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Catalyst- and solvent-free bisphosphinylation of isothiocyanates: a practical method for the synthesis of bisphosphinoylaminomethanes†

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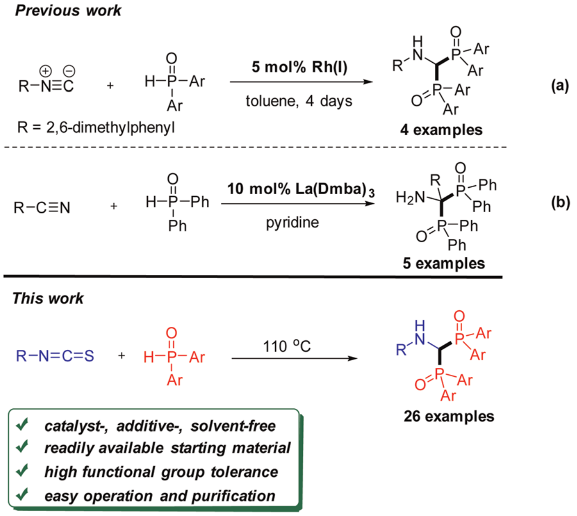
A general and convenient double addition of phosphine oxides to isothiocyanates is described. It is a practically useful protocol for the construction of bisphosphinoylaminomethanes. The reaction can be carried out smoothly under metal- and solvent-free conditions. It also features a broad substrate scope, simple operation and purification. A possible mechanism involving a tandem double nucleophilic addition/H_2S elimination/*in situ* imine reduction process is proposed.

Introduction

Organophosphorus reagents are an important class of compounds in organic synthesis, pharmaceutical chemistry, coordination chemistry, and materials science.[1] Recently, the phosphinoyl group as a directing group for C–H activation has also been reported.[2] Therefore, synthetic methods of constructing organophosphorus compounds have received great attention in the past decade.[3] Among them, bisphosphorous aminomethane derivatives have gained significant attention. Several clinical drugs containing the bisphosphorous aminomethane framework have been used to treat a variety of diseases such as hypercalcemia and osteoporosis.[4] Some derivatives are reported to possess herbicidal,[5] antibacterial,[6] and antiparasitic activities.[7] However, synthetic methods for these bisphosphorus compounds have been limited,[8] especially for bisphosphinoyl derivatives. As shown in Scheme 1a, Han *et al.* demonstrated that bisphosphinoylaminomethanes were obtained by rhodium catalysed double addition of diarylphosphine oxide to isocyanide.[9] Very recently, Schmidt *et al.* developed a lanthanum-catalyzed reaction through the bisphosphinylation of nitriles (Scheme 1b).[10] Although these protocols are efficient, they all used expensive catalysts, such as Rh and La reagents. They also have other drawbacks including a limited substrate scope and a long reaction time. Therefore, from a sustainability perspective, developing a general and environmentally benign approach for the construction of bisphosphinoylaminomethanes would be highly desirable.



Scheme 1 The synthesis of bisphosphinoylaminomethanes.

Isothiocyanates are versatile intermediates in organic synthesis. Because of their high electrophilicity, isothiocyanates could be easily trapped by many nucleophiles for constructing synthetically useful structures through the carbon–carbon and carbon–heteroatom bond formation.[11] In addition, they could also be used as nucleophiles[12] and radical receptors.[13] Recently, our group has introduced a series of convenient methods with isothiocyanates to provide sulphur-containing heterocyclic compounds.[14] As an ongoing endeavour to demonstrate the wide-ranging applications of isothiocyanates, we describe herein a new convenient protocol to synthesize bisphosphinoylaminomethanes from isothiocyanates and

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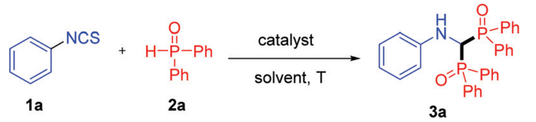
phosphine oxides under solvent-free conditions. The bis-addition of phosphine oxides to isothiocyanates could be an attractive method for the construction of the C–P bond, due to the following advantages: (1) The reaction was carried out under catalyst-, additive-, and solvent-free conditions. (2) The procedure is easy to operate, and pure products can be readily afforded by washing the crude adducts with a small amount of solvent. (3) An interesting mechanism involving a double nucleophilic addition/H_2S elimination/*in situ* imine reduction cascade is proposed.

Results and discussion

Initially, phenyl isothiocyanate **1a** and diphenylphosphine oxide **2a** were employed as model substrates for reaction condition optimization. To our delight, the reaction proceeded smoothly to afford the desired product **3a** in 45% yield in the presence of $Cu(OAc)_2$ in 1,4-dioxane at 110 °C for 6 h (Table 1, entry 1). However, no improvement was observed when other low-cost Lewis acids such as $Fe(OAc)_2$ and $Mn(OAc)_2{\cdot}4H_2O$ were examined (Table 1, entries 2 and 3). Interestingly, the yield of **3a** was increased to 53% in the absence of Lewis acid, indicating that the acid was not essential in the transformation (Table 1, entry 4). Comparable yields were obtained in other solvents such as acetonitrile, toluene, and DCE (Table 1, entries 5–7). To our surprise, the yield of **3a** was increased to 70% under solvent-free conditions (Table 1, entry 8).[15] Furthermore, the reaction also proceeded well under air (Table 1, entry 9), which makes the operation more convenient. A diminished yield was obtained when the reaction was carried out at a lower temperature (Table 1, entry 10), while a comparative yield was achieved at a higher temperature (Table 1, entry 11). Finally, the optimized procedure involved stirring **1a** and **2a** under catalyst- and solvent-free conditions at 110 °C for 6 h.

Table 1 Optimization of the reaction conditions[a]



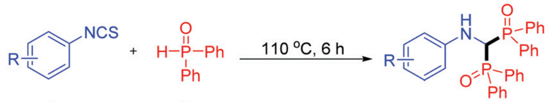
1a **2a** **3a**

Entry	Catalyst (equiv.)	Solvent	*T* [°C]	Yield[b] (%)
1	$Cu(OAc)_2$ (1.0)	1,4-Dioxane	110	45
2	$Fe(OAc)_2$ (1.0)	1,4-Dioxane	110	30
3	$Mn(OAc)_2{\cdot}4H_2O$ (1.0)	1,4-Dioxane	110	43
4		1,4-Dioxane	110	53
5		CH_3CN	110	49
6		Toluene	110	55
7		DCE	110	47
8			110	70
9[c]			**110**	**70**
10[c]			100	52
11[c]			120	68

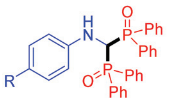
[a] Reaction conditions: **1a** (0.4 mmol), **2a** (0.8 mmol), 6 h, under a N_2 atmosphere. [b] Isolated yield based on **1a**. [c] Under air.

With the optimized conditions being established, the substrate scope of isothiocyanates **1** was explored (Table 2). Isothiocyanates bearing electron-withdrawing substituents (–COOMe, –COMe, –CN, $–CF_3$, $–NO_2$) at the *para* position of the phenyl ring all served as good substrates, and the corresponding products **3b–f** were obtained in good yields (76–87%). Substrates containing halogen groups (–F, –Cl, –Br) also transformed smoothly to products **3g–i** in good yields (74–77%), facilitating further functionalization. Whereas when isothiocyanates bearing an electron-donating group such as the methyl group and the methoxy group were employed, the products **3j** and **3k** were generated in moderate yields. These results indicate that the electronic properties of isothiocyanates play an important role in the reactions. In addition, isothiocyanates with a chloro substituent at the *ortho*- or *meta*-position of the phenyl ring could react with **2a** to afford the products **3l** and **3m** in 66% and 71% yields, respectively. It is noteworthy that the reaction also proceeded with sterically hindered *ortho* substituents, albeit with relatively lower yields (**3n** and **3o**). Moreover, the reaction was compatible with disubstituted substrates, providing the corresponding products **3p** and **3q** in good yields. A heterocycle such as pyridine was also tolerated in the reaction, and the product **3r** was isolated in 57% yield. The structures of compounds **3** were undoubtedly confirmed by the X-ray crystallographic analysis of **3o** (see the ESI, Fig. S1†). Aliphatic (methyl or cyclohexyl) isothiocya-

Table 2 Substrate scope of isothiocyanates **1** with **2a**[a,b]

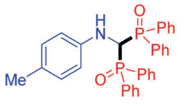


1 **2a** **3**

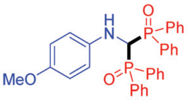


3a (70%)

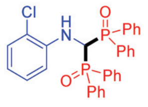
3a: R = H, 70%
3b: R = COOMe, 87%
3c: R = $COCH_3$, 83%
3d: R = CN, 76%
3e: R = CF_3, 82%
3f: R = NO_2, 78%
3g: R = F, 75%
3h: R = Cl, 74%
3i: R = Br, 77%



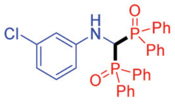
3j (55%)



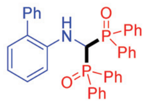
3k (57%)[c]



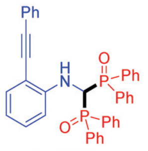
3l (66%)



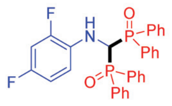
3m (71%)



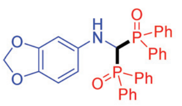
3n (48%)



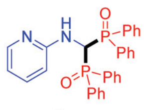
3o (56%)



3p (74%)



3q (65%)



3r[c,d] (57%)

[a] Reaction conditions: **1** (0.4 mmol), **2** (0.8 mmol). [b] Isolated yields. [c] Reactions performed at 90 °C. [d] The reaction time was 1 h.

nates were also employed under the optimized reaction conditions, however, instead of the bisphosphinylation, the *mono*-addition adducts were obtained in good yields. In addition, a similar *mono*-addition product was generated when phenyl isocyanate was used to react with **2a**.[16]

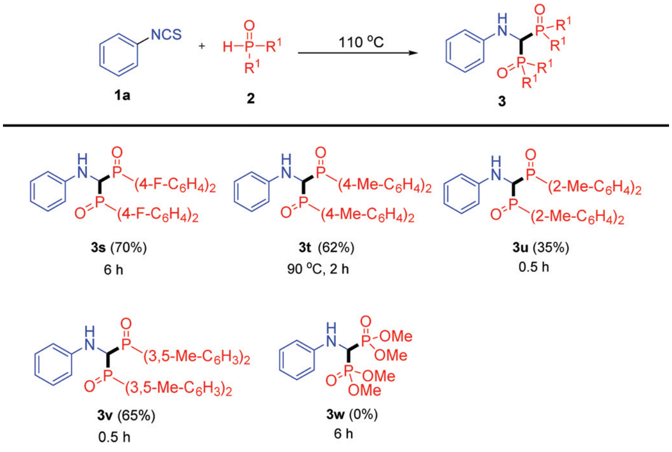
It is worth mentioning that this solvent-free protocol is operationally simple. Firstly, isothiocyanates and diphenylphosphine oxide were mixed in a 15 mL sealed tube. Then, a homogeneous solution was generated when heating the mixture to 110 °C. After completion, ethyl acetate was added to the mixture. The pure product **3** was obtained as a solid by simple filtration (see the ESI, Fig. S2†).

Having established the scope of isothiocyanates **1**, we moved on to screen the scope of P-reagents **2** (Table 3). Regardless of their electronic properties, the desired products **3s** and **3t** were afforded with good yields. The reaction also proceeded smoothly with the *ortho* methyl group on P-reagents, albeit with a lower yield (35%). In addition, the 3,5-dimethyl substrate still achieved **3v** in 65% yield. Unfortunately, no desired product **3w** was generated when dimethyl phosphonate was used.

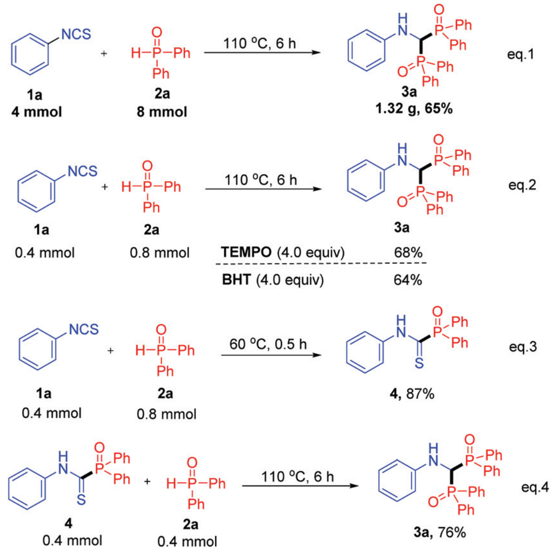
To demonstrate the practicality of this transformation, a scaled-up synthesis was performed under the standard conditions (Scheme 2, eqn (1)). The reaction of 4 mmol isothiocyanate **1a** with **2a** produced the corresponding product **3a** in 65% yield (1.32 g).

Some control experiments were conducted to elucidate the reaction mechanism. Firstly, considering that the reactions with $Ph_2P(O)H$ usually proceeded in a radical pathway, 4 equiv. of 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO) or 2,6-di-*tert*-butyl-4-methylphenol (BHT) were added to a mixture of **1a** and **2a**. The reaction was not influenced and product **3a** was isolated in 68% or 64% yield, respectively (Scheme 2, eqn (2)). These results indicated that the reaction might not proceed in a radical pathway. Remarkably, an intermediate thioamide **4** was separated in 87% yield when the reaction temperature was decreased to 60 °C (Scheme 2, eqn (3)), which smoothly converted to product **3a** under the standard conditions, confirming the hypothesis that compound **4** was an important intermediate (Scheme 2, eqn (4)).

Table 3 Substrate scope of P-reagents **2** with **1a**[a,b]



[a] Reaction conditions: **1** (0.4 mmol), **2** (0.8 mmol). [b] Isolated yields.

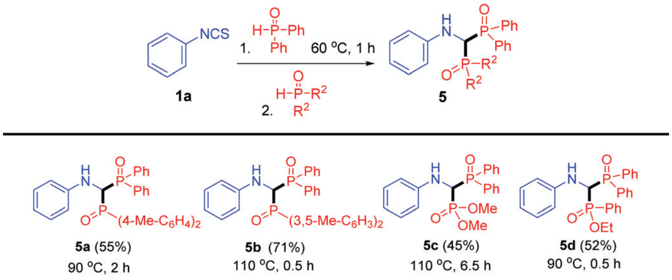


Scheme 2 Gram-scale reactions and control experiments.

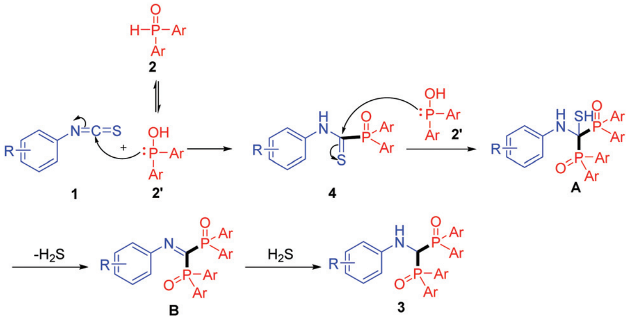
Inspired by the isolation of thioamide **4** (Scheme 2, eqn (3)), we proposed that bisphosphinoylaminomethanes **5** would be obtained with two different phosphorus reagents (Table 4). Compared to products **3**, the synthesis of bisphosphinoylaminomethane derivatives with two different P-substituents is still undeveloped. To our delight, the reactions of **1a** with two different diarylphosphine oxides were carried out smoothly, and the desired products **5a** and **5b** were generated in 55% and 71% yields, respectively. It is worth mentioning that dimethyl phosphonate and ethyl phenylphosphinate were also tolerated, and the unsymmetrical products **5c** and **5d** were generated in moderate yields.

Based on the above experimental results, a possible mechanism is proposed for this transformation. As described in Scheme 3, initially, the diarylphosphine oxide **2** can tautomerize to the P–OH form **2′**.[17] Then, thioamide **4** is formed by the

Table 4 Substrate scope of two different P-reagents **2** with **1a**[a,b]



[a] Reaction conditions: **1a** (0.4 mmol), **2a** (0.4 mmol), disubstituted phosphine oxide (0.4 mmol). [b] Isolated yields.



Scheme 3 Proposed reaction mechanism.

nucleophilic addition of **2′** to the NCS group in **1**. Next, a second nucleophilic addition[18] occurs on the C=S bond of thioamide **4** to generate intermediate **A**. Consequently, the 1,1-bisphosphorylimine **B** is produced with H_2S elimination.[19] Finally, reduction of the imine with the *in situ* generated H_2S results in the formation of bisphosphinoylaminomethane derivatives **3** with loss of sulfur element (see Fig. S5†). To the best of our knowledge, the efficient imine reduction by the *in situ* generated H_2S is unprecedented.

Conclusions

In conclusion, we have developed the first bisphosphorylation reaction of isothiocyanates. The environmentally friendly reaction proceeded smoothly in a solvent-free manner, and no extra catalysts and additives are required. A variety of bisphosphinoylaminomethanes can be readily isolated in pure form by simply washing the crude products with ethyl acetate. This protocol is very practical and easily scaled-up, which provides a direct way for the preparation of bisphosphoryl derivatives.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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18 The nucleophilic addition process was further confirmed by the Hammett correlation study. See the ESI, Fig. S3.†

19 The generation of H_2S was confirmed by using lead acetate paper. See the ESI, Fig. S4.†