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A Novel and Convenient Method for Synthesis of Carbamoyl and Thiocarbamoyl Phosphonates

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ABSTRACT: *A simple, efficient, and general method has been developed for the synthesis of carbamoyl and thiocarbamoyl phosphonic esters using $CaCl_2$ as an efficient Lewis base catalyst. Carbamoyl and thiocarbamoyl phosphonic esters were obtained in good yield (37%–65%) and purity under mild conditions by the reaction of diethyl phosphite with isocyanates and isothiocyanates in the presence of $CaCl_2$. This method is easy, rapid, and good-yielding reaction for the synthesis of carbamoyl and thiocarbamoyl phosphonic esters.* © 2009 Wiley Periodicals, Inc. Heteroatom Chem 20:250–253, 2009; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20538

INTRODUCTION

Phosphorus-carbon bond formation has attracted growing attention due to their novel application in organic synthesis and bio-organic chemistry. α-Functionalized phosphonic acids are valuable intermediates for the preparation of medicinal compounds and synthetic intermediates [1–5]. Among α-functional phosphonic acids, carbamoylphosphonates are important class of compounds that exhibit a variety of interesting and useful properties. Recently, carbamoylphosphonates have been reported as a new zinc-binding group for selective matrix metalloproteinases (MMP) inhibitors [6,7]. In contrast to the widely studied α-functional phosphonic acid derivatives [8–12], relatively few papers have reported on the chemistry of carbamoylphosphonates, although there is evidence that carbamoylphosphonates are pharmaceutically active [13–16]. The base-catalyzed reaction of dialkyl phosphite with isocyanates and isothiocyanates by alkali metals or their alkoxides has been reported in the literature for the preparation of carbamoylphosphonates [17,18]. The Arbuzov reaction of cabamoyl chlorides with trialkyl phosphite also reported as an applicable method for the preparation carbamoylphosphonates [19]. However, these highly reactive reagents suffer from high toxicity and low selectivity that limit its general use. Recently, phosphonoformylation of primary amine by triethyl phosphonothiolformate has been reported as a novel method for the synthesis of carbamoylphosphonates [6].

In recent years, the development of a more economical and environment friendly conversion processes has gaining interest. Calcium chloride is inexpensive, commercially available and has recently been shown to act as a very excellent Lewis base catalyst in organic transformation [20–22]. In continuation of our interest in developing novel methodologies for the synthesis of organophosphorous compounds [23–31], herein we report an efficient, practical, environmentally benign, and good yielding method for the synthesis of carbamoylphosphonates from isocyanates and isothiocyanates.

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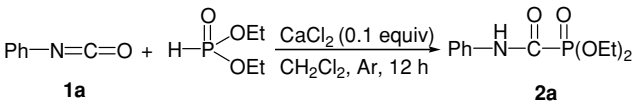
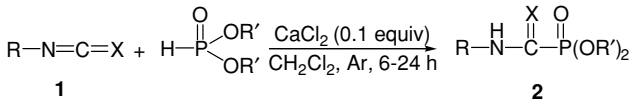


1a **2a**

SCHEME 1 Synthesis of diethyl anilinocarbonylphosphonate from phenylisocyanates.



1 **2**

X=O, S

SCHEME 2 Synthesis of carbamoyl and thiocarbamoylphosphonates.

RESULTS AND DISCUSSION

Initially, we have carried out the reaction of phenyl isocyanate, as a model compound, with diethyl phosphite in the presence of calcium chloride as a catalyst in a variety of solvents. Conversion of phenyl isocyanate to corresponding carbamoylphosphonate was generally completed in chlorinated solvents compared with protic solvents such as methanol and ethanol. We found that reaction of phenyl isocyanate with diethyl phosphite for 12 h in dichloromethane gave diethyl phenyl carbamoylphosphonate in 65% yield (Scheme 1).

In the absence of any catalyst, phenyl isocyanate did not undergo the conversion reaction with diethyl phosphite in dichloromethane at room temperature for 48 h.

To study the scope and limitation of the reaction, various isocyanates and isothiocyanates were subjected to treatment with dialkyl phosphite in the presence of calcium chloride in dichloromethane at room temperature. As shown in Scheme 2 and Table 1, the reaction of a mixture of aromatic and aliphatic isocyanates with diethyl phosphite in dichloromethane at room temperature under Ar atmosphere afforded the corresponding carbamoylphosphonates in good yields (**2a–2c**). The reactions also proceeded with isothiocyanates using calcium chloride as catalyst to give corresponding thiocarbamoylphosphonates in moderate to good yield (**2d–2g**). Dibenzyl phosphite also reacted with isocyanates and isothiocyanates to give corresponding phosphonates in good yields (**2h–2j**). The reactions were clean with no tar formation (Scheme 2). Some of the carbamoylphosphonates prepared by this method have been used as MMP inhibitors [6,7].

In summary, simple work-up, fast reaction rates, mild reaction conditions, good yields, and the relatively clean reactions with no tar formation make this method an attractive and a useful contribution to present methodologies. Indeed, a wide range of isocyanates and isothiocyanates were converted into the corresponding carbamoyl and thiocarbamoyl phosphonates using this method.

EXPERIMENTAL

Chemicals were either prepared in our laboratories or purchased from Merck, Fluka, and Aldrich Chemical Companies. NMR spectra were taken with a 250 Brucker Avance instrument with the chemical shifts being reported as δ ppm and couplings expressed in hertz. Silica gel column chromatography was carried out with Silica gel 100 (Merck no. 10184).

*General Procedure for the Synthesis of Carbamoyl and Thiocarbamoyl Phosphonates from Isocyanates and Isothiocyanates (**2**)*

Calcium chloride (0.25 mmol) was added to a stirred mixture of dialkylphosphite (3 mmol) in

TABLE 1 Synthesis of Carbamoyl and Thiocarbamoylphosphonates from Isocyanates and Isothiocyanates in the Presence of Dialkyl Phosphite Using Calcium Chloride as Catalyst

Product	*R*	*X*	*R′*	*Reaction Time (h)*	*Yield (%)*[a]
2a	C_6H_5-	O	Et–	12	65
2b	4-Me-3-ClC_6H_3-	O	Et–	12	55
2c	Cyclohexyl	O	Et–	18	62
2d	C_6H_5-	S	Et–	24	45
2e	*p*-$NO_2C_6H_4-$	S	Et–	6	56
2f	*p*-$CH_3C_6H_4-$	S	Et–	12	52
2g	Ph-CH_2-CH_2-	S	Et–	18	61
2h	Cyclohexyl	O	$PhCH_2-$	12	60
2i	Ph-CH_2-	O	$PhCH_2-$	12	58
2j	C_6H_5-	S	$PhCH_2-$	24	37

[a]Conversions were monitored by TLC analysis.
[b]Yields refer to the isolated pure products after column chromatography.

dichloromethane (5 mL) at room temperature. Isocyanate or isothiocyanate (2.5 mmol) was added to the reaction mixture, and the mixture was stirred for 6–24 h at room temperature under Ar atmosphere. Evaporation of the mixture under reducing pressure gave oily mixture. The oily mixture residue was purified by column chromatography on alumina (hexane/EtOAc = 5:1) to give pure product in 37%–65% yield. All products gave satisfactory spectral data in accordance with the assigned structures and literature reports.

*Diethyl anilinocarbonylphosphonate (**2a**)* [17]. ^{1}H NMR (250 MHz, $CDCl_3$): 1.37 (t, 6H, $J = 7.0$ Hz), 4.15–4.38 (m, 4H), 7.15 (t, 1H, $J = 7.2$ Hz), 7.33 (t, 2 H, $J = 7.5$ Hz), 7.67 (d, 2H, $J = 7.5$ Hz), 9.39 (s, 1H, NH). ^{31}P NMR (101.2 MHz, $CDCl_3$, H_3PO_4): −1.26 ppm;

*Diethyl [(3-Chloro-4-methylphenyl)amino] carbonylphosphonate(**2b**)*. ^{1}H NMR (250 MHz, $CDCl_3$): 1.39 (t, 6H, $J = 7.0$ Hz), 2.33 (s, 3H), 4.18–4.40 (m, 4H), 7.18 (d, 1H, $J = 8.25$ Hz), 7.49 (d, 1H, $J = 8.25$ Hz), 7.81 (s, 1H), 9.48 (s, NH). ^{31}P NMR (101.2 MHz, $CDCl_3$, H_3PO_4): −1.58 ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): 16.2 (d, $J_{PC} = 5.7$ Hz), 19.6, 64.7 (d, $J_{PC} = 6.9$ Hz), 118.5, 120.8, 131.0, 133.2, 134.5, 135.5 (d, $J_{PC} = 13.8$ Hz), 164.2 (d, $J_{PC} = 227.7$ Hz). Anal. Calcd for $C_{12}H_{17}ClNO_4P$. C, 47.20; H, 5.62; N, 4.59. Found: C, 46.95; H, 5.52; N, 4.39.

*Diethyl (Cyclohexylamino)carbonylphosphonate (**2c**)* [13]. ^{1}H NMR (250 MHz, $CDCl_3$): 1.05–1.95 (m, 16H), 3.70–3.85 (m, 1H), 4.05–4.30 (m, 4H), 6.90–7.10 (br, 1H, NH). ^{31}P-NMR (101.2 MHz, $CDCl_3$, H_3PO_4): −0.24 ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): 16.2 (d, $J_{PC} = 6.3$ Hz), 24.7, 25.2, 32.6, 48.5 (d, $J_{PC} = 6.9$ Hz), 64.2 (d, $J_{PC} = 6.3$ Hz), 165.5 (d, $J_{PC} = 224.3$ Hz).

*Diethyl Anilinocarbonothioylphosphonate (**2d**)* [16]. ^{1}H NMR (250 MHz, $CDCl_3$): 1.39 (t, 6H, $J = 7.0$ Hz), 4.15–4.38 (m, 4H), 7.28 (t, 1H, $J = 7.2$ Hz), 7.46 (t, 2H, $J = 7.5$ Hz), 7.98 (d, 2H, $J = 7.5$ Hz), 10.50–10.70 (br, 1H, NH). ^{31}P NMR (101.2 MHz, $CDCl_3$, H_3PO_4): −1.05 ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): 16.3 (d, $J_{PC} = 6.3$ Hz), 65.3 (d, $J_{PC} = 7.5$ Hz), 122.0, 127.5, 129.1, 137.9 (d, $J_{PC} = 15.7$ Hz), 193.5 (d, $J_{PC} = 185.3$ Hz).

*Diethyl [(4-Nitrophenyl)amino]carbonothioylphosphonate (**2e**)*. ^{1}H NMR (250 MHz, $CDCl_3$): 1.39 (t, 6H, $J = 7.0$ Hz), 4.10–4.38 (m, 4H), 8.15–8.35 (m, 4H), 10.90–11.10 (br, 1H, NH). ^{31}P NMR (101.2 MHz, $CDCl_3$, H_3PO_4): −2.21 ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): 16.20 (d, $J_{PC} = 6.3$ Hz), 65.7 (d, $J_{PC} = 6.3$ Hz), 121.8, 124.8, 129.8, 147.2, 192.8 (d, $J_{PC} = 186.7$ Hz). Anal. Calcd for $C_{11}H_{15}N_2O_5PS$. C, 41.50; H, 4.75; N, 8.80. Found: C, 41.35; H, 4.63; N, 8.52.

*Diethyl [(4-Methylphenyl)amino]carbonothioylphosphonate (**2f**)*. ^{1}H NMR (250 MHz, $CDCl_3$): 1.39 (t, 6H, $J = 7.0$ Hz), 2.37 (s, 3H), 4.20–4.38 (m, 4H), 7.23 (d, 1H, $J = 7.5$ Hz), 7.85 (d, 1H, $J = 7.5$ Hz), 10.40–10.60 (br, 1H, NH). ^{31}P NMR (101.2 MHz, $CDCl_3$, H_3PO_4): −0.84 ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): 16.2 (d, $J_{PC} = 6.3$ Hz), 21.2, 65.3 (d, $J_{PC} = 6.3$ Hz), 121.9, 127.5, 129.1, 137.6 (d, $J_{PC} = 15.7$ Hz), 192.3 (d, $J_{PC} = 186.4$ Hz). Anal. Calcd for $C_{12}H_{18}NO_3PS$. C, 50.61; H, 6.32; N, 4.88. Found: C, 50.50; H, 6.20; N, 4.71.

*Diethyl [(2-Phenylethyl)amino]carbonothioylphosphonate (**2g**)*. ^{1}H NMR (250 MHz, $CDCl_3$): 1.31 (t, 6H, $J = 7.0$ Hz), 3.00 (t, 2H, $J = 7.5$ Hz), 3.85–4.05 (m, 2H), 4.10–4.35 (m, 4H), 7.10–7.45 (m, 5H), 9.40–9.60 (br, 1H, NH). ^{31}P NMR (101.2 MHz, $CDCl_3$, H_3PO_4): −1.13 ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): 16.2 (d, $J_{PC} = 6.3$ Hz), 33.4, 46.1 (d, $J_{PC} = 8.8$ Hz), 65.0 (d, $J_{PC} = 6.3$ Hz), 126.8, 128.7, 129.8, 137.9, 192.5 (d, $J_{PC} = 181.1$ Hz). Anal. Calcd for $C_{13}H_{20}NO_3PS$. C, 51.81; H, 6.69; N, 4.65. Found: C, 51.65; H, 6.42; N, 4.60.

*Dibenzyl (Cyclohexylamino)carbonylphosphonate (**2h**)*. ^{1}H NMR (250 MHz, $CDCl_3$): 1.05–1.45 (m, 5H), 1.50–1.95 (m, 5H), 3.60–3.90 (m, 1H), 5.15 (dd, 4H, $J_{HH} = 2.2$ Hz and $J_{HP} = 8.25$ Hz), 6.80–6.90 (br, 1H, NH), 7.35 (s, 10H). ^{31}P NMR (101.2 MHz, $CDCl_3$, H_3PO_4): −0.29 ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): 24.7, 25.2, 32.5, 48.6 (d, $J_{PC} = 6.9$ Hz), 69.5 (d, $J_{PC} = 6.9$ Hz), 128.1, 128.7, 128.6, 135.3 (d, $J_{PC} = 6.3$ Hz), 164.3 (d, $J_{PC} = 223.3$ Hz). Anal. Calcd for $C_{21}H_{26}NO_4P$. C, 65.09; H, 6.77; N, 3.62. Found: C, 64.85; H, 6.58; N, 3.60.

*Dibenzyl (Benzylamino)carbonylphosphonate (**2i**)*. ^{1}H NMR (250 MHz, $CDCl_3$): 4.43 (d, 2H, $J = 5.5$ Hz) (m, 1H), 5.15 (dd, 4H, $J_{HH} = 1.75$ and $J_{HP} = 8.25$ Hz), 7.35 (s, 10H), 7.50–7.80 (br, 1H, NH). ^{31}P NMR (101.2 MHz, $CDCl_3$, H_3PO_4): −0.70 ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): 43.3 (d, $J_{PC} = 8.2$ Hz), 69.7 (d, $J_{PC} = 6.9$ Hz), 127.8, 128.0, 128.2, 128.6, 128.8, 135.2, 135.3, 136.7, 165.3 (d, $J_{PC} = 225.2$ Hz). Anal. Calcd for $C_{22}H_{22}NO_4P$. C, 66.81; H, 5.61; N, 3.54. Found: C, 66.60; H, 5.45; N, 3.38.

*Dibenzyl Anilinocarbonothioylphosphonate (**2j**)*. ^{1}H NMR (250 MHz, $CDCl_3$): 5.20–5.33 (m, 4H), 7.25–7.47 (m, 13H), 7.89 (d, 2H, $J = 8.0$ Hz), 10.35–10.60

(br, 1H, NH). ^{31}P NMR (101.2 MHz, $CDCl_3$, H_3PO_4): −1.80 ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): 70.8 (d, $J_{PC} = 6.4$ Hz), 122.0, 128.2–129.1 (m, Ar), 137.8 (d, $J_{PC} = 15.5$ Hz), 191.5 (d, $J_{PC} = 181.3$ Hz). Anal. Calcd for $C_{21}H_{20}NO_3PS$. C, 63.46; H, 5.07; N, 3.53. Found: C, 63.55; H, 4.90; N, 3.37.

REFERENCES

[1] Engel, R. Chem Rev 1977, 77, 349.
[2] Kaboudin, B. Phosphorus Sulfur Silicon Relat Elem 2002, 177, 1749.
[3] Afarinkia, K.; Rees, C. W. Tetrahedron 1990, 46, 7175.
[4] Kaboudin, B.; Haghighat, H.; Yokomatsu, T. J Org Chem 2006, 71, 6604.
[5] Blazis, V. J.; Koeller, K. J.; Spilling, C. D. J Org Chem 1995, 60, 931.
[6] Farkas, E.; Katz, Y.; Rhusare, S.; Reich, R.; Roschenthaler, G.-V.; Konigsmann, M.; Breuer, E. J Biol Inorg Chem 2004, 9, 307.
[7] Breuer, E.; Salomon, C. J.; Katz, Y.; Chen, W.; Lu, S.; Roschenthaler, G.-V.; Hadar, R.; Reich, R. J Med Chem 2004, 47, 2826.
[8] Yokomatsu, T.; Yamagishi, T.; Shibuya, S. Tetrahedron: Asymmetry 1993, 4, 1779.
[9] Kaboudin, B.; Rahmani, A. Synthesis 2003, 2705.
[10] Kukhar, V. P.; Hudson, H. R. (Eds.). Aminophosphonic and Aminophosphinic Acids: Chemistry and Biological Activity; Wiley: Chichester, UK, 2000.
[11] For a review, see: Collinsová, M.; Jirácek, J. Curr Med Chem 2000, 7, 629.
[12] Matziari, M.; Georgiadis, D.; Dive, V.; Yiotakis, A. Org Lett 2001, 3, 659.
[13] Breuer, E.; Katz, Y.; Hadarb, R.; Reich, R. Tetrahedron: Asymmetry 2004, 15, 2415.
[14] Skarpos, H.; Vorobeva, D. V.; Osipov, S. N.; Odinets, I. L.; Breuer, E.; Roschenthaler, G.-V. Org Biomol Chem 2006, 4, 3669.
[15] Canac, Y.; Aniol, G. E.; Conejero, S.; Donnadieu, B.; Bertrand, G. Eur J Inorg Chem 2006, 5076.
[16] Bulpin, A.; Le, S.; Gourvennec, R.; Masson, S. Phosphorus Sulfur Silicon 1994, 89, 119.
[17] Fox, R. B.; Venezky, D. L. J Am Chem Soc 1956, 78, 1661.
[18] Tashma, Z. J Org Chem 1982, 47, 3012.
[19] Reetz, T.; Chadwick, D. H.; Hardy, E. E.; Kaufman, S. J Am Chem Soc 1955, 77, 3813.
[20] Miura, K.; Nakagawa, T.; Hosomi, A. J Am Chem Soc 2002, 124, 536.
[21] Gangadasu, B.; Narender, P.; China, R. B.; Jayathirtha, R. V. Indian J Chem, Sect B 2006, 45, 1259.
[22] Kaboudin, B.; Zahedi, H. Chem Lett 2008, 37, 540.
[23] Kaboudin, B.; Haruki, T.; Yamaghishi, T.; Yokomatsu, T. Tetrahedron 2007, 63, 8199.
[24] Kaboudin, B.; Haruki, T.; Yamagishi, T.; Yokomatsu, T. Synthesis 2007, 3226.
[25] Kaboudin, B.; Jafari, E. Synthesis 2006, 3063.
[26] Kaboudin, B.; Elhamifar, D. Synthesis 2006, 224.
[27] Kaboudin, B.; Sorbiun, M. Tetrahedron Lett 2007, 48, 9015.
[28] Kaboudin, B.; Jafari, E. Synthesis 2007, 1823.
[29] Kaboudin, B.; Haghighat, H.; Yokomatsu, T. Tetrahedron: Asymmetry 2008, 19, 862.
[30] Kaboudin, B.; Jafari, E. Synlett 2008, 1837.
[31] Kaboudin, B.; Jafari, E. Synthesis 2008, 2683.