A Novel Catalytic Three-Component Synthesis (Kabachnick–Fields Reaction) of α-Aminophosphonates from Ketones

Elena D. Matveeva,* Tatyana A. Podrugina, Elena V. Tishkovskaya, Larisa G. Tomilova, Nikolay S. Zefirov*

Department of Chemistry, Moscow Lomonosov University, Moscow, Russia
Fax +7(95)9390290; E-mail: edmatveeva@mail.ru; E-mail: zefirov@org.chem.msu.ru

Received 11 July 2003

Abstract: A novel and highly convenient catalytic variant of the synthesis of α-aminophosphonates on basis of the Kabachnik–Fields reaction [three-component reaction of ketones, diethylphosphite and either benzylamine (series **a**) of ammonium carbonate (series **b**)] in the presence of tetra-*tert*-butylphthalocyanines has been developed. This method affords α-aminophosphonates in acceptable yields for various ketones, including cyclic, sterically hindered and cage ketones. The unsubstituted α-aminophosphonic acids were also obtained from the corresponding esters of series **b**.

Key words: α-aminophosphonates, catalysis, tetra-*tert*-butylphthalocyanines, ketones, α-aminophosphonic acids

α-Aminophosphonic acids may be considered as phosphorous analogues of α-amino acids ('bioisosterism'),[1] and have received considerable attention owing to their pronounced biological activities. These entities have been shown to serve as inhibitors of GABA-receptors, inhibitors of various proteolytic enzymes, inhibitors of dialkylglycine decarboxylase, peptide mimetics, antibiotics, and pharmacological agent, including antitumor, antihypertensive and antibacterial agents.[2–15]

Various synthetic methods for α-aminophosphonic acids and α-aminophosphonates have therefore been reported.[5,8,9] However, the classical approach to their synthesis is the Kabachnik–Fields reaction,[10–15] which is a one-pot, three-component operation with carbonyl compound, amine and dialkyl phosphite. This approach is especially satisfactory for reactions with aldehydes, and this protocol was even used for parallel synthesis.[16] In contrast, only a scarce example of the reaction of rather simple ketones (mainly, acetone, acetophenone and cyclohexanone) has been documented.[2,4,7,9]

The mechanism of this reaction is still not clearly understood,[12–14] but one of many possible pathways includes nucleophilic addition of phosphites to the transient imines. In fact, reaction of phosphites with imines is really promoted by alkali metal alkoxide or Lewis acids.[17,18] In principle, the Kabachnik–Fields reaction (a three-component process) can also be catalyzed by an acid or base. Indeed, there are also a few examples of catalytic variants of this reaction, and lanthanide triflate/magnesium sulfate,[19] scandium(tris-dodecyl sulfate),[20] lanthanide triflates/ionic liquids[21] and indium(III) chloride[7] were used as the catalysts. The first three examples were satisfactory mainly for aromatic aldehydes; the last one included aliphatic aldehydes and only few ketones. Thus, an efficient procedure for synthesis of α-aminophosphonic acids and α-aminophosphonates from ketones, especially hindered ones, is needed.

In this report, we describe a novel and efficient catalytic method for the synthesis of α-aminophosphonates and α-aminophosphonic acids with the involvement of various ketones. The reactions were performed with diethylphosphite and amines in presence of tetra-*tert*-butyl-substituted phthalocyanines **Pht-1–Pht-3**[22] as catalysts.

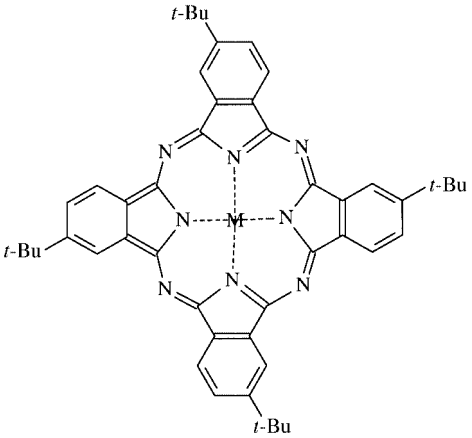
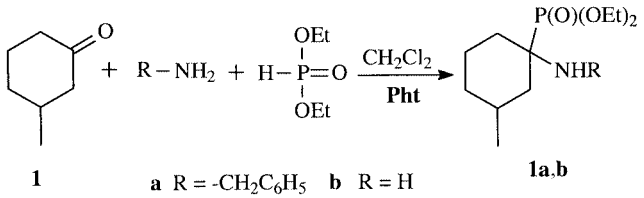


Figure 1 **Pht-1** M = AlCl; **Pht-2** M = Co(II); **Pht-3** M = Ni(II)

First, the reaction of 3-methylcyclohexanone, **1**, with benzylamine and diethylphosphite was tested as a model reaction. Without any catalysis we obtained product **1a** in 20% yield. When tetra-*tert*-butylphthalocyanine derivatives were used as catalysts, the reaction proceeded smoothly to produce **1a** in better yields (55% for derivatives **Pht-2** and 50% for **Pht-3**), reaching the maximum 98% in the case of **Pht-1** (10 mol%). This showed that use of phthalocyanines, and especially **Pht-1**, effectively catalyse the reaction indeed.

Secondly, the reaction of 3-methylcyclohexanone (**1**), diethylphosphite and ammonia carbonate was tested in the presence of **Pht**[23] using ethanol as the solvent. When **Pht-1** was used as a catalyst, the reaction proceeds smoothly to afford the desired product **1b** in a good yield (70%). Thus, the suggested catalyst permits the synthesis of α-aminophosphonate **1b** with unsubstituted primary amino group.

SYNLETT 2003, No. 15, pp 2321–2324
Advanced online publication: 07.11.2003
DOI: 10.1055/s-2003-42118; Art ID: G16803ST



1 **a** R = -$CH_2C_6H_5$ **b** R = H **1a**,**b**

Scheme 1

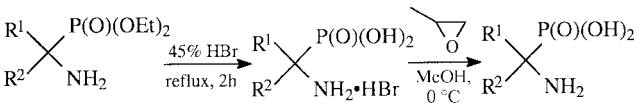
This encouraged us to develop the general procedure for ketones. The reaction of various ketones and diethylphosphite with either benzylamine (series **a**) or ammonia carbonate (series **b**) in the presence of **Pht-1** (10 mol%) in CH_2Cl_2, C_2H_5OH or toluene gave the corresponding α-aminophosphonates as shown in Table 1. Not only cyclohexanones (entries 2, 4) but sterically hindered ketones (entries 9, 12) worked well to give the corresponding phosphonates in acceptable yields, although the camphor (entry 11) afforded the desired product only for case **a** in lower yield. It is necessary to stress that many of the obtained α-aminophosphonates are novel compounds and inaccessible by other methods.[25]

The composition and structures of synthesized α-benzylaminophosphonates and α-aminophosphonates were established by elemental analysis,[26] IR[27] and ^{1}H NMR, ^{13}C NMR and ^{31}P NMR spectra.[28] In the ^{31}P NMR spectrum all synthesized α-aminophosphonates have signals at δ = 22.00–31.00 ppm which are typical for compounds of this class.[24]

^{1}H NMR spectra of α-aminophosphonates can be quite complicated due either possible existence of diastereomers or diastereotopy of some groups or both. Indeed, in some cases [Table 1: 3-methylcyclohexanone (**1**), 4-*tert*-butylcyclohexanone (**4**), camphor (**11**), norbornanone (**12**)] one has to take into account the possible formation of mixtures of *cis*- and *trans*-isomers. The signal of the Me group of **1a** shows the formation of two diastereomers in 2:1 ratio. Analogously, the ^{31}P NMR spectra of **11a** and **12a** also show the formation of two diastereomers in ratio of 3:2. On the other hand, the ^{1}H NMR spectra of α-benzylaminophosphonate (**4a**) exhibits one signal for *tert*-butyl group which indicates the presence of only one of two possible diastereomers.

In the ^{1}H NMR spectra for symmetric ketones [Table 1: cyclohexanone (**2**), 4-*tert*-butylcyclohexanone (**4**), diisopropylketone (**9**), adamantanone (**10**)], the ethoxy groups are equivalent and their signals are typical for ethoxy groups.[29] If the resulting α-aminophosphonates have the diastereotopic ethoxy groups [Table 1: 3-methylcyclohexanone (**1**), acetophenone (**3**), tetralone (**5**), indanone derivatives (**6-8**)], the situation leads to a duplication of the corresponding signals.[30,31]

The pure unsubstituted α-aminophosphonic acids were obtained from the corresponding esters of series **b** (**1b**, **4b**, **6b**, **8b**) using the following steps (Scheme 2): (i) acid hydrolysis with 45% HBr, which gives the corresponding hydrobromides in good yields; (ii) treatment with propylene oxide in methanol at 0 °C. α-Aminophosphonic acids (**1c**, **4c**, **6c**, **8c**) were obtained using this protocol in 60–80% yields.



Scheme 2

In summary, a novel and highly convenient catalytic method of the synthesis of α-aminophosphonates in the presence of tetra-*tert*-butylphthalocyanines has been performed and the applicability of this method to ketones was demonstrated. α-Aminophosphonic acid was obtained in 60–80% yields on basis of the synthesized α-aminophosphonates.

Table 1 The Ketones Used and the Yields of Corresponding α-Aminophosphonates[a,25]

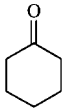
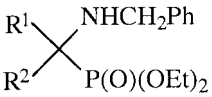
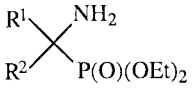
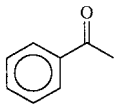
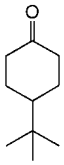
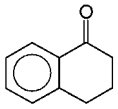
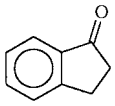
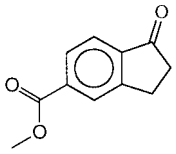
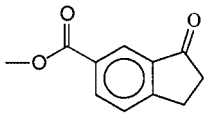
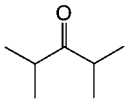
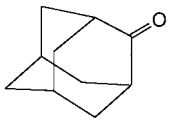
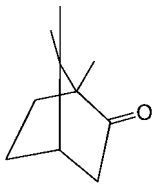
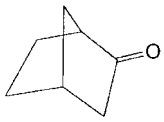
	Ketones	Yields of α-aminophosphonates (%)	
		R^1, R^2, $NHCH_2Ph$, $P(O)(OEt)_2$ (Series **a**)	R^1, R^2, NH_2, $P(O)(OEt)_2$ (Series **b**)
1		98 (**1a**)[b]	85 (**1b**)[c]
2		85 (**2a**)[b]	70 (**2b**)[c]

Table 1 The Ketones Used and the Yields of Corresponding α-Aminophosphonates[a,25] (continued)

	Ketones	Yields of α-aminophosphonates (%)	
		 (Series **a**)	 (Series **b**)
3		92 (**3a**)[b]	50 (**3b**)[b]
4		93 (**4a**)[b]	52 (**4b**)[c]
5		74 (**5a**)[c]	57 (**5b**)[c]
6		50 (**6a**)[c]	35 (**6b**)[c]
7		65 (**7a**)[b]	–
8		98 (**8a**)[b]	15 (**8b**)[c]
9		16 (**9a**)[d]	20 (**9b**)[d]
10		23 (**10a**)[d]	39 (**10b**)[c]
11		18 (**11a**)[c]	–
12		50 (**12a**)[c]	20 (**12b**)[c]

[a] Used 0.2 mmol (10 mol%) Ptc-1.
[b] Carried out in CH_2Cl_2 at r.t. for 12 h.
[c] Carried out in EtOH at 78 °C for 24 h.
[d] Carried out in toluene at 110 °C for 24 h.

Acknowledgment

This work was supported by grants from RFFI No. 01-03-33085, No. 02-03-32163; UR 05.03.003; Grant of President of Russia for support of Scientific School -2051.2003.3.

References

(1) Sheridan, R. P. *J. Chem. Inf. Comput. Sci*. **2002**, *42*, 103.
(2) Grembecka, J.; Mucha, A.; Cierpicki, T.; Kafarski, P. *J. Med. Chem.* **2003**, *46*, 2641.
(3) Bird, J.; De Mello, R. C.; Harper, G. P.; Hunter, D. J.; Karran, E. H.; Markwell, R. E.; Miles-Williams, A. J.; Rahman, S. S.; Ward, R. W. *J. Med. Chem.* **1994**, *37*, 158.
(4) McLeod, D. A.; Brinkworth, R. I.; Ashley, J. A.; Janda, K. D.; Wirsching, P. *Bioorg. Med. Chem. Lett.* **1991**, 653.
(5) Moore, J. D.; Sprott, K. T.; Hanson, P. R. *J. Org. Chem.* **2002**, *67*, 8123.
(6) Liu, W.; Rogers, C. J.; Fisher, A. J.; Toney, M. *Biochemistry* **2002**, *41*, 12320.
(7) Ranu, B. C.; Hajra, A.; Jana, U. *Org. Lett.* **1999**, *1*, 1141.
(8) Kim, K. S.; Hurh, E. Y.; Youn, J. N.; Park, J. I. *J. Org. Chem.* **1999**, *64*, 9272.
(9) Osipov, S. N.; Artyushin, O. I.; Kolomiets, A. F.; Bruneau, C.; Dixneuf, P. H. *Synlett* **2000**, 1031.
(10) Kabachnik, M. I.; Medved', T. Ya. *Dokl. Akad. Nauk SSSR* **1952**, 689; *Chem. Abstr*. **1953**, *47*, 2724b.
(11) Fields, E. K. *J. Am. Chem. Soc.* **1952**, *74*, 1528.
(12) Kuchar, V. P.; Solodenko, V. A. *Russ. Chem. Rev*. **1987**, *56*, 1504.
(13) Cherkasov, R. A.; Galkin, V. I. *Russ. Chem. Rev.* **1998**, *67*, 940.
(14) Kuchar, V. P.; Svistunova, N. Yu.; Solodenko, V. A.; Soloshonok, V. A. *Russ. Chem. Rev.* **1993**, *62*, 284.
(15) Uziel, J.; Genêt, J. P. *Zh. Org. Khim.* **1997**, *33*, 1605.
(16) LaPointe, A. M. *J. Comb. Chem.* **1999**, *1*, 101.
(17) Pudovik, A. N. *Dokl. Akad. Nauk SSSR* **1952**, *83*, 865; *Chem. Abstr*. **1953**, *47*, 4300.
(18) Laschat, S.; Kunz, H. *Synthesis* **1992**, 90.
(19) Quian, C.; Huang, T. *J. Org. Chem.* **1998**, *63*, 4125.
(20) Manabe, K.; Kobayashi, S. *Chem. Commun.* **2000**, 669.
(21) Lee, S.-gi.; Park, J. H.; Kang, J.; Lee, J. K. *Chem. Commum.* **2001**, 1698.
(22) Tomilova, L. G.; Rodionova, G. N.; Lucyanetz, E. A. *Koord. Chim.* **1979**, *5*, 549; *Chem. Abstr*. **1979**, *91*, 221595d.
(23) Kochmann, W.; Gunter, E.; Rothling, T. *Z. Chem.* **1976**, *16*, 184.
(24) Fadel, A.; Tesson, N. *Eur. J. Org. Chem.* **2000**, 2153.
(25) **General Procedure:** To the solution of ketone (2 mmol) in solvent (3 mL, see Table 1), the benzylamine (2 mmol) or $NH_4(CO_3)_2$ (6 mmol), anhyd $MgSO_4$ (2 mmol) and **Pht-1**[22] (10 mol%; 0.2 mmol) as a catalyst were added. The reaction mixture was heated for 3–4 h. Then diethylphosphite (2.4 mmol) was added. The reaction mixture was stirred for 12–24 h (see Table 1). The desiccant was then filtered and washed with 2 mL of CH_2Cl_2. The solvent was evaporated, and the residue was purified by chromatography on silica gel (eluent: CH_2Cl_2/MeOH = 20:1). In the case of steric hindered and cage ketones (adamantanone-2, camphor and norbornanone) 50% amine excess is required.
(26) All obtained compounds gave satisfactory elemental analyses with the range of C ±0.3%, H ±0.2%, N ±0.3%.
(27) IR spectra registration was carried out in condensed phase and in the solution in CCl_4. There are stretches absorptions at 1200 cm^{-1} (P=O), 3200–3400 cm^{-1} (N–H and NH_2) and 1180 cm^{-1} (C–O) in the IR spectra of given compounds. IR spectra of α-benzylaminophosphonates solutions were measured under the dilution forty times over. At that intensity and frequency the absorption bands of phosphonic and NH-associated groups did not change. This fact is evidence of the presence of intramolecular hydrogen bonds.
(28) Selected NMR data are presented below. Compound **1a**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (d, 3 H, CH_3-cycl.), 1.34, 1.36 (2 t, 6 H, $2CH_3$), 1.53, 1.66, 1.87 (3 m, 9 H, cycl., NH), 3.92 (d, $^3J_{PH}$ = 3.2 Hz, 2 H, CH_2-Bz), 4.16 (br m, 4 H, OCH_2), 7.31, 7.38 (2 m, 5 H, arom.) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 16.32 (d, $^3J_{CP}$ = 4.6 Hz, CH_3), 19.68 (d, *J* = 12.2 Hz, CH_3, cycl.), 22.15, 25.38, 28.65, 34.09, 37.61 (cycl.), 46.84 (CH_2-Bz), 56.30 (d, $^1J_{PC}$ = 141.9 Hz, C-1), 61.83, 61.34 ($^2J_{PC}$ = 6.1 Hz, OCH_2), 126.39, 127.78, 127.87, 141.09 (C arom.) ppm. ^{31}P NMR (400 MHz, $CDCl_3$): δ = 28.52 ppm. IR: 1240 (P=O), 3340, 3470 (NH) cm^{-1}.
Compound **10a**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12, 1.27 (2 t, 6 H, $2CH_3$), 1.34, 1.64, 2.10, 2.24 (4 m, 14 H, cycl.), 2.75 (br s, 1 H, NH), 3.55 (A part AB syst, J_{AB} = 13.2 Hz, 1 H, CH_2Bz), 3.83 (B part AB syst, J_{AB} = 13.2 Hz, 1 H, CH_2Bz), 3.80, 3.94, 4.10 (3 m, 4 H, OCH_2), 7.27, 7.37 (2 m, 5 H, Ar) ppm. ^{13}C NMR: δ = 16.36, 16.58 (2 d, $^3J_{CP}$ = 6.3 Hz, CH_3), 24.66, 25.29, 31.31, 34.13, 35.82, 44.18 (cycl.), 51.19 (d, *J* = 12.6 Hz, CH_2-Bz), 60.12 (d, $^1J_{PC}$ = 154.1 Hz, C-1, cycl.), 62.98, 63.15, ($^2J_{PC}$ = 7.8 Hz, OCH_2), 127.29, 128.10, 128.52, 128.87 (C Ar). ^{31}P NMR: δ = 22.5 ppm. IR: 1235 (P=O), 3260, 3360 (NH) cm^{-1}. Anal. Calcd for $C_{21}H_{32}NPO_3$(377): C, 66.84; H, 8.49; N, 3.71; P, 8.22. Found: C, 67.87; H, 7.50; N, 3.57.
Compound **10b**. ^{1}H NMR ($CDCl_3$): δ = 1.36 (t, 6 H, $2CH_3$), 1.52, 1.74, 1.85, 2.13, (3 m, 10 H, cycl.), 2.35, 2.42 (2 m, 4 H cycl.), 3.01 (br s, 2 H, NH_2), 4.21 (m, 4 H, OCH_2), 7.27, 7.37 (2 m, 5 H, Ar) ppm. ^{13}C NMR: δ = 16.08 (CH_3), 26.13, 26.62, 31.66, 31.77, 33.27, 33.41, 38.77, 46.88 (cycl.), 62.19 (d, $^2J_{PC}$ = 7.8 Hz, OCH_2) ppm. ^{31}P NMR: δ = 25.39 ppm. IR: 1245 (P=O), 3280 (NH_2) cm^{-1}.
Compound **12a**. ^{1}H NMR ($CDCl_3$): δ = 1.05, 1.15 (2 m, 2 H, cycl.), 1.34, 1.35 (2 t, 6 H, $2CH_3$), 1.51, 1.88, 2.12, 2.26, 2.60 (5 m, 10 H, cycl.), 3.69 (A part AB syst., J_{AB} = 13.4 Hz, 1 H, CH_2Bz), 3.85 (B part AB syst, J_{AB} = 13.4 Hz, 1 H, CH_2Bz), 3.99–4.23 (m, 4 H, OCH_2), 7.21, 7.31, 7.37 (3 m, 5 H, Ar) ppm. ^{31}P NMR: δ = 30.53, 31.44 (2 s, 2:1) ppm.
(29) These signals are at 1.30–1.36 ppm (t, CH_3) and at 4.10–4.20 ppm (complicated multiplet OCH_2 $^2J_{PH}$ = 3.1 Hz).
(30) In ^{1}H NMR spectra, the protons of CH_3 groups were observed at δ = 1.15 and 1.30 ppm (2 t, 1:1). The diastereotopic protons of two diastereotopic OCH_2 groups appear as several multiplets at 3.80–4.50 ppm ($^2J_{PH}$ = 3.1 Hz): either four multiplets in ratio 1:1:1:1 or the superposition of three multiplets in ratio 1:2:1. In ^{1}H NMR spectra of α-benzylaminophosphonates (series **a**) the signals of diastereotopic benzyl protons resonate at 3.50–3.70 ppm as two doublets (J_{AB} = 12.8 Hz).
(31) There is the corresponding duplication of signals of the diastereotopic ethoxy group in ^{13}C NMR spectra. In fact, CH_3 groups resonate as two doublets at δ = 16.00 ppm ($^3J_{PC}$ = 6.3–6.5 Hz) and the OCH_2 group as two doublets at 62.00–63.00 ppm ($^2J_{PC}$ = 8.6 Hz). These values are in agreement with available literature data.[24] The quaternary carbon atom resonates at δ = 50.00-60.00 ppm ($^1J_{PC}$ = 140–150 Hz).[27]