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Highly Atom-Economic One-Pot Formation of Three Different C−P Bonds: General Synthesis of Acyclic Tertiary Phosphine Sulfides

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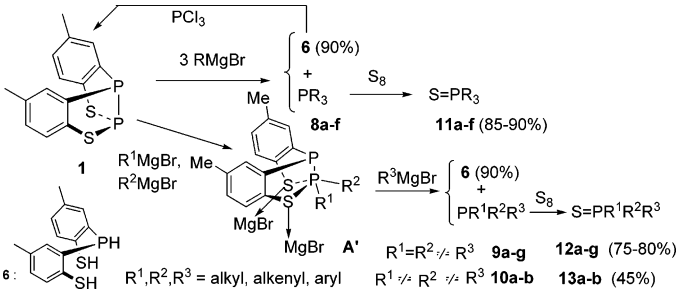

The reaction of benzothiadiphosphole **1** with an equimolar mixture of R^1MgBr and R^2MgBr gave intermediate **A′**, which, after only 4−5 min, was treated with an equimolar amount of R^3MgBr, giving the asymmetric phosphine $PR^1R^2R^3$ in 45% overall yield (75−80% yield when $R^1 = R^2$ and 85−90% yield when $R^1 = R^2 = R^3$) and the byproduct **6** in 90% yield. The treatment of **6** with PCl_3 quantitatively regenerates the starting reagent **1**. Treatment of the phosphines with elemental sulfur gave the corresponding sulfides.

Introduction

Tertiary phosphines are attracting considerable current interest due to their central role in coordination chemistry[1] and homogeneous catalysis.[2] However, the methods available for synthesizing acyclic tertiary phosphines containing different groups are long and tedious, sometimes difficult and dangerous, and in the case of tertiary asymmetric phosphines, give poor yields.[3−11] In addition, all of these procedures are made up of sequences of several reactions, some of which require forcing conditions. Although the publications on the synthesis of triaryl- or trialkylphosphines and their organic derivatives and their complexes are very numerous, the literature on the synthesis of trialkenylphosphines or alkenyl-containing phosphines is very limited. For example, trivinylphosphine was originally prepared via the Grignard method using vinylmagnesium bromide[12,13]and PCl_3

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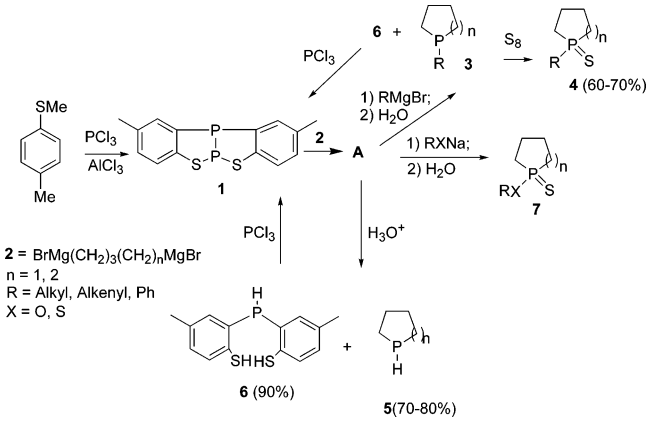
SCHEME 1

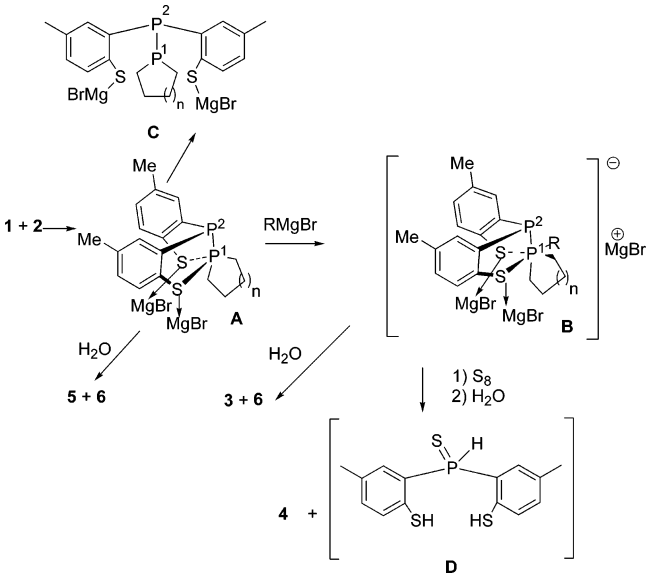


and subsequently has been synthesized via vinylsodium[14] and by a direct route from elemental phosphorus via potassium phosphide and acetylene.[15] All of these methods require controlled conditions (low temperature) but even under optimal conditions produce only low to moderate yields.[12b,13a] The tendency to produce only low to moderate yields has been attributed to the P−P coupling reactions of intermediates that form during the preparation of most tertiary phosphines with Grignard reagents.[16,17]

Recently, we reported[18] a new synthesis of tertiary cyclic phosphines **3**, and their sulfides **4**, using a reagent we developed,[19] the benzothiadiphosphole **1**, which is easily obtained by treatment of *p*-methylthioanisole with PCl_3 and $AlCl_3$ (Scheme 1). In particular, the simultaneous or the sequential addition of equimolar amounts of a bis(Grignard reagent) **2** (n = 1, 2) and a mono-Grignard reagent RMgBr (R = alkyl, phenyl, alkenyl) to 1 equiv of **1** gives tertiary cyclic phosphines **3** and, after addition of elemental sulfur, their sulfides **4** in good yields at room temperature (Scheme 1).

More recently,[20] we reported a very efficient and economic new method for the one-pot preparation of secondary cyclic phosphines **5** (five- and six-membered) in 70−80% yields. This method consists of treatment at room temperature of **1** with 1 equiv of the bis(Grignard reagent) **2**. Treatment of the resulting reaction mixture with aqueous acid then gives secondary cyclic phosphines **5** and the end product **6**, which is the residue of **1**. Treatment of **6** with PCl_3 then quantitatively and immediately regenerates the starting reagent **1**, which can be reused without further purification. The same end product **6** is found in the final reaction mixture obtained in the preparation of tertiary cyclic phosphines **3**; thus, the general synthesis of cyclic tertiary and secondary phosphines in Scheme 1 is atom economic and environmentally friendly. These results were tentatively explained by the intervention of hypervalent phosphorus intermediates[21] such as **A** and **B** (Scheme 2), the formation of which may be favored by the "dibenzo-butterfly" moiety of reagent **1**.

SCHEME 2



In the intermediate **A**, the coordination of the Mg atom to sulfur would make the P^1 atom susceptible to further attack, giving the very unstable intermediate **B** (or its isomeric forms), which immediately collapses to the final phosphinic product. It should be noted that only in the second step can a nucleophilic reagent, such as sodium alcoholate or thiolate, be used to give the corresponding 1-alkoxy cyclic phosphine derivatives **7** (Scheme 1).[22] In contrast, sodium alcoholate or thiolate cannot be used in the first step of this reaction. In fact, we found for several alcoholates (e.g., RONa) that reaction of the alcoholate with **1** did not give the corresponding phosphite $(RO)_3P$ in any appreciable amount. This observation may lend support to our hypothesis that in the first step the reaction of the bis(Grignard) reagent and **1** is not a conventional double S_N2 substitution, which would be expected to give intermediate **C**, but rather a reaction that preferentially gives the intermediate **A** with a hypervalent phosphorus atom (as reported in Scheme 2) through a pathway that might involve radical species.[23] In the intermediate **A**, the presence of an additional ring

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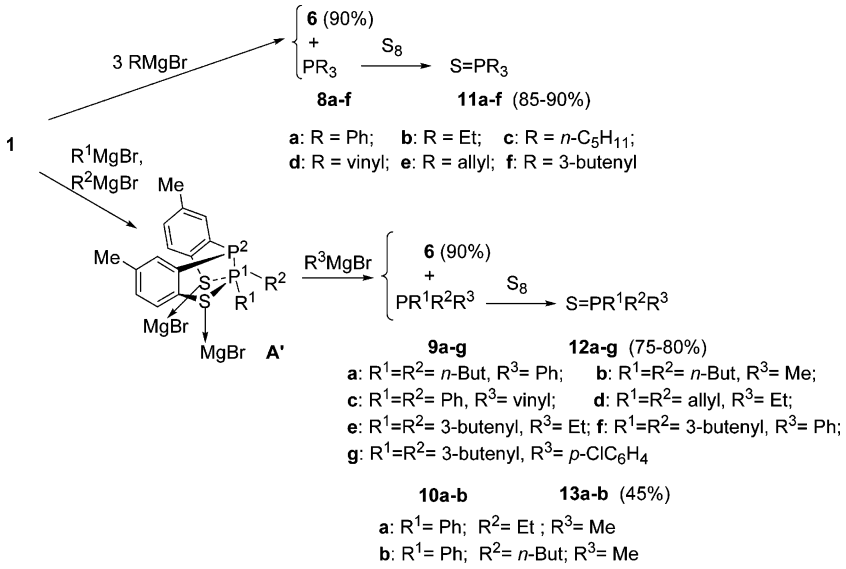
SCHEME 3



around the P^1 atom, formed by attack of the bis(Grignard) reagent, is a factor of further stability.[24] This is confirmed by the fact that when the reaction is carried out with simultaneous addition of a bis(Grignard) reagent and a mono-Grignard reagent (RMgX) in equimolar amounts, we observed almost exclusive formation of the cyclic phosphines **3** and any acyclic PR_3 which, for three simple S_N2 reactions, would be favored.

To develop further applications of this reaction, we studied the reaction of **1** with mono-Grignard reagents (RMgBr) with a view to testing the possibility that the lack of formation of an additional ring around the P^1 atom again permits the formation of hypervalent intermediates such as **A** and **B**, from which it may be possible to obtain acyclic triorganophosphines and the end product **6**.

Herein, we report the results obtained that made it possible to achieve a very simple and highly atom-economic one-pot synthesis of symmetric and unsymmetric acyclic triorganophosphines using the phosphorus atom donor reagent **1**, which can be easily reformed and recycled at the end of the reaction. It should be noted that by using this one-pot procedure, we were also able to synthesize phosphines and their sulfides containing one or more alkenylic groups without formation of any byproduct due to P−P coupling reaction, as occurs when Grignard reagents are used to obtain these tertiary phosphines.[16,17]

Results and Discussion

From the beginning of our research, we found that the reaction between **1** and mono-Grignard reagents (Scheme 3) is more complex than the corresponding reaction in which a bis-Grignard reagent is used in the first step[18,19] (Scheme 1). In fact, if we added equimolar amounts of three different mono-Grignard reagents in three successive steps, we obtained a very complex reaction mixture without appreciable formation of the corresponding tertiary phosphines $PR^1R^2R^3$. The absence of the tertiary phosphines $PR^1R^2R^3$ suggested that the reaction proceeds via an intermediate such as **A′** (Scheme 3), which can be formed when mono-Grignard reagents are used. The intermediate **A′** is expected to have a shorter lifetime than **A** because the latter molecule is stabilized by the presence of the additional ring formed by the reaction of **1** with the bis(Grignard) reagent. With this in mind, we tried various procedures in which only a very short time elapsed between the addition of the three Grignard reagents. The simplest procedure tested was the simultaneous addition of 3 mol of RMgBr. When $R^1 = R^2 = R^3$, the yields are very high, as in the synthesis of phosphines **8** (85−90% yield), which are obtained by simple addition of three moles of RMgBr to a THF solution of one mole of **1**. It should be noted that using this procedure it is possible to obtain vinyl and allyl phosphines (**8d**,**e**) in better yields and in a more facile manner than using previously reported methods.[12−15] After quenching the reaction mixture with acid (HCl) water we obtained **8** and the end product **6** in 90% yield (Scheme 3). These two compounds can be easily separated by treating the organic solution with aqueous NaOH; in this way, the sodium salt of compound **6** dissolves in the aqueous solution, whereas the organic phase contains almost pure phosphine **8**, which can be further purified by bulb-to-bulb distillation. Compound **6** can be recovered, as reported previously,[20] from the basic aqueous layer by acidification and extraction, and then transformed to **1** for reuse.

When $R^1 = R^2 \neq R^3$, a mixture of tertiary phosphines is obtained in which $P(R^1)_2R^3$ (**9**) is the most prevalent (about 45% of the mixture, from GC−MS analysis). When $R^1 \neq R^2 \neq R^3$, $PR^1R^2R^3$ (**10**) is the most prevalent product, although it is only obtained in about 23% yield; the other nine possible symmetric tertiary phoshines such as $P(R^1)_3$ or $P(R^1)_2R^2$ are obtained in smaller yields (about 3% and 11%, respectively), indicating that the reaction is driven by statistical factors and implies a contemporaneous and equiprobable attack of the three different Grignard reagents on the phosphorus atom, independent of their

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steric hindrance. This can be explained by considering the structure of **1**, which possesses a folded geometry that is very suitable for this kind of attack. This behavior, which might be named the "butterfly effect", was recently observed in the facile formation of transition metal complexes containing a "dibenzo butterfly" moiety.[25]

To increase the yield of the desired product beyond the statistical limit, we tried a second procedure in which the different RMgBr reagents were added in two steps with very short reaction times (4−5 min, to avoid the decomposition of **A′**, which is more unstable[26] than **A**) between the first and second steps. In this manner, it could be predicted, on a statistical basis, that the addition in the first step of equimolar amounts of two different Grignard reagents (R^1MgBr and R^2MgBr), followed by the addition in the second step of the third Grignard reagent (R^3MgBr) would give a final mixture containing $PR^1R^2R^3$ (50%), $P(R^1)_2R^3$ (25%), and $P(R^2)_2R^3$ (25%). In fact, when we used this two-step procedure we obtained asymmetric phosphines (**10a**,**b**) or their sulfides **13a**,**b** in 45% yield together with about 20−25% of the other symmetric phosphine sulfides, which were separated by column chromatography. In this procedure, the end product **6** can be recovered and recycled as described above. Using this one-pot two-step procedure, symmetric disubstituted phosphines **9a**−**g** (and their sulfides **12a**−**g)** were obtained in 75−80% yield. It should be noted that phosphines **8**, **9**, and **10** were analyzed only by GC-MS analysis, and were not isolated. Rather, they were immediately treated with sulfur to obtain the corresponding sulfides **11**, **12**, and **13** (Scheme 3), which are stable and thus were isolated and fully characterized.

It is worth noting that the synthesis reported herein makes it possible to obtain, in a simple one-pot procedure, sulfide derivatives of symmetric and asymmetric acyclic tertiary phosphines, also containing alkenyl groups (**11d**−**f** and **12c**−**g**); the synthesis of such compounds, which are of great interest in organic chemistry, has been previously studied only to a very limited extent.

Conclusion

In conclusion, the one-pot synthesis of symmetric and asymmetric tertiary acyclic phosphines reported herein can be achieved through a very simple, efficient, low-cost method and gives higher yields than previously reported methods. In these procedures, the byproduct **6** was recovered and transformed into the starting reagent **1**, making the process very atom-economic and environmentally friendly. It should be noted that this method can also be used to easily obtain trivinyl- or triallyl phosphines or alkenyl-containing phosphines, making this procedure a new general protocol and a very convenient, quite unique, method for the simultaneous construction of three different C−P bonds.

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(26) This hypervalent intermediate **A′** is presumably more unstable than **A** because it not contains the additional ring derived by bis-(Grignard reagent) as in **A**. For a review on the stability of hypervalent phosphorus species, see ref 24.

Experimental Section

One-Step Procedure: Synthesis of Phosphine Sulfides with Simultaneous Addition of Grignard Reagents. The three Grignard reagents (R^1MgBr, R^2MgBr, R^3MgBr, 1.2 mmol of each) were simultaneously added to a solution of benzothiadiphosphole (**1**) (1.0 mmol) in anhydrous THF under a dry nitrogen atmosphere. After 30−40 min, the solvent was partially evaporated and the reaction mixture was treated with aqueous acid solution (HCl). Extraction with CH_2Cl_2 gave a mixture of phosphines and the residue **6**. The phosphines were easily separated from **6** by treating the organic solution with aqueous NaOH; after this treatment, the sodium salt of **6** was dissolved in the aqueous solution, whereas the phosphines were in the organic phase. Treatment of this layer with a slight excess of elemental sulfur gave the corresponding sulfides, which were purified by flash chromatography and fully characterized. Compound **6**[20] was recovered (90%) from the basic aqueous layer by acidification and extraction with dichloromethane, and was then purified by distillation and stored under argon. Simple treatment of a dry solution of compound **6** with an equimolar amount of PCl_3 led to the regeneration of the starting reagent **1** in almost pure form, allowing it to be reused without further purification.

The yields of the phosphines obtained by the one-step procedure are as follows:

When $R^1 = R^2 = R^3$, phosphine sulfides (**11a**−**f**) were obtained in 85−90% yields. Triphenylphosphine (**8a**) and triethylphosphine (**8b**) and their sulfides **11a** and **11b** were characterized by comparison with physicochemical data of commercially available authentic samples. When $R^1 = R^2 \neq R^3$, the reaction mixture contains a mixture of phosphines $P(R^1)_2R^3$, $P(R^1)_3$, $PR^1(R^3)_2$, and $P(R^3)_3$ in relative proportions (calculated by GC−MS analysis) of about 45%, 29%, 23%, and 3%, respectively. When $R^1 \neq R^2 \neq R^3$, the reaction mixture contains a mixture of phosphines, in which $PR^1R^2R^3$ is the most prevalent (23% yield; calculated by GC−MS analysis). The other nine possible symmetric tertiary phosphines such as $P(R^1)_3$ or $P(R^1)_2R^2$ were present in smaller proportions (about 3% and 11%, respectively).

In these last two cases, phosphines **9** and **10** and the corresponding sulfides **12** and **13** were obtained in higher yields using the two-step procedure described below.

Two-Step procedure: Preparation of Phosphine Sulfides 12a−g and 13a,b. The first Grignard reagent (R^1MgBr, 2.4 mmol) was added to a solution of benzothiadiphosphole (**1**) (1.0 mmol) in anhydrous THF under a dry nitrogen atmosphere. After 4−5 min, the second Grignard reagent (R^2MgBr, 1.2 mmol) was added. After about 30−40 min, the reaction mixture was treated as described above for the one-step procedure. Phosphine sulfides **12a**−**g** were purified by FC and isolated in 75−80% yield. Phosphine sulfides **13a** and **13b** were obtained in 45% yield (they were easily separated from the other phosphine sulfides by FC) as described above for the preparation of compounds **12**; in this case, two different Grignard reagents, R^1MgBr (1.2 mmol) and R^2MgBr (1.2 mmol), instead of 2.4 mmol of the same organometallic, were added to **1** in the first step and the Grignard reagent R^3MgBr (1.2 mmol) was added in the second step.

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Supporting Information Available: General experimental details, full characterization data for compounds **11**, **12**, and **13**, and copies of the ^{1}H, ^{13}C, and ^{31}P NMR spectra of compounds **11b**−**f**, **12a**−**g**, and **13a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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