Catalyst-Free Microwave-Assisted Synthesis of α-Aminophosphonates in a Three-Component System: $R^1C(O)R^2$–$(EtO)_2P(O)H$–RNH_2

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Abstract: An effective catalyst-free microwave-assisted synthesis of α-aminophosphonates from ketones in a three-component system was shown. The method affords α-aminophosphonates in high yields from various ketones including natural porphyrine derivatives.

Key words: α-aminophosphonates, α-aminophosphonic acid, ketones, natural porphyrin, steroid

The synthesis of α-aminophosphonates exhibiting high biological activity has recently attracted a lot of attention.[1–3] Due to their structural analogy with α-aminoacids, this type of organophosphorous compound is widely used for the development of new inhibitors of enzymes, neuroactive compounds, antibiotics, and plant-growth regulators.[4,5]

Among a number of synthetic approaches to α-amino phosphonates one of the most powerful methods is the Kabachnik–Fields reaction.[6] However this method, usually applied to aldehydes, has been much less studied with ketones.[7,8]

The lower activity of ketones in comparison to aldehydes necessitates either harsh conditions (heating in an autoclave) or the use of various catalysts.[2,9]

Meanwhile, the application of microwave irradiation has often been demonstrated to enable facile realization of reactions, which otherwise require harsh conditions and are too slow for practical purposes.[10,11] Moreover, the microwave-assisted reactions are believed to satisfy the demands of 'green chemistry' allowing for solvent-free conditions to be employed.

Previously we have suggested a method for the synthesis of α-aminophosphonates, based on the reaction of ald- and ketimines with dialkylphosphites in the presence of CdI_2 under microwave irradiation.[12]

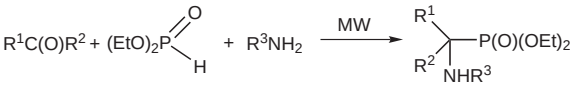
It was first shown that the synthesis of α-aminophosphonates and α-aminophosphonic acids from ketones can be successfully carried out in a three-component system [ketone–$(EtO)_2P(O)H$–RNH_2] without catalyst under microwave irradiation. Aliphatic, aromatic, heterocyclic, and carbocyclic ketones were used in the reaction (see Table 1).

The microwave-assisted reaction of ketones with $(EtO)_2P(O)H$ and primary amines (RNH_2, R = Bz, *t*-Bu, *c*-C_6H_{11}) has been found not only to produce α-aminophosphonates in high yields, but also to decreases the reaction time greatly. Comparative data on the synthesis of α-aminophosphonates from ketones under microwave irradiation and under conventional heating are presented in Table 1.

In the most of the examples the reaction was carried out under solvent-free conditions in a domestic microwave oven (102 W). It should be noted that the effective application of non-expensive domestic microwave ovens in many organic preparations has been extensively documented.[13] The reaction has been carried out in an Erlenmeyer flask over 10–28 minutes using the following ratio of reagents: ketone–$(EtO)_2P(O)H$–RNH_2, 1:3:1[14] (Scheme 1). The necessity to use an excess of dialkylphosphite is accounted for by the partial decomposition of this reagent under microwave irradiation.

The reaction was monitored by the means of IR and ^{31}P NMR spectroscopy, and TLC (Silufol, hexane–ethyl acetate, 5:1). α-Amino phosphonates were isolated in 74–94% yield and the phosphorous atoms were found to have a chemical shift in the range 19.5–32.5 ppm. It was found, that the addition of Lewis acids (CdI_2, $AlCl_3$) may lead to further decrease of the reaction time, but did not affect the yields. Also, it should be noted that ketone structure does not greatly affect the reaction rate under microwave irradiation.

The application of microwave irradiation allows the preparation of α-aminophosphonates from such ketones as benzophenone and adamantanone-2,[2] which give poor yields using conventional heating.



Ia–j **IIa–j** **IIIa–j**

Scheme 1 **I**, **II**, **III**: **a**: R^1, R^2 = *c*-C_6H_{10}, R^3 = *c*-C_6H_{11}; **b**: R^1, R^2 = *c*-C_6H_{10}, R^3 = CH_2Ph; **c**: R^1 = R^2 = *i*-Pr, R^3 = CH_2Ph; **d**: R^1 = R^2 = Ph, R^3 = CH_2Ph; **e**: R^1 = Me, R^2 = Ph, R^3 = *t*-Bu; **f**: R^1 = Me, R^2 = 5-methyl-2-phuryl, R^3 = CH_2Ph; **g**: R^1 = Me, R^2 = 5-methyl-2-thienyl, R^3 = CH_2Ph; **h**: R^1 = Me, R^2 = naphthyl, R^3 = CH_2Ph; **i**: R^1 = Me, R^2 = 7-methoxy-1,2,3,4-tetrahydronaphthyl-2, R^3 = CH_2Ph; **j**: R^1, R^2 = 2-adamantyl, R^3 = CH_2Ph.

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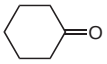
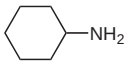
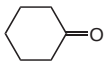
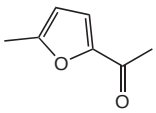
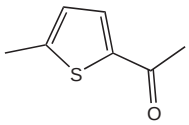
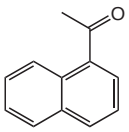
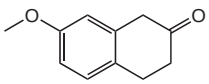
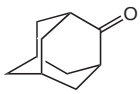
Table 1 α-Aminophosphonates from the Reaction of Ketones, Primary Amines, and Diethylphosphite

	Ketones	Amines	MW		Conventional heating (45 °C)	
			Time (min)	Yields of α-aminophosphonates (%)	Time (h)	Yields of α-aminophosphonates (%)
IIIa			8	86	6	76
IIIb		$PhCH_2NH_2$	10	92	9	64
IIIc[a]	$(i\text{-Pr})_2C{=}O$	$PhCH_2NH_2$	20	73	72	0
IIId	$Ph_2C{=}O$	$PhCH_2NH_2$	20	81	72	0
IIIe		*t*-$BuNH_2$	18	79	72	2
IIIf		$PhCH_2NH_2$	19	84	24	50
IIIg		$PhCH_2NH_2$	9	83	12	57
IIIh		$PhCH_2NH_2$	28	72	72	1.5
IIIi[a]		$PhCH_2NH_2$	19	75	72	1
IIIj[a]		$PhCH_2NH_2$	22	74	72	0

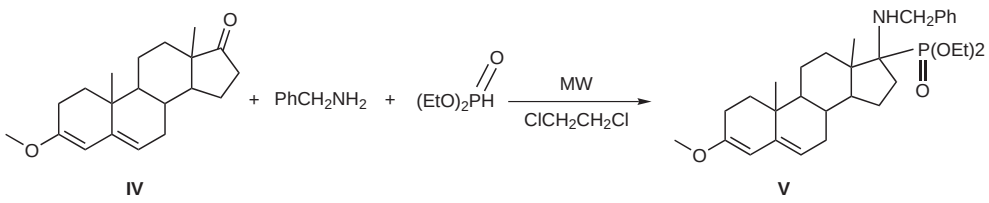
[a] Carried out in $C_2H_4Cl_2$.

3-Methoxy-androsta-3,5-diene-17-one and a ketone from a natural porphyrin derivative were used in the reaction for the first time.

Analogously, α-aminophosphonate **V** was obtained, after heating for 24 minutes in $C_2H_4Cl_2$, in 79% yield (see Scheme 2).[15] The ^{31}P NMR spectrum revealed two signals at 23 ppm and 26 ppm corresponding to two stereoisomers.

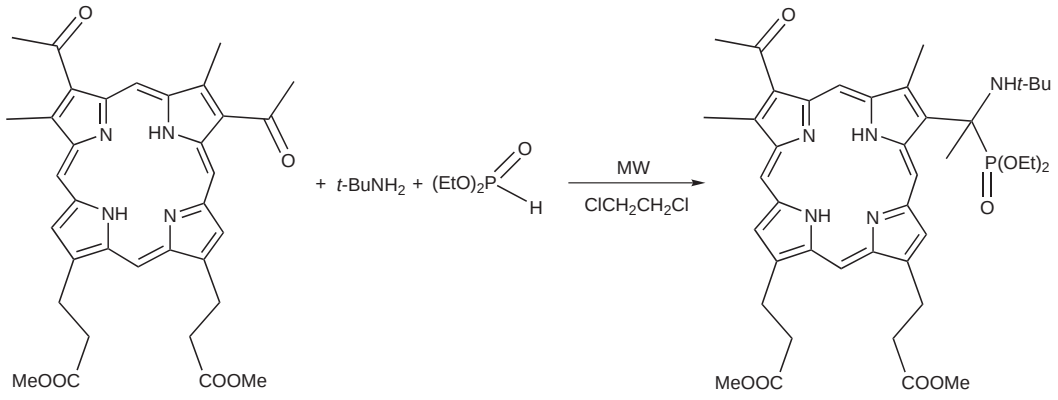
The reaction of natural porphyrin derivative **VI** with *t*-$BuNH_2$ and $(EtO)_2P(O)H$ was carried out in $C_2H_4Cl_2$ under microwave irradiation for 4 minutes.[16] Porphyrin **VII** was obtained in 82% yield; the ^{31}P NMR spectrum revealed a single product α-aminophosphonate **VII**, the only signal appearing at 25.8 ppm.

We have also studied the reaction of ketones with bis(trimethylsilylphosphite) and primary amines under microwave irradiation. The bis(trimethylsilyl)phosphonate group can be easily transformed into phosphonic acid by methanolysis.[17] The reaction of cyclohexanone, bis(trimethylsilyl)phosphate, and α-phenylethylamine gave a phosphonate ester, which was transformed into α-aminophosphonic acid **VIII** in 81% yield.[18]



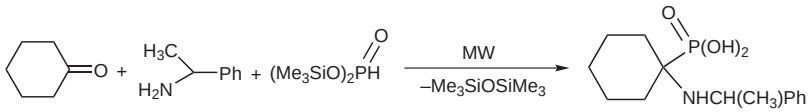
IV **V**

Scheme 2



VI **VII**

Scheme 3



VIII

Scheme 4

In summary, a novel catalyst-free version of the Kabachnik–Fields reaction under microwave irradiation is presented in this work, which allows α-aminophosphonates to be prepared from various ketones, including naturally occurring ketones.

Acknowledgment

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(14) **General Procedure**: a) *Microwave irradiation:* Appropriate ketone (**IIIa**–**j**, 0.02 mol), anhydrous amine (0.02 mol) and freshly distilled $(EtO)_2P(O)H$ (0.06 mol) were placed into 25 mL flask and exposed to microwave irradiation at 102 W using a domestic oven (Daewoo, KOR-4125G) for 10–28 min. The residue was purified by chromatography on silica (eluent: hexane–EtOAc, 3:2).
All experiments were repeated several times in order to ensure reproducibility.
b) *Conventional method*: A mixture of ketone (0.05 mol), amine (0.05 mol) and diethyl phosphite was refluxed in benzene (20 mL) for an appropriate time. On completion, the solvent was evaporated and the residue was purified by chromatography on silica (eluent: hexane–EtOAc, 3:2).
All new compounds gave satisfactory elemental analyses (C ± 0.2, H ± 0.3, N ± 0.3).
^{1}H NMR, ^{31}P NMR and microanalytical data for some newly obtained α-aminophosphonates are as follows.
Compound IIIc: bp 70–73 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12 (t, ^2J = 6.5 Hz, 6 H, CH_3CH_2O), 1.31 [s, 12 H, $(CH_3)_2CH$], 2.02 (m, 2 H, 2 × $(CH_3)_2CH$), 2.91 (br s, 1 H, NH) 3.82 (q, J = 7.8, 6.3 Hz, 4 H, CH_3CH_2O), 3.97 (q, J = 7.1, 6.0 Hz, 2 H, CH_2-NH), 7.40 (m, 5 H, arom). ^{31}P NMR (162 MHz, $CDCl_3$): δ = 26.1. Anal. Calcd for $C_{18}H_{32}NPO_3$: C, 63.34; H, 9.38; N, 4.11. Found: C, 63.15; H, 9.40; N, 4.13.
Compound IIId: bp 108–109 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (t, ^2J = 7.6 Hz, 6 H, OCH_2CH_3), 3.94 (dd, J = 7.6, 6.2 Hz, 2 H, $NHCH_2$), 4.08 (q, J = 7.1, 6.2 Hz, 4 H, 2 × OCH_2CH_3), 4.16 (br s, 1 H, NH), 7.62, 7.49, 7.31 (m, 15 H, arom). ^{31}P NMR (162 MHz, $CDCl_3$): δ = 28.0. Anal. Calcd for $C_{24}H_{28}NPO_3$: C, 70.13; H, 6.67; N, 3.21. Found: C, 70.41; H, 6.85; N, 3.42.
Compound IIIg: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (t, ^2J = 7.6 Hz, 6 H, OCH_2CH_3), 1.7 (s, 3 H, CH_3), 2.24 (s, 3 H,

CH_3), 3.63 (br s, 1 H, NH), 4.07 (q, *J* = 7.6, 5.2 Hz, 4 H, OCH_2CH_3), 4.09 (dd, *J* = 7.9, 6.4 Hz, 2 H, $NHCH_2$), 6.47 (d, *J* = 2.3 Hz, 1 H, thiophene), 6.56 (d, *J* = 3.4 Hz, 1 H, thiophene), 7.36 (m, 5 H, arom). ^{31}P NMR (162 MHz, $CDCl_3$): δ = 24.8 ppm. Anal. Calcd for $C_{17}H_{26}NSPO_3$: C, 57.46; H, 7.32; N, 3.94. Found: C, 57.48; H, 7.53; N, 3.65.
Compound IIIh: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33 (t, *J* = 7.6 Hz, 6 H, OCH_2CH_3), 1.65 (d, *J* = 10.6 Hz, CH_3), 3.89 (br s, 1 H, NH), 3.94 (dd, *J* = 7.6, 5.9 Hz, 2 H, $NHCH_2$), 4.02 (q, *J* = 7.6, 5.2 Hz, 4 H, OCH_2CH_3), 7.62, 7.49, 7.31 (m, 12 H, arom). ^{31}P NMR (162 MHz, $CDCl_3$): δ = 24.1 ppm. Anal. Calcd for $C_{23}H_{28}NPO_3$: C, 69.52; H, 7.05; N, 3.53. Found: C, 69.46; H, 7.34; N, 3.81.

(15) To a solution of the ketone **IV** (0.001 mol) in $ClCH_2CH_2Cl$ (1.5 mL), $PhCH_2NH_2$ (0.001 mol) and freshly distilled $(EtO)_2P(O)H$ (0.003 mol) were added. The reaction mixture was exposed to microwave irradiation at 102 W using a domestic oven (Daewoo, KOR-4125G) for 24 min. The residue was purified by chromatography on silica (eluent: hexane–EtOAc, 3:2).
α-Aminophosphonate Derived from 3-Methoxy-androsta-3,5-diene-17-one (V): mp 143–145 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (m, 1 H, 9-CH), 0.94 (s, 3 H, 18-CH_3), 1.04 (s, 3 H, 19-CH_3), 1.29 (t, *J* = 7.6 Hz, 6 H, OCH_2CH_3), 1.62 (m, 1 H, 8-CH), 1.82 (m, 14 H, all CH_2-ring), 2.25 (dd, *J* = 7.6, 5.9 Hz, 2 H, $NHCH_2$), 2.57 (br s, 1 H, NH), 3.61 (s, 3 H, CH_3O), 3.99 (q, *J* = 7.9, 5.4 Hz, 4 H, OCH_2CH_3), 5.39 (s, 1 H, 6-CH), 7.37 (m, 5 H, arom). ^{31}P NMR (162 MHz, $CDCl_3$): δ = 23.0 and 26.0 ppm. MS (ESI^+): *m*/*z* = 391.2 [$C_{31}H_{45}NO_4P$ + H$(EtO)_2P(O)$].

(16) To solution of ketone **VI** (0.048 mol) in $ClCH_2CH_2Cl$ (1.5 mL), $PhCH_2NH_2$ (0.048 mol) and freshly distilled $(EtO)_2P(O)H$ (0.144 mol) were added. The reaction mixture was exposed to microwave irradiation at 102 W using a domestic oven (Daewoo, KOR-4125G) for 4 min. The residue was purified by chromatography on silica (eluent: CH_2Cl_2–MeOH, 100:1).
α-Aminophosphonate Derived from 3,8-Diacetyl–13,17–bis(methoxycarbonylethyl)-2,7,12,18-tetramethyl-porphyrin (VII): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.24, 9.99, 9.85, 9.84 (s, 4 H, *meso*-H), 4.34–4.28 (two overlapping t, *J* = 7.4, 7.1 Hz, 4 H, 2 × $CH_2CH_2CO_2CH_3$), 4.22–4.12 [q, *J* = 7.1, 6.0 Hz, 8 H, 3^1-P(O)$(OCH_2CH_3)_2$], 4.16 (br s, 1 H, NH), 3.65, 3.65, 3.64, 3.57, 3.55, 3.52 (s, 18 H, 2 × $CH_2CH_2CO_2CH_3$ and 4 × CH_3-ring), 3.23–3.19 (two overlapping t, 4 H, 2 × $CH_2CH_2CO_2CH_3$), 1.68 (m, 2 H, 2 × CH), 1.30–1.26 [t, *J* = 7.1 Hz, 12 H, 3^1-P(O)$(OCH_2CH_3)_2$], 1.24 and 1.23 [s, 9 H, 3^1-NHC$(CH_3)_3$], –4.21 (br s, 2 H, 2 × NH-ring). ^{31}P NMR (162 MHz, $CDCl_3$): δ = 19.5 ppm. MS (ESI^+): 624.7 [$C_{52}H_{80}N_6O_{10}P_2$ + 2 H – 2 *t*-Bu – 2 $(EtO)_2P(O)$].

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(18) Cyclohexanone (0.02 mol), $PhCH(CH_3)NH_2$ (0.02 mol) and freshly distilled trimethylsilylphosphite (0.06 mol) were placed into 50 mL flask and exposed to microwave irradiation at 102 W using a domestic oven (Daewoo, KOR-4125G) for 18 min. The residue was purified by chromatography on silica (eluent: hexane–EtOAc, 3:2).
α-Aminophosphonic Acid VIII: bp 229 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (d, *J* = 7.6 Hz, 3 H, CHC*H*$_3$), 1.26 (m, 10 H, *c*-C_6H_{10}), 3.58 (s, 2 H, OH), 3.95 (q, *J* = 7.9, 6.4 Hz, 1 H, NHCH), 7.25 (m, 5 H, arom), 7.51 (br s, 1 H, NH). ^{31}P NMR (162 MHz, $CDCl_3$): δ = 19.8 ppm. Anal. Calcd for $C_{14}H_{22}NPO_3$: C, 59.36; H 7.77; N, 4.95. Found: C, 59.08; H, 7.53; N, 5.02.