Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 4243–4245

TETRAHEDRON LETTERS

Microwave-assisted synthesis of α-aminophosphinic acids from hypophosphorus acid salts under solvent free conditions

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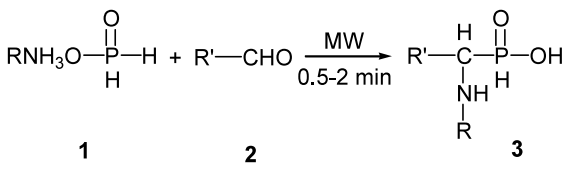
Received 9 February 2003; revised 27 March 2003; accepted 4 April 2003

Abstract—A simple, efficient, and general method has been developed for the synthesis of α-aminophosphinic acids from hypophosphorus salts under solvent-free conditions using microwave irradiation. α-Aminophosphinic acids were obtained in high yield under mild conditions by reaction of the amine salts of hypophosphorus acid with aldehydes in the presence of microwave irradiation.

Organophosphorus compounds have found a wide range of application in the areas of industrial, agricultural, and medicinal chemistry owing to their biological and physical properties as well as their utility as synthetic intermediates.[1] α-Functionalized phosphinic acids are valuable intermediates for the preparation of medicinal compounds and synthetic intermediates. α-Aminophosphinic acids, the phosphinic acid analogues of α-amino carboxylic acids, are an important class of compounds that exhibit a variety of interesting and useful properties. Compounds containing an α-aminoalkylphosphinic acid functional group are of considerable importance because of their anti-bacterial,[2] herbicidal[3] and fungicidal[4] activities. In contrast to the widely studied α-aminophosphonic acid derivatives,[5–8] relatively few papers have been reported on the chemistry of α-aminophosphinic acids, although there is evidence that α-aminophosphinic acids are pharmaceutically active. Many effective methods for the preparation of α-aminoalkylphosphonic acids have been developed, but few synthetic routes to α-aminophosphinic acids have been reported. These methods involve prolonged heating of anhydrous hypophosphorus acid with a Schiff's base and Mannich-type reactions of amines with aldehydes and anhydrous hypophosphorus acid.[9] However, both of these methods have problems, including harsh reaction conditions, anaerobic and anhydrous conditions, long reaction times and side reactions.[10] To avoid the problems associated with handling anhydrous H_3PO_2, hypophosphorus salts (highly crystalline, high-melting, cheap, and non-hygroscopic) have been developed as safer and convenient reagents for the synthesis of phosphinic acids.[11] The application of microwave energy to accelerate organic reactions is of increasing interest and offers several advantages over conventional techniques.[12] Syntheses which normally require lengthy periods, can be achieved conveniently and very rapidly in a microwave oven. As part of our efforts to explore the utility of microwave-assisted reactions for the synthesis of organophosphorus compounds,[13–18] we report a new method for the preparation of α-aminophosphinic acids from hypophosphorus acid salts under solvent-free conditions, using microwave irradiation producing high yields of α-aminophosphinic acids (Scheme 1, Table 1).

As shown in Scheme 1 and Table 1, the reaction of a mixture of anilinium hypophosphite[19] with aromatic and aliphatic aldehydes (**2a–j**) under microwave irradiation, afforded the desired products in good yields (**3a–j**). Cyclohexylammonium hypophosphite also reacted to give the desired compounds in good yields (**3k–l**). The reaction of (*R*)-(+)-phenylethylammonium hypophosphite with aldehydes gave the desired compounds in good yields. The reactions were clean with no tar formation.[20]



Scheme 1.

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0040-4039/03/$ - see front matter
doi:10.1016/S0040-4039(03)00893-1

Table 1. Reaction of a hypophosphorus acid salts with aldehydes under microwave irradiation

	R **1**	R′ **2**	Reaction time (min)	Yield (%)[a] **3**
a	C_6H_5-	C_6H_5-	0.5	66
b	C_6H_5-	*p*-$CH_3C_6H_4$-	2	68
c	C_6H_5-	*p*-$CH_3OC_6H_4$-	1.5	65
d	C_6H_5-	*p*-$(CH_3)_2CHC_6H_4$-	2	70
e	C_6H_5-	*m*-BrC_6H_4-	1	68
f	C_6H_5-	*m*-ClC_6H_4-	1	65
g	C_6H_5-	*m*-$CH_3OC_6H_4$-	1.5	68
h	C_6H_5-	*o*-ClC_6H_4-	1	75
i	C_6H_5-	1-$C_{10}H_7$-	2	78
j	C_6H_5-	C_6H_5-CH=CH-	1	80
k	Cyclohexyl	C_6H_5-	1	60
l	Cyclohexyl	C_6H_5-CH=CH-	1	65
m	(*R*)-(+)-1-Phenylethyl-	C_6H_5-	1	66[b]
n	(*R*)-(+)-1-Phenylethyl-	C_6H_5-CH=CH-	1	78[c]

[a] Isolated yields.
[b] Diastereomeric ratio is 55:45 based on ^{31}P NMR.
[c] Diastereomeric ratio is 60:40 based on ^{31}P NMR.

In summary, low consumption of solvent, fast reaction rates, mild reaction conditions, good yields, the simple work-up, and relatively clean reactions with no tar formation make this method an attractive and a useful contribution to the present methodologies. Indeed, a wide range of aldehydes and amine salts were converted to the corresponding α-aminophosphinic acids using this method.

Acknowledgements

The Institute for Advanced Studies in Basic Sciences (IASBS) is thanked for supporting this work.

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19. Procedure for the preparation of hypophosphorus acid salts (**1**): The amine (0.1 mol) was added to stirred anhydrous hypophosphorus acid (6.6 g, 0.1 mol, water was removed under vacuum from a commercially available *50%* solution, for the method used, see: Fitch, P. J. *J. Am. Chem. Soc*. **1964**, *86*, 61) in ethanol with cooling to prevent the temperature rising above 25°C. The precipitated salts were filtered off and washed with dry ethanol and then with dry ether. All salts gave satisfactory spectral data in accord with the assigned structures. For (*R*)-(+)-1-phenylethylammonium hypophosphite as an example: white crystals; mp 118–20°C; $[\alpha]_D = +53.5$ (*c* 1.87, CH_3OH); ^1H NMR (D_2O/TMS/500 MHz): 1.44 (3H, d, $J = 6.9$ Hz), 4.32 (1H, q, $J = 6.9$ Hz), 6.86 (2H, d, $J_{H-P} = 500$ Hz), 7.32 (5H, m); ^{31}P NMR (D_2O/H_3PO_4): 6.87 ppm; IR (KBr): 3600–2015, 1201 (P=O), 1059, 970 (P–O) cm^{-1}.
20. This solvent-free reaction method is operationally simple. 10 mmol of hypophosphorus acid salt was added to 10 mmol of aldehyde and the mixture was irradiated with microwaves for 0.5–2 min at 720 W (a kitchen-type microwave was used in all experiments). Sodium hydroxide (1.6 g, 50%) was added dropwise to the reaction mixture and this was extracted with ether (3×20 ml) until the ether layer appeared completely colorless. The aqueous portion was freed from residual ether by heating. After cooling, the aqueous solution was added dropwise, with rapid stirring, to 20 ml of 3N hydrochloric acid. The precipitated α-aminophosphinic acid was filtered and redissolved in aqueous sodium hydroxide, the solution was extracted with ether, and the α-aminophosphonic acid reprecipitated by adding to aqueous hydrochloric acid as shown above. After filtration, washing with water, and drying in vacuo over phosphorus pentoxide a light yellow powder was obtained. All products gave satisfactory spectral data in accord with the assigned structures. For **3m** as an example ^1H NMR (CD_3OD/TMS-500 MHz): 1.64 (3H, d, $J = 6.9$ Hz), 3.76, 4.01 (1H, 2d, $J = 13.8$ Hz, -CHP), 4.21, 4.70 (1H, 2q, $J = 6.9$ Hz), 6.94, 7.02 (1H, 2d, $J_{H-P} = 500$ Hz), 7.26–8.02 (10H, m); ^{31}P NMR (D_2O/H_3PO_4): 15.16, 16.44 (45:55); IR (KBr): 3650–2120 (-NH_3), 1201 (P=O), 1055–930 (P–O) cm^{-1}.