5 equiv) was added in one portion. After heating at 100 °C, brine was added at rt. Then the mixture was extracted with diethyl ether. The organic layer was dried ($MgSO_4$), filtered, and evaporated. The residue was purified by column chromatography on silica gel. (Diethylaminomethyl)diphenylphosphine sulfide:[9] $^{1}$H NMR 0.85 (6H, t, Me); 2.59 (4H, q, CHMe); 3.59 (2H, d, PCHN); 7.41–7.51 (6H, m, Ph); 7.98–8.05 (4H, m, Ph); $^{31}$P NMR 36.04. Diphenyl(pyrrolidinomethyl)phosphine sulfide:[9] $^{1}$H NMR 1.66 (4H, m, CH); 2.55 (4H, m, NCH); 3.67 (2H, d, PCHN); 7.41–7.50 (6H, m, Ph); 7.91–7.98 (4H, m, Ph); $^{31}$P NMR 36.60. Diphenyl(piperidinomethyl)phosphine sulfide:[9] $^{1}$H NMR 1.35 (2H, m, $CH_2$); 1.44 (4H, m, $CH_2$); 2.39 (4H, m, NCH); 3.42 (2H, d, PCHN); 7.43–7.51 (6H, m, Ph); 7.98–8.05 (4H, m, Ph); $^{31}$P NMR 35.09. ((*S*)-2-Methoxymethylpyrrolidinomethyl)-diphenylphosphine sulfide: $^{1}$H NMR 1.37–1.43 (1H, m); 1.61–1.70 (2H, m); 1.80–1.86 (1H, m); 2.42 (1H, dd); 2.90–3.05 (1H, m); 3.10–3.30 (3H, m); 3.19 (3H, s, Me); 3.60 (1H, d); 4.40 (1H, dd); 7.44–7.50 (6H, m, Ph); 7.90–8.00 (4H, m, Ph); $^{31}$P NMR 37.20.
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