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Microwave-assisted High Diastereoselective Synthesis of α-Aminophosphonates under Solvent and Catalyst Free-conditions

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Abstract. A simple, efficient and general method has been developed for the high diastereoselective synthesis of α-aminophosphonates through "one-pot" three-component reaction of alkyl and aryl aldehydes with (*S*)-α-methylbenzylamine or (*S*)-3,3-dimethyl-2-butylamine and dimethyl phosphite (Kabachnik-Fields reaction), which proceeds in short time using microwave irradiation under solvent and catalyst free-conditions. This method could be useful in the large-scale synthesis of α-aminophosphonates in short reaction time.
Key words: Three-component Reaction, Diastereoselective Synthesis, α-aminophosphonates, Microwave, Green-Chemistry.

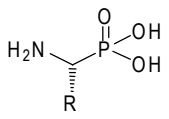
Resumen. Se desarrolló un método eficiente, general y simple para la síntesis altamente diastereoselectiva de α-aminofosfonatos a través de una reacción "one-pot" de tres componentes de aldehídos alifáticos y aromáticos con (*S*)-α-metilbencilamine o (*S*)-3,3-dimetil-2-butilamina y fosfito de dimetilo (reacción de Kabachnik-Fields), la cual procede en tiempos cortos utilizando irradiación de microondas en ausencia de disolvente y catalizador. Este método podría ser de utilidad para la síntesis de α-aminofosfonatos a gran escala y en tiempos cortos de reacción.
Palabras clave: Reacción tres-componentes, síntesis diastereoselectiva, α-aminofosfonatos, microondas, química-verde.

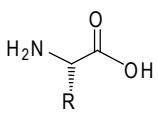
Introduction

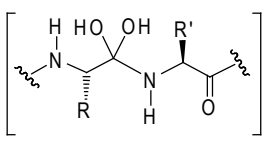
In the last two decades, the α-aminophosphonic acids **1** and their phosphonate derivatives have received considerable attention in synthetic organic and medicinal chemistry, since they are analogues of the natural α-amino acids **2**, versatile intermediates and act as transition state mimics **3** during peptide bond hydrolysis.

The utility of the α-aminophosphonates as peptidomimetics, pharmacogenetic agents, antitumoral enzymatic inhibitors, haptens of catalytic antibodies, inhibitors of UDP-galactopyranose mutase and plant glutamine synthetase, antitumoral, antibiotics and pharmacologic agents are well documented [1,2]. For that reason, the synthesis of α-aminophosphonates has received considerable attention and significant progress has been made to develop more efficient methods for the synthesis of these compounds [3]. In this context, the "one-pot" three-component reaction (Kabachnik-Fields reaction) is one of the most useful methods for the synthesis of α-aminophosphonates due to its versatility and high yields. Recently, the "one-pot" three-component synthesis of α-aminophosphonates starting from aldehydes, amines and dialkyl or trialkyl phosphites has been reported using various catalysts such as $M(ClO_4)_n$ [4], $BF_3.OEt_2$ [5], $In(X)_n$ [6], $Bi(X)_n$ [7], $M(OTf)_n$ [8], MCl_3 [9], $ZrOCl_2$ and H-beta zeolite [10], complex of tetra-*tert*-butyl-phthalocyanine aluminum chloride (*t*-PcAlCl) [11], yttria-zirconia [12], TiO_2 [13], CdI_2 [14], $NbCl_5$ [15], ($KAl(SO_4)_2$-$12H_2O$) [16], SiO_2-$AlCl_3$ [17], CuO [18], task-specific ionic liquid (TSIL) [19], I_2 [20], [PyH]X [21], [bnmim][HSO_4] [22], nano Fe_3O_4 [23], $Al(H_2PO_4)_3$ [24], $Yb(PFO)_3$ [25], PPh_3 [26], tosyl chloride [27], TMSCl [28], and AcOH [29]. However, in spite of their potential utility, these procedures typically suffer from one or more disadvantages such as the use of expensive or less available or stoichiometric amount of catalyst, where specialized handling techniques and tedious work-up are necessary, as well as non-recyclability of the catalyst, long reaction time, vigorous reaction conditions, requirement of excess of reagent, use of solvent, unsatisfactory yields, and lack of generality. Consequently, there is still needs to develop a more efficient, simple, milder and high yield protocol. In this context, the "one-pot" three-component reaction under solvent and catalyst free-conditions [30-32] is an excellent alternative for the synthesis of α-aminophosphonates. Additionally, a combination of catalyst and ultrasonic [33] or microwave [34] irradiation leads to very strong acceleration of these reactions.

In view that the biological activity related to α-aminophosphonic acids and derivatives depends on the absolute configuration of the stereogenic center α at the phosphorus atom [35], the development of a green approach for their stereoselective synthesis is desirable. In this context, and in connection with our green chemistry program, we recently reported an efficient and "one-pot" three-component procedure for the diastereoselective synthesis of α-aminophosphonates. The reactions were carried out by heating the reagents (aldehyde, chiral amines and dimethyl phosphite) at 80 ºC over a period of 5-8 h, depending on aldehyde structure [30]. In order to optimize the reaction conditions for the diastereoselective synthesis of both aliphatic and aromatic α-aminophosphonates in a short time, herein we report an eco-friendly, simple and efficient method based on a "one-pot" three-component reaction of aliphatic and aromatic aldehydes with the chiral amines **4**-**9** and dimethyl phosphite,


(*R*-**1**


(*S*)-**2**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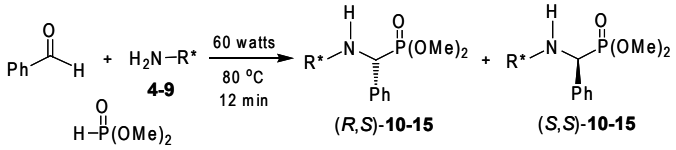
using microwave-irradiation, and under solvent and catalyst free-conditions [36, 37].

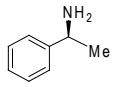
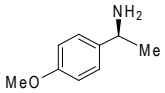
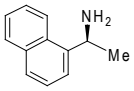
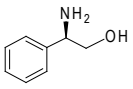
Results and Discussion

We first investigated the "one-pot" three-component reaction of benzaldehyde with (*S*)-α-methylbenzylamine **4** [(*S*)-MBA] and dimethyl phosphite at 80 °C and 60 watts under solvent and catalyst free-conditions [38]. Under these conditions, we found that microwave irradiation causes a strong acceleration of this process (reaction time was shorten, going from 5-8 h to just a 12 min) to give the (*R*,*S*)- and (*S*,*S*)-α-aminophosphonates **10a** in 81% yield as a 75:25 diastereoisomeric ratio (dr), which was determined according to their ^{31}P NMR signals at 27.54 and 27.21 ppm, respectively. The stereochemistry of the α-aminophosphonates was established on the basis of our previous results [30], and by comparison with the results reported in the literature [4a, b].

After the optimization of the experimental conditions with the chiral amine (*S*)-α-MBA, **4**, we extended this "one-pot" three-component reaction with other chiral amines such as (*S*)-4-methoxy-α-methylbenzylamine, **5**, (*S*)-1-(1'-naphthyl)ethylamine, **6**, (*S*)-1,2,3,4-tetrahydro-1-naphthylamine, **7**, (*R*)-phenylglycinol, **8**, and (*S*)-3,3-dimethyl-2-butylamine, **9**. Thus, the reaction of benzaldehyde with the chiral amines **5-7** and dimethyl phosphite predominantly affords the (*R*,*S*)-α-aminophosphonates **11a-13a** (Table 1, entries 2-4). When (*R*)-phenylglycinol **8** was used as the chiral amine, (*R*,*R*)-α-aminophosphonate **14a** was obtained as the major diastereoisomer (Table 1, entry 5) [4a, 29]. The three-component reaction of benzaldehyde with the chiral amines **5-8** and dimethyl phosphite proceeds with good chemical yields but with only moderate diastereoselectivity. On the other hand, using the (*S*)-3,3-dimethyl-2-butylamine, **9** the reaction principally gave the (*R*,*S*)-α-aminophosphonate **15a** in 86% yield and 89:11 dr (Table 1, entry 6). The stereochemistry of the obtained α-aminophosphonates **11a-15a** was

Table 1. Synthesis of α-aminophosphonates **10a-15a** under microwave irradiation.



Entry	Chiral amine	Product	Yield (%)[a]	(*R*,*S*):(*S*,*S*)[b]	δ ^{13}P NMR
1	 **4**	**10a**	81	75:25	27.21[c] 27.54[d]
2	 **5**	**11a**	69	74:26	27.20[c] 27.50[d]
3	 **6**	**12a**	80	75:25	27.20[c] 27.48[d]
4	 **7**	**13a**	79	71:29	27.02[d] 27.26[c]
5	 **8**	**14a**	71	32:68[e]	26.98[c] 27.36[d]
6	 **9**	**15a**	86	89:11	27.07[c] 27.43[d]

[a]The yield was determined after purification.
[b](*R*,*S*):(*S*,*S*) ratio was determined by ^{31}P NMR at 81 MHz in the crude product.
[c]Minor diastereoisomer.
[d]Major diastereoisomer.
[e]In this case the diastereoisomers (*S*,*R*) and (*R*,*R*) were obtained.

Table 2. Synthesis of α-aminophosphonates **10a-f** and **15a-f** under microwave irradiation.

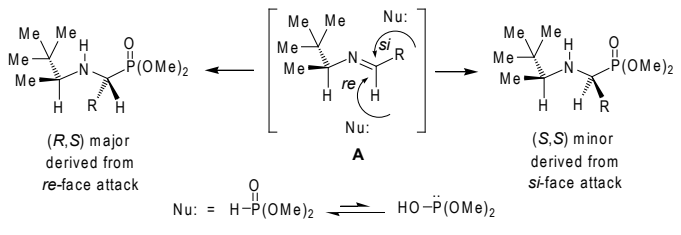
Entry	R	R'	Product	Yield (%)[a]	(*R*,*S*):(*S*,*S*)[b]
1	Ph	Ph	**10a**	81	75:25
2	*p*-ClC_6H_4	Ph	**10b**	85	73:27
3	*p*-$MeOC_6H_4$	Ph	**10c**	81	78:22
4	*i*-Bu	Ph	**10d**	80	70:30[c]
5	*i*-Pr	Ph	**10e**	73	72:28[c]
6	*t*-Bu	Ph	**10f**	66	78:22[c]
7	Ph	*t*-Bu	**15a**	81	89:11
8	*p*-ClC_6H_4	*t*-Bu	**15b**	82	83:17
9	*p*-$MeOC_6H_4$	*t*-Bu	**15c**	86	88:12
10	*i*-Bu	*t*-Bu	**15d**	84	98:02[c]
11	*i*-Pr	*t*-Bu	**15e**	79	90:10[c]
12	*t*-Bu	*t*-Bu	**15f**	71	93:07[c]

[a]Isolated yields.
[b]Determined by ^{31}P NMR (81 MHz)examination of the crude reaction mixture.
[c]The reactions were carried out at 70 °C.

established by correlation of the spectroscopic data with those obtained for α-aminophosphonate **7a**.

With these optimized conditions in hand, the "one-pot" three-component reaction of aliphatic and aromatic aldehydes with chiral amines **4** and **9** and dimethyl phosphite was carried out, obtaining the corresponding (*R*,*S*)- and (*S*,*S*)-α-aminophosphonates **10a-f** (Table 2, entries 1-6) and **15a-f** (Table 2, entries 6-12) with good yield and diastereoselectivity. A slight decrease in reaction rate was observed when aliphatic aldehydes were used.

Based on our previous studies [30] and those reported in the literature [39], the origin of diastereoselectivity in the "one-pot" three-component reaction of aldehydes, (*S*)-3,3-dimethyl-2-butylamine **9** and $(MeO)_2P(O)H$ under microwave irradiation can be explained as illustrated in Scheme 1. The initial condensation reaction of aldehyde and **9** gave the corresponding Schiff base **A**, which adopts a conformation where the proton of the chiral fragment is eclipsed with the imine double bond, as should be expected from the 1,3-allylic strain model [40]. The conformation with the *t*-Bu-C- or Me-C moieties eclipsed with N=C-H fragment are appreciably higher in energy as has been



Scheme 1. Proposed mechanism for nucleophilic attack of $(MeO)_2P(O)H$ onto Schiff bases.

determined by ab initio MO and DFT studies. Consequently, the nucleophilic attack of dimethyl phosphite onto the Schiff base **A** takes place at the *re* face (less hindered face) to affords the α-aminophosphonates (*R*,*S*) as the major diastereoisomers.

In summary, we found a high diastereoselective "one-pot" three-component reaction of aldehydes, chiral amines and dimethyl phosphite under solvent and catalyst free-conditions using microwave irradiation. We also established that Schiff bases intermediates derived from (*S*)-3,3-dimethyl-2-butylamine **9** shows higher C=N π-facial selectivities than those found in the Schiff bases derived from commonly used (*S*)-α-methylbenzylamine **4** or the chiral amines **5-8**. This procedure could be used in the synthesis of large amounts of α-aminophosphonates in short reaction times.

Experimental Section

General Information: All commercial reagents were used as received without further purification. Microwave reactions were performed in a CEM Discover System (with a power of 60 W). Flash chromatography was performed using 230-400 mesh Silica Flash 60® silica gel. Thin layer chromatography was performed with pre-coated TLC sheets of silica gel (60 F254, Merck). NMR spectra were recorded with a Varian System instrument (400 MHz for ^1H, and 100 MHz for ^{13}C) and a Mercury instrument (81 MHz for ^{31}P) and calibrated with $CDCl_3$ as solvent and TMS as internal standard signal. Chemical shifts (δ) are reported in parts per million. Coupling constants (*J*) are given in Hz. High resolution FAB^+ and CI^+ mass spectra (HRMS) were obtained in a JEOL HRMStation JHRMS-700. Microanalyses were determined in an Elemental VARIO EL III machine.

General procedure for the synthesis of α-aminophosphonates under microwave irradiation: A mixture of aldehyde (1.0 equiv.) and chiral amine (1.0 equiv.) in an open flask without any solvent and catalyst was irradiated with MW (60 W) at 80 °C for 2 min. The flask was cooled at room temperature and dimethyl phosphite (1.05 equiv.) was added. The reaction mixture was again irradiated at 80 °C for 10 min. The crude products were analyzed by ^{31}P NMR spectroscopy at 81 MHz, and then purified by column chromatography on silica gel, obtaining the corresponding (*R*,*S*)- and (*S*,*S*)-α-aminophosphonates. All spectroscopy data for α-aminophosphonates **10a-f** and **15a-f** have been reported by us [30].

Dimethyl (R,S)- and (S,S)-{(Phenyl)[(1-phenylethyl)amino]methyl}phosphonate (**10a**): A mixture of benzaldehyde (250 mg, 2.35 mmol), (*S*)-α-MBA (280 mg, 2.35 mmol), and dimethyl phosphite (250 mg, 2.46 mmol) was irradiated at 80 °C for 12 min. Product **10a** was obtained (601 mg, 81%) as a white solid; mp 60 °C.

Dimethyl (R,S)- and (S,S)-{(4-Chlorophenyl)[(1-phenylethyl)amino]methyl}phosphonate (**10b**): A mixture of 4-chlorobenzaldehyde (250 mg, 1.78 mmol), (*S*)-α-MBA (210 mg, 1.78 mmol), and dimethyl phosphite (200 mg, 1.87 mmol) was irradiated at 80 °C for 12 min. Product **10b** was obtained (521 mg, 85%) as an oil.

Dimethyl (R,S)- and (S,S)-{(4-Methoxyphenyl)[(1-phenylethyl)amino]methyl}phosphonate (**10c**): A mixture of 4-methoxybenzaldehyde (250 mg, 1.83 mmol), (*S*)-α-MBA (210 mg, 1.83 mmol), and dimethyl phosphite (200 mg, 1.92 mmol) was irradiated at 80 ºC for 12 min. Product **10c** was obtained (490 mg, 81%) as a yellow oil.

Dimethyl (R,S)- and (S,S)-{3-Methyl-1-[(1-phenylethyl)amino]butyl}phosphonate (**10d**): A mixture of isovaleraldehyde (250 mg, 2.90 mmol), (*S*)-α-MBA (350 mg, 2.90 mmol), and dimethyl phosphite (330 mg, 3.04 mmol) was irradiated at 70 ºC for 12 min. Product **10d** was obtained (697 mg, 80%) as a yellow oil.

Dimethyl (R,S)- and (S,S)-{2-Methyl-1-[(1-phenylethyl)amino]propyl}phosphonate (**10e**): A mixture of isobutyraldehyde (250 mg, 3.46 mmol), (*S*)-α-MBA (410 mg, 3.46 mmol), and dimethyl phosphite (400 mg, 3.63 mmol) was irradiated by MW at 70 ºC for 12 min. Product **10e** was obtained (704 mg, 73%) as a yellow oil.

Dimethyl (R,S)- and (S,S)-{2,2-Dimethyl-1-[(1-phenylethyl)amino]propyl}phosphonate (**10f**): A mixture of *tert*-butylacetaldehyde (250 mg, 2.90 mmol), (*S*)-α-MBA (330 mg, 2.90 mmol), and dimethyl phosphite (330 mg, 3.04 mmol) was irradiated at 70 ºC for 12 min. Product **10f** was obtained (538 mg, 66%) as an oil.

Dimethyl (R,S)- and (S,S)-{(Phenyl)[(1,2,2-trimethylpropyl)amino]methyl}phosphonate (**15a**): A mixture of Benzaldehyde (250 mg, 2.35 mmol), (*S*)-3,3-dimethyl-2-butylamine(237 mg, 2.35 mmol), and dimethyl phosphite (250 mg, 2.46 mmol) was irradiated at 80 ºC for 12 min. Product **15a** was obtained (568 mg, 81%) as a solid; mp 66 ºC.

Dimethyl (R,S)- and (S,S)-{(4-Chlorophenyl)[(1,2,2-trimethylpropyl)amino]methyl}-phosphonate (**15b**): A mixture of 4-chlorobenzaldehyde (250 mg, 1.78 mmol), (*S*)-3,3-dimethyl-2-butylamine (179 mg, 1.78 mmol), and dimethyl phosphite (200 mg, 1.87 mmol) was irradiated at 80 ºC for 12 min. Product **15b** was obtained (640 mg, 82%) as an oil.

Dimethyl (R,S)- and (S,S)-{(4-Methoxyphenyl)[(1,2,2-trimethylpropyl)amino]methyl}-phosphonate (**15c**): A mixture of 4-methoxybenzaldehyde (250 mg, 1.83 mmol), (*S*)-3,3-dimethyl-2-butylamine (180 mg, 1.83 mmol), and dimethyl phosphite (200 mg, 1.92 mmol) was irradiated at 80 ºC for 12 min. Product **15c** was obtained (504 mg, 86%) as an oil.

Dimethyl (R,S)- and (S,S)-{3-Methyl-1-[(1,2,2-trimethylpropyl)amino]butyl}phosphonate (**15d**): A mixture of isovaleraldehyde (250 mg, 2.90 mmol), (*S*)-3,3-dimethyl-2-butylamine (290 mg, 2.90 mmol), and dimethyl phosphite (330 mg, 3.04 mmol) was irradiated at 70 ºC for 12 min. Product **15d** was obtained (671 mg, 84%) as an oil.

Dimethyl (R,S)- and (S,S)-{2-Methyl-1-[(1,2,2-trimethylpropyl)amino]propyl}phosphonate (**15e**): A mixture of isobutyraldehyde (250 mg, 3.46 mmol), (*S*)-3,3-dimethyl-2-butylamine (350 mg, 3.46 mmol), and dimethyl phosphite (400 mg, 3.53 mmol) was irradiated at 70 ºC for 12 min. Product **15e** was obtained (661 mg, 79%) as an oil.

Dimethyl (R,S)- and (S,S)-{2,2-Dimethyl-1-[(1,2,2-trimethylpropyl)amino]propyl}-phosphonate (**15f**): A mixture of *tert*-butylacetaldehyde (250 mg, 2.90 mmol), (*S*)-3,3-dimethyl-2-butylamine (490 mg, 2.90 mmol), and dimethyl phosphite (330 mg, 3.04 mmol) was irradiated at 70 ºC for 12 min. Product **15f** was obtained (961 mg, 71%) as an oil.

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