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Cesium Carbonate-Promoted P-Alkylation of Phosphinecarboxamides

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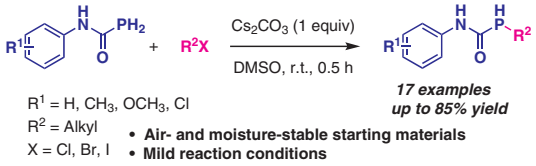

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Abstract An effective method for the P-alkylation of *N*-arylphosphinecarboxamides was demonstrated. Primary *N*-arylphosphinecarboxamides without additional protection underwent P-monoalkylation with various alkyl halides in the presence of cesium carbonate as a promoter. The reactivity of phosphinecarboxamides was also explored.

Key words alkylation, phosphinecarboxamides, arylalkylphosphinecarboxamides, secondary phosphines, alkyl halides

Organic phosphine compounds are widely used in flame-retardant materials, photoelectric materials, pharmaceutical chemistry, and organic synthesis.[1] Therefore, the preparation of organophosphorus compounds is considered one of the most important research topics in the field of organic synthesis. Jupp and Goicoechea conducted a series of studies on the synthesis and properties of urea analogue phosphinecarboxamides,[2] including the synthesis of (phosphino)carbonyl amino acids,[3] *N*-(prop-2-yn-1-yl)phosphinecarboxamides, and phosphorus-containing heterocycles. These novel compounds might ultimately be used for the synthesis of chiral phosphines or as precursors to polymeric materials.[4] The coordination chemistry of phosphinecarboxamides, which have similar electronic properties to those of PH_3 and of trialkyl phosphites, has also been investigated.[5] In the chemical vapor deposition synthesis of zinc phosphide thin films, phosphinecarboxamide is a safer and more efficient precursor than highly toxic, corrosive, and flammable phosphine, which was previously used.[6]

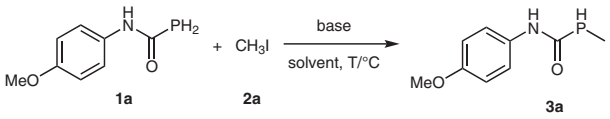
Generally, primary phosphines can be used as starting materials for the synthesis of secondary phosphines by P-alkylation; for example, BuLi has been used to achieve deprotonation in the alkylation of primary phosphines.[7] However, primary phosphines (or phosphanes) are typically extremely air-sensitive, pyrophoric, noxious, and toxic.[8] Furthermore, stoichiometry is important, because overalkylation is common in these reactions. To avoid these difficulties, phosphine–borane complexes, which are inert toward moisture and air, have been used.[9] Although alkylation of these compounds can be more easily controlled than that of the nonadducts, secondary amines needed to be used to deprotect and release the free phosphine from the adduct.[10] Compared with general primary alkyl- or arylphosphines,[11] phosphinecarboxamides are relatively stable to air and moisture, and they have low toxicity and are safe and nonflammable. On the basis of the properties of phosphinecarboxamides, and the synthesis of *N*-arylphosphinecarboxamides by our group,[12] it became necessary to explore the reactivity of *N*-arylphosphinecarboxamides.

Here, we report a chemoselective method for the direct P-monoalkylation of *N*-arylphosphinecarboxamides with a broad range of alkyl halides by using Cs_2CO_3 as base. We also investigated the reaction of *N*-arylphosphinecarboxamides with some nucleophilic reagents, such as morpholine or thiophenol.

Initially, *N*-(4-methoxyphenyl)phosphinecarboxamide (**1a**) and iodomethane (**2a**) were used as model substrates to explore the optimal reaction conditions (Table 1). In the absence of a base, no reaction occurred in DMSO at room temperature after 0.5 hours (Table 1, entry 1). A 23% yield of the P-monoalkylation product **3a** was isolated when K_2CO_3 (1 equiv) was added as a base (entry 2). A short survey of bases indicated that Cs_2CO_3 performed most efficiently in this transformation (entries 3–6). We then screened various solvents, and found that DMSO was the most suitable solvent for this transformation (entries 7–10). Heating the reaction led to a decreased yield of product **3a** (entry 11), possibly as a result of the instability of the phosphinecar-

boxamide at the higher temperature. Prolonging reaction times led to a slight lowering of the yield of the reaction (entry 12).

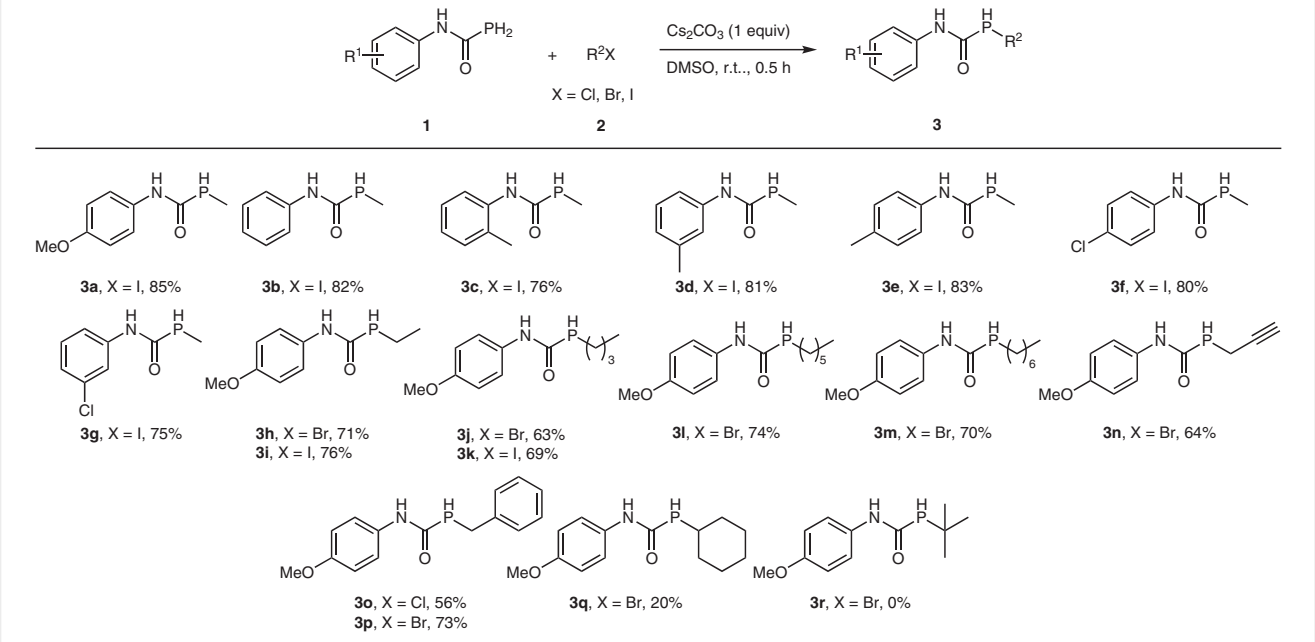
Table 1 Optimization of Reaction Conditions[a]



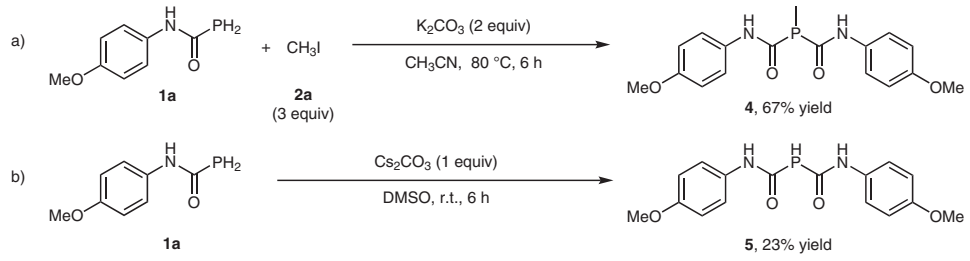
Entry	Base	Solvent	Yield[b] (%)
1	–	DMSO	–[c]
2	K_2CO_3	DMSO	23
3	K_3PO_4	DMSO	43
4	Cs_2CO_3	DMSO	85
5	Et_3N	DMSO	15
6	DBU	DMSO	64
7	Cs_2CO_3	DMF	53
8	Cs_2CO_3	acetone	60
9	Cs_2CO_3	*i*-PrOH	34
10	Cs_2CO_3	MeCN	70
11[d]	Cs_2CO_3	DMSO	50
12[e]	Cs_2CO_3	DMSO	66

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol, 1.2 equiv), base (0.2 mmol), solvent (4.0 mL), r.t., 0.5 h.
[b] Yields of isolated product
[c] NR = no reaction.
[d] This reaction was conducted at 60 °C.
[e] This reaction was conducted for 12 h.

Having determined the optimal conditions (Table 1, entry 4), we examined the scope and limitations of this method (Scheme 1).[13] First, the reactions of a series of *N*-arylphosphinecarboxamides were evaluated with iodomethane as a methylating reagent. *N*-Arylphosphinecarboxamide bearing an electron-rich methyl or methoxy group afforded the desired products **3a–e** smoothly in yields of 76–85%. The slightly lower yield of the *ortho*-methyl-substituted *N*-arylphosphinecarboxamide **3c** indicated that the reaction was slightly sensitive to a steric effect in the *N*-arylphosphinecarboxamide. In the same way, this reaction was also applicable to *N*-arylphosphinecarboxamides bearing electron-withdrawing substituents, and the products **3f** and **3g** were obtained in high yields of 80 and 75%, respectively. Next, the reactions of a series of alkyl halides **2** were evaluated. Under the standard conditions, several primary alkyl bromides or iodides (1-bromoethane, 1-iodoethane, 1-bromobutane, 1-iodobutane, 1-bromohexane, and 1-bromoheptane) reacted with **1** (R^1 = 4-MeO) to afford the desired secondary phosphines **3h–m** in yields of 63–76%. Activated alkyl halides (benzyl chloride, benzyl bromide, or propargyl bromide) afforded the desired products **3n–p** in yields of 56–73%. The yield was affected by the activity of the benzyl halide (**3o** versus **3p**). Disappointingly, cyclohexyl bromide gave only a 20% isolated yield of the P-monoalkylated product **3q**, and the introduction of a sterically hindered substituent, for example in 2-bromo-2-methylpropane, resulted in failure to obtain the corresponding product, possibly due to a detrimental steric effect.



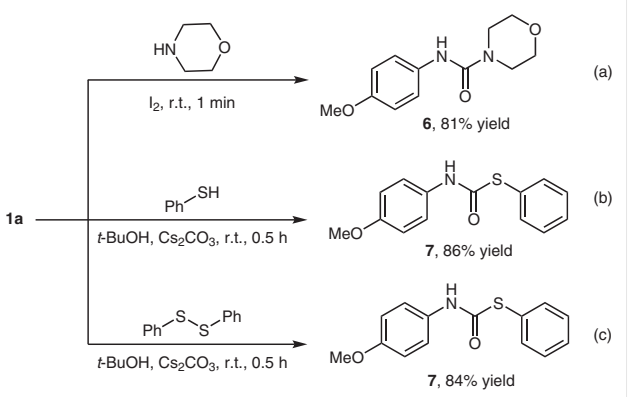
Scheme 1 Substrate scope for the reaction of *N*-arylphosphinecarboxamides with alkyl halides



Scheme 2 Control experiments

When we used an excess of iodomethane in an attempt to obtain the dimethylated product under the standard conditions (2.0 equiv Cs_2CO_3 as a base and DMSO as the solvent at room temperature), the expected dimethylated product was not formed, but a small amount of product **4** (12% yield) together with the major product **3a** (61% yield) were obtained. We explored various reaction conditions in an attempt to improve the yield of product **4** and, finally, we found that product **4** could be obtained in 67% yield by using 2.0 equivalents of K_2CO_3 as a base and MeCN as the solvent at 80 °C [Scheme 2(a)]. We found that when no methyl iodide was added, **2a** reacted with itself in the presence of Cs_2CO_3 (1 equiv) as base and DMSO as solvent to form the biuret [$NH(CONH_2)_2$] analogue **5** [Scheme 2(b)].[14] This result was similar to one previously reported,[15] and other related anionic species, such as $[P(CO_2Me)_2]^-$, generated by using a different synthetic protocol, have previously been reported.[16]

Because no thorough study has been made of the chemical properties of *N*-arylphosphinecarboxamides, it is necessary to report some of the properties we found in the following experiments, which should be helpful in further researches on *N*-arylphosphinecarboxamides. The I_2-promoted substituted reaction of **1a** with morpholine (1 equiv) resulted in the formation of *N*-(4-methoxyphenyl)morpholine-4-carboxamide (**6**) [Scheme 3(a)]. Similarly, the reaction of **1a** with thiophenol or diphenyl disulfide gave the P-substituted product *S*-phenyl (4-methoxyphenyl)thiocarbamate (**7**) [Schemes 3(b) and 3(c)]. We therefore believe that an addition–elimination process occurred in which the carbonyl site of the phosphoramide was easily attacked by the nucleophiles, with removal of phosphorus in the form of PH_3.



Scheme 3 The reaction of phosphinecarboxamide **1a** with the nucleophilic reagents morpholine, thiophenol, and diphenyl disulfide

In summary, we have established an efficient and chemoselective Cs_2CO_3-promoted method for the direct P-monoalkylation of primary phosphinecarboxamides with alkyl halides in the absence of additives or catalysts, permitting the preparation of a range of secondary phosphines in good yields. The reaction has the advantages of mild reaction conditions, starting materials that are stable to air and moisture, and short reaction times. Meanwhile, we found that nucleophilic reagents, such as morpholine, thiophenol, and diphenyl disulfide, readily attack the carbonyl group of *N*-arylphosphinecarboxamides, resulting in an addition–elimination reaction to form ureas or thiocarbamates. These studies have implications in relation to the exploration of the reactivity of phosphinecarboxamides.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611364.

References and Notes

(1) (a) De Clercq, E. *Med. Res. Rev.* **2011**, *31*, 118. (b) Katti, K. V.; Gali, H.; Smith, C. J.; Berning, D. E. *Acc. Chem. Res.* **1999**, *32*, 9. (c) Queffélec, C.; Petit, M.; Janvier, P.; Knight, D. A.; Bujoli, B. *Chem. Rev.* **2012**, *112*, 3777. (d) McManus, H. A.; Guiry, P. J. *Chem. Rev.* **2004**, *104*, 4151. (e) Weber, L. *Angew. Chem. Int. Ed.* **2002**, *41*, 563; *Angew. Chem.* **2002**, *114*, 583. (f) Fleming, J. T.; Higham, L. J. *Coord. Chem. Rev.* **2015**, *297*, 127. (g) Meeuwissen,

J.; Detz, R.; Sandee, A. J.; de Bruin, B.; Siegler, M. A.; Spek, A. L.; Reek, J. N. H. *Eur. J. Inorg. Chem.* **2010**, 2992. (h) Clarke, T. P.; Landis, C. R. *Tetrahedron: Asymmetry* **2004**, *15*, 2123.
(2) Jupp, A. R.; Goicoechea, J. M. *J. Am. Chem. Soc.* **2013**, *135*, 19131.
(3) Faria, E. N.; Jupp, A. R.; Goicoechea, J. M. *Chem. Commun.* **2017**, *53*, 7092.
(4) Robinson, T. P.; Goicoechea, J. M. *Chem. Eur. J.* **2015**, *21*, 5727.
(5) Geeson, M. B.; Jupp, A. R.; McGrady, J. E.; Goicoechea, J. M. *Chem. Commun.* **2014**, *50*, 12281.
(6) Beddoe, S. V. F.; Cosham, S. D.; Kulak, A. N.; Jupp, A. R.; Goicoechea, J. M.; Hyett, G. *Dalton Trans.* **2018**, *47*, 9221.
(7) Quin, L. D. *A Guide to Organophosphorus Chemistry*; Wiley-Interscience: New York, **2000**.
(8) (a) Higham, L. J. In *Phosphorus Compounds: Advanced Tools in Catalysis and Material Sciences*; Peruzzini, M.; Gonsalvi, L., Ed.; Springer: Dordrecht, **2011**, Chap. 1, 1.
(9) Imamoto, T.; Oshiki, T.; Onozawa, T.; Kusumoto, T.; Sato, K. *J. Am. Chem. Soc.* **1990**, *112*, 5244.
(10) (a) Lebel, H.; Morin, S.; Paquet, V. *Org. Lett.* **2003**, *5*, 2347. (b) Blank, N. F.; McBroom, K. C.; Glueck, D. S.; Kassel, W. S.; Rheingold, A. L. *Organometallics* **2006**, *25*, 1742. (c) Anderson, B. J.; Guino-o, M. A.; Glueck, D. S.; Golen, J. A.; DiPasquale, A. G.; Liable-Sands, L. M.; Rheingold, A. L. *Org. Lett.* **2008**, *10*, 4425.
(11) Stewart, B.; Harriman, A.; Higham, L. J. *Organometallics* **2011**, *30*, 5338.
(12) Wu, Y.-H.; Li, Z.-F.; Wang, W.-P.; Wang, X.-C.; Quan, Z.-J. *Eur. J. Org. Chem.* **2017**, 5546.
(13) **Phosphinecarboxamides 3a–q; General Procedure**
The appropriate *N*-arylphosphinecarboxamide **1** (0.2 mmol) and haloalkane **2** (0.24 mmol, 1.2 equiv) were added to a sealed tube charged with a mixture of Cs_2CO_3 (0.2 mmol, 1 equiv) in DMSO (4 mL), and the resulting mixture was stirred at r.t. for 0.5 h. When the reaction was complete (TLC), H_2O (30 mL) was added and the mixture was extracted with EtOAc. The organic phase was separated, dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by column chromatography [silica gel, PE–EtOAc (4:1)].
***N*-(4-Methoxyphenyl)-1-methylphosphinecarboxamide (3a)**
White solid; yield: 33 mg (85%); mp 75–76 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.69 (s, 1 H), 7.39 (d, *J* = 8.4 Hz, 2 H), 6.81 (d, *J* = 8.4 Hz, 2 H), 4.02 (dq, *J* = 206.4, 7.8 Hz, 1 H), 3.76 (s, 3 H), 1.36 (dd, *J* = 7.2, 3.0 Hz, 3 H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 176.67 (d, *J* = 14.6 Hz), 156.48, 131.01 (d, *J* = 4.1 Hz), 121.80, 114.09, 55.44, 1.10 (d, J_{C-P} = 8.1 Hz, PCH_3). ^{31}P NMR (162 MHz, $CDCl_3$): δ = –74.42. HRMS(ESI): *m/z* [M + H]$^+$ Calcd for $C_9H_{13}NO_2P$: 198.0678; Found: 198.0679.
(14) Wiedemann, G. *Ann. Phys. Chem.* **1848**, *150*, 67.
(15) Jupp, A. R.; Trott, G.; Payen de la Garanderie, É.; Holl, J. D. G.; Carmichael, D.; Goicoechea, J. M. *Chem. Eur. J.* **2015**, *21*, 8015.
(16) Becker, G.; Hübler, K.; Niemeyer, M.; Seidler, N.; Thinus, B. *Z. Anorg. Allg. Chem.* **1996**, *622*, 197.