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Microwave-Assisted Reactions of Schiff Bases with Diethyl Phosphonate in the Presence of CdI_2

M. M. Kabachnik, E. V. Zobnina, and I. P. Beletskaya

Faculty of Chemistry, Lomonosov Moscow State University, Vorob'evy gory 1, Moscow, 119899 Russia

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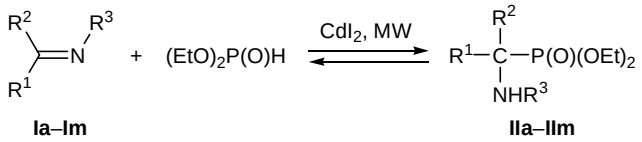
Abstract—The reaction of diethyl phosphonate with Schiff bases derived from aldehydes and ketones in the presence of cadmium iodide is strongly accelerated by microwave irradiation, and the corresponding α-aminophosphonates are formed in high yields.

Schiff bases are known to react with diethyl phosphonate to give α-aminophosphonates which constitute an important class of biologically active compounds [1–3]. These reactions continuously attract attention from the viewpoints of both stereoselective synthesis of α-aminophosphonates [4, 5] and optimization of the reaction conditions [6, 7]. The use of microwave irradiation (MW) to accelerate various organic reactions has been well documented [8]. This technique has also found application in the chemistry of organophosphorus compounds. Microwave-assisted Arbuzov reaction [9], arylation of diethyl phosphonate in the presence of metal-complex catalysts [10], Wittig reaction [11], and synthesis of α-aminophosphonates in the three-component system amine–aldehyde–diethyl phosphonate [12, 13] have been reported. However, the latter reaction has been performed only with aromatic aldehyde imines.

We previously developed a procedure for the synthesis of α-aminophosphonates by reaction of Schiff bases with diethyl phosphonate using CdI_2 as catalyst [6]. The reactions were carried out by heating the reactants to 45°C over a period of 4–10 h, depending on the Schiff base structure. With the goal of optimizing the conditions for the synthesis of both aliphatic and aromatic α-aminophosphonates, in the present work we examined reactions of various aldimines and ketimines with diethyl phosphonate in the presence of CdI_2 under microwave irradiation.

We found that a combination of CdI_2 catalysis and microwave irradiation leads to very strong acceleration of the process (the reaction time shortens from 3–10 h to a few minutes or sometimes seconds) and considerable increase in the product yields (see table). The reactions of Schiff bases **Ia**–**Im** with diethyl phosphonate were carried out without a solvent in the presence of 5 mol % of CdI_2 under microwave irradiation. The progress of the reactions was monitored by ^{31}P NMR and IR spectroscopy and thin-layer chromatography. According to the ^{31}P NMR data, the conversion of both aliphatic and aromatic aldehyde and ketone imines was almost complete, and the corresponding α-aminophosphonates **IIa**–**IIm** were isolated in 86–95% yield. It should be noted, that the yield of the final product depended only slightly on the substrate structure. The results are summarized in table. In all cases, the yields of α-aminophosphonates in the microwave-assisted reaction were greater than in the thermal reaction.

Less reactive ketimines also readily react with diethyl phosphonate in the presence of CdI_2 under microwave irradation, but the reaction time was longer (up to 10 min). For example, the reactions with *N*-*tert*-butylbutylideneamine (**Ia**) and *N*-cyclohexylbutylideneamine (**Ib**) with diethyl phosphonate were complete in 45 s, while ketimines **If**, **Ig**, **Ij**, and **Im** with



Ia–Im **IIa–IIm**

I, **II**, R^1 = H, R^2 = Pr, R^3 = *t*-Bu (**a**); R^1 = H, R^2 = Pr, R^3 = *cyclo*-C_6H_{11} (**b**); R^1 = H, R^2 = Pr, R^3 = PhCH(Me) (**c**); R^1 = H, R^2 = R^3 = Ph (**d**); R^1 = H, R^2 = Ph, R^3 = PhCH(Me) (**e**); R^1 = H, R^2 = Et, R^3 = *t*-Bu (**f**); R^1 = H, R^2 = Et, R^3 = *cyclo*-C_6H_{11} (**g**); R^1R^2C = *cyclo*-C_6H_{10}, R^3 = *cyclo*-C_6H_{11} (**h**); R^1 = R^2 = *cyclo*-C_5H_8, R^3 = *cyclo*-C_6H_{11} (**i**); R^1 = R^2 = *cyclo*-C_5H_8, R^3 = PhCH(Me) (**j**); R^1R^2C = *cyclo*-C_6H_{10}, R^3 = PhCH(Me) (**k**); R^1 = Pr, R^2 = Pr, R^3 = *cyclo*-C_6H_{11} (**l**); R^1 = Me, R^2 = 5-methyl-2-furyl, R^3 = *t*-Bu (**m**).

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Synthesis of α-aminophosphonates in the presence of CdI_2 under microwave irradiation and on heating

Initial Schiff base no.	Microwave assistance		Heating (45°C)	
	reaction time, min	yield, %	reaction time, h	yield, %
Ia	0.75	92	4.5	77
Ib	0.75	89	3	80
Ic	5	95	7	83
Id	2.5	93	5	75
Ie	7.5	91	7	82
If	0.67	92	3.5	83
Ig	0.83	93	4	80
Ih	1.75	91	6	76
Ii	3	95	7.5	50
Ij	8	88	6	81
Ik	8	93	5.5	58
Il	9.5	86	8	63
Im	10	89	–	–

the same substituents on the nitrogen atom required irradiation for ~2–10 min to obtain the corresponding α-aminophosphonates. No phosphorylation of *N-tert*-butyl-1-(5-methyl-2-furyl)ethylideneamine (**Im**) occurred even on heating for 24 h at 45°C, and raising the temperature to 140°C (2 h) led to formation of no more than 20% of aminophosphonate **IIm**. The same reaction performed under microwave irradiation was complete in 10 min, and aminophosphonate **IIm** was obtained in 89% yield.

Thus the reaction of Schiff bases with diethyl phosphonate in the presence of CdI_2 is strongly accelerated by microwave irradiation, and various α-aminophosphonates can be obtained in such a way with high yields.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker DPX-300 instrument (300 MHz) in $CDCl_3$ using tetramethylsilane as external reference. The ^{31}P NMR spectra were measured on a Varian FT-80A spectrometer (32.4 MHz) using 85% H_3PO_4 as external reference. Silufol plates were used for thin-layer chromatography (eluent hexane–ethyl acetate, 5:1). The newly synthesized aminophosphonates were characterized by analytical data, and the others were identified by comparing their physical constants with those given in [6].

Reaction of diethyl phosphonate with *N-tert*-butylbutylideneamine (Ia). A 25-ml flat-bottom flask was charged with 0.02 mol (2.7 g, 2.5 ml) of diethyl phosphonate and 0.007 g of cadmium(II) iodide, and 0.02 mol (2.5 g, 3.1 ml) of compound **Ia** was added. The flask was placed into a domestic microwave furnace and was irradiated for 45 s at a power of 102 W. The mixture was distilled under reduced pressure to isolate 4.9 g (92%) of compound **IIa**, bp 69–71°C (14 mm), n_D^{20} = 1.4250. ^{31}P NMR spectrum: δ_P 29.0 ppm. α-Aminophosphonates **IIb**–**IIm** were synthesized in a similar way.

Compound **IIb**. Yield 5.2 g (89%), bp 112–114°C (20 mm), n_D^{20} = 1.4485. ^{31}P NMR spectrum: δ_P 25.9 ppm.

Compound **IIc**. Yield 5.9 g (95%), bp 134–135°C (25 mm), n_D^{20} = 1.4553. ^{31}P NMR spectrum: δ_P: 25.5 ppm. Found, %: C 63.26; H 6.01; P 10.20. $C_{16}H_{18}NO_3P$. Calculated, %: C 63.37; H 5.94; P 10.23.

Compound **IId** was isolated by recrystallization from ethanol; preliminarily, cadmium(II) iodide was separated by column chromatography on silica gel using hexane–ethyl acetate (3:2) as eluent. Yield 5.9 g (93%), mp 89–91°C. ^{31}P NMR spectrum: δ_P 26.9 ppm.

Compound **IIe**. Yield 9.4 g (91%), bp 181–185°C (8 mm), n_D^{20} = 1.6015. ^{1}H NMR spectrum, δ, ppm: 1.15 t (6H, C**H**$_3$CH$_2$O, ^2J = 6.5 Hz), 3.74 q (4H, CH$_3$C**H**$_2$O), 3.90 d (1H, CHP, ^2J = 16.9 Hz), 4.32 q (1H, C**H**NH), 7.13 m (5H, C$_6$**H**$_5$NH), 7.20 m (5H, C$_6$**H**$_5$CH). ^{31}P NMR spectrum: δ_P 28.5 ppm.

Compound **IIf**. Yield 4.6 g (92%), bp 115–118°C (10 mm), n_D^{20} = 1.4251. ^{1}H NMR spectrum, δ, ppm: 1.06 t (3H, C**H**$_3$CH$_2$, ^2J = 7 Hz), 1.15 s [9H, C(CH$_3$)$_3$], 1.45 m (2H, CH$_3$C**H**$_2$), 1.51 t (6H, C**H**$_3$CH$_2$O, ^2J = 6.8 Hz), 3.04 m (1H, CHP), 4.28 q (4H, CH$_3$C**H**$_2$O). ^{31}P NMR spectrum: δ_P 24.8 ppm.

Compound **IIg**. Yield 5.1 g (93%), bp 98–100°C (20 mm), n_D^{20} = 1.4470. ^{1}H NMR spectrum, δ, ppm: 0.82 t (3H, C**H**$_3$CH$_2$, ^2J = 7 Hz), 1.12 t (6H, C**H**$_3$CH$_2$O, ^2J = 6.8 Hz), 1.35 m (11H, C$_6$H$_{11}$), 1.86 m (2H, CH$_3$C**H**$_2$), 2.87 m (1H, CHP), 3.45 q (4H, CH$_3$C**H**$_2$O). ^{31}P NMR spectrum: δ_P 24.6 ppm.

Compound **IIh**. Yield 5.7 g (91%), bp 96–98°C (8 mm), n_D^{20} = 1.4882. ^{31}P NMR spectrum: δ_P 27.6 ppm.

Compound **IIi**. Yield 5.7 g (95%), bp 114–116°C (8 mm), n_D^{20} = 1.5085. ^{31}P NMR spectrum: δ_P 19.2 ppm.

Compound **IIj**. Yield 5.6 g (88%), bp 150–151°C (10 mm), n_D^{20} = 1.5170. ^{31}P NMR spectrum: δ_P 37.3 ppm. Found, %: C 63.98; H 8.39; P 9.26. $C_{18}H_{28}NO_3P$. Calculated, %: C 64.09; H 8.31; P 9.20.

Compound **IIk**. Yield 6.3 g (93%), bp 163–164°C (10 mm), n_D^{20} = 1.4860. ^{1}H NMR spectrum, δ, ppm: 1.42 t (6H, C**H**$_3$CH$_2$O, ^2J = 6.8 Hz), 1.48 m (11H, C_6H_{11}), 1.55 d (3H, C**H**$_3$CH, ^2J = 7.5 Hz), 4.25 q (4H, CH$_3$C**H**$_2$O), 4.45 q (1H, NHC**H**). ^{31}P NMR spectrum: δ_P 32.4 ppm. Found, %: C 63.85; H 8.50; P 8.79. $C_{19}H_{30}NO_3P$. Calculated, %: C 64.96; H 8.55; P 8.83.

Compound **IIl**. Yield 4.3 g (86%), oily substance. ^{31}P NMR spectrum: δ_P 23.8 ppm.

Compound **IIm** was isolated as described above for **IId**. Yield 2.4 g (89.3%), mp 51°C. ^{31}P NMR spectrum: δ_P 21.6 ppm. Found, %: C 57.00; H 8.66; N 4.60; P 9.80. $C_{15}H_{28}NO_4P$. Calculated, %: C 56.78; H 8.83; N 4.42; P 9.77.

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