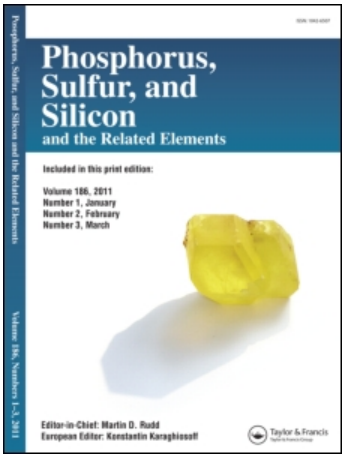


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

SYNTHESIS OF AMINOBENZYLPHOSPHONOUS ACIDS VIA DIRECT AMIDOALKYLATION OF HYPOPHOSPHOROUS ACID

Roman Tyka[a]; Gerhard Hägele[b]
[a] Institute of Organic and Physical Chemistry, Technical University of Wroclaw, Wroclaw, Poland [b] Institute of Inorganic Chemistry and Structural Chemistry, University of Düsseldorf, Universitätsstraße 1, Düsseldorf, C.F.R.

To cite this Article Tyka, Roman and Hägele, Gerhard(1989) 'SYNTHESIS OF AMINOBENZYLPHOSPHONOUS ACIDS VIA DIRECT AMIDOALKYLATION OF HYPOPHOSPHOROUS ACID', Phosphorus, Sulfur, and Silicon and the Related Elements, 44: 1, 103 — 107
To link to this Article: DOI: 10.1080/10426508908043712
URL: http://dx.doi.org/10.1080/10426508908043712

Phosphorus, Sulfur, and Silicon, 1989, Vol. 44, pp. 103–107
Reprints available directly from the publisher
Photocopying permitted by license only

SYNTHESIS OF AMINOBENZYLPHOSPHONOUS ACIDS VIA DIRECT AMIDOALKYLATION OF HYPOPHOSPHOROUS ACID

ROMAN TYKA
Institute of Organic and Physical Chemistry, Technical University of Wroclaw, Wybrzeze Wyspianskiego 27, PL-50-370 Wroclaw, Poland

and

GERHARD HÄGELE
Institute of Inorganic Chemistry and Structural Chemistry, University of Düsseldorf, Universitätsstraße 1, D-4000 Düsseldorf, G.F.R.

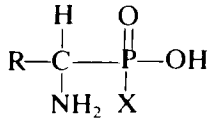
(Received June 27, 1988)

Aminobenzylphosphonic acids are obtained by amidoalkylation of hypophosphorous acid with *N,N'*-arylidene bisamides.

Key words: Aminobenzylphosphonous acid; amidoalkylation; hypophosphorous acid; *N,N*-arylidene bisamides.

INTRODUCTION

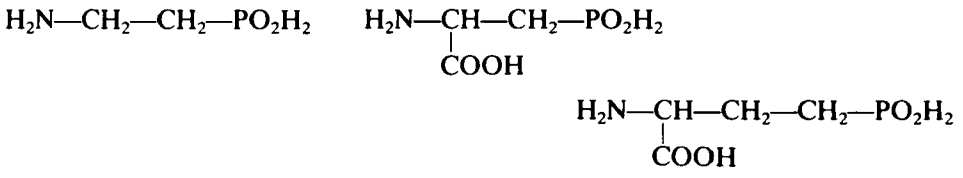
There are three types of 1-aminoalkylphosphorus acids having carbon-to-phosphorus bonds:



1 X = OH	1-aminoalkylphosphonic acids
2 X = alkyl, aryl	1-aminoalkylphosphinic acids
3 X = H	1-aminoalkylphosphonous acids

The more familiar groups of 1-aminoalkylphosphonic acids **1**[1,2] and 1-aminoalkylphosphinic acids **2**[3] have been studied intensively in both academic and industrial laboratories with respect to interesting chemical aspects and remarkable biological activities.[4]

On the contrary very little is known regarding the 1-aminoalkylphosphonous acids **3**. As far as we know no natural sources for 1-aminoalkylphosphonous acids of type **3** were detected up to now. But the analogous 2- and the 3-aminoalkylphosphonous acids were isolated by Japanese workers[5,6] from streptomyces hygroscopicus and supported the increasing attention drawn towards this class of natural trivalent phosphorus compounds.

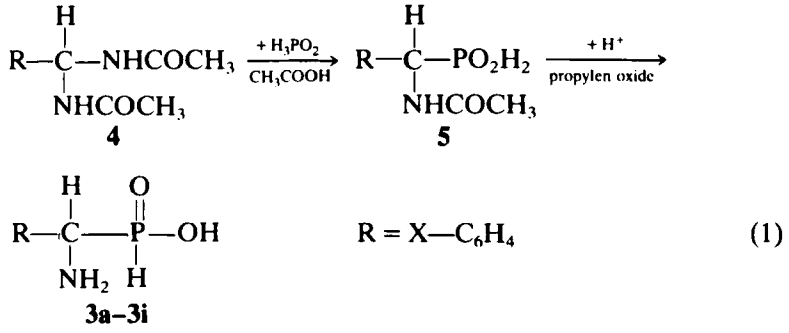


In general the hitherto known synthetic approaches for 1-aminoalkylphosphonous acids made use of a direct addition of hypophosphorous acid H_3PO_2 to activated —C=N-double bonds from Schiff's bases (provided directly or produced in situ) and oximes.[7–11]

In particular we wish to draw the reader's interests towards excellent studies given by Baylis and coworkers, who made a fullscope synthetic approach to 17 1-aminoalkylphosphonous acids with structures isosteric to natural protein amino acids. Some of the compounds prepared have interesting antimicrobial activities or plant growth inhibiting properties.[10,11]

RESULTS

In the paper presented here we wish to report on a convenient synthetic route to the yet unknown aminobenzylphosphonous acids. A novel approach is used omitting Schiff's bases or oximes as starting compounds. In this case amidoalkylation of hypophosphorous acid is achieved by means of *N,N'*-arylidene bisamides, easily accessible precursors, as shown in Equation (1):



(1)

3	a	b	c	d	e	f	g	h	i
X	H	p-CH_3	o-CH_3	o-Cl	m-Cl	p-Cl	p-OCH_3	m-NO_2	p-Br

This is the first report on a successful direct amidoalkylation of hypophosphorous acid, though the Mannich reaction of H_3PO_2[12a] and amidoalkylation of other trivalent phosphorus compounds has been done earlier.[12b] Only bisamides **4** prepared from *aromatic* aldehydes undergo reactions according to Equation (1), while bisamides derived of aliphatic aldehydes are unreactive. Intermediates **5** were not isolated.

Structures and purities of **3a–3i** were established unequivocally by NMR, IR and elemental analysis. Results are summarised in Tabels I–IV.

It is interesting to note the following NMR-parameters: δ_H (PH) = 7.03 – 7.16 ppm; $|^1J_{PH}|$ = 518–528 Hz; δ_H (PCH) = 4.06–4.80 ppm; $^2J_{PH}$ = (–)13 Hz. δ_H (PCH) is sensitive towards the substitution pattern of the aromatic ring

TABLE I

Yields, melting points, molecular formulae and molecular weights for aminobenzylphosphonous acids **3a–3i**

Compounds **3a–3i**		Yield %	M.p. °C	Molecular formula	Molecular weight
3a	H	70	242–243	$C_7H_{10}NO_2P$	171.14
3b	*p*-CH_3	72	237–238	$C_8H_{12}NO_2P$	185.16
3c	*o*-CH_3	30	228–230	$C_8H_{12}NO_2P$	185.16
3d	*o*-Cl	31	229–231	$C_7H_9ClNO_2P$	205.58
3e	*m*-Cl	48	235–236	$C_7H_9ClNO_2P$	205.58
3f	*p*-Cl	41	249–250	$C_7H_9ClNO_2P$	205.58
3g	*p*-OCH_3	69	233–235	$C_8H_{12}NO_3P$	201.16
3h	*m*-NO_2	51	247–248	$C_7H_9N_2O_4P$	216.14
3i	*p*-Br	56	246–247	$C_7H_9BrNO_2P$	250.03

TABLE II

^{1}H-NMR-data for aminobenzylphosphonous acids **3a–3i**. Chemical shift values in ppm vs. $[(CH_3)_3Si]_2O$, couplings constants in Hz.
Ar: centre for multiplet structure of aromatic ring protons, not fully analyzed

Compounds **3a–3i**	δ_H (CH)	$\|^2J_{PCH}\|$	δ_H (PH)	$\|^1J_{PH}\|$	δ_H (CH_3)	δ_H (Ar)
3a	4.33	13	7.10	518	—	7.73
3b	4.13	13	7.00	518	2.62	7.53
3c	4.50	13	7.03	524	2.66	7.62
3d	4.80	13	7.05	526	—	7.66
3e	4.26	13	7.13	522	—	7.66
3f	4.06	13	7.06	520	—	7.73
3g	4.10	13	7.06	518	4.06	7.47
3h	4.26	13	7.06	524	—	8.16
3i	4.20	13	7.16	528	—	7.57

TABLE III

IR data (cm^{-1}) for aminobenzylphosphonous acids **3a–3i**

Compounds **3a–3i**	Hydrogen-bonding	P—H	P=O	P—O
3a	3600–2450	2320	1200	1060
3b	3600–2330	2390	1190	1050
3c	3600–2390	2360	1180	1030
3d	3600–2400	2330	1190	1050
3e	3600–2350	2320	1170	1030
3f	3600–2380	2310	1190	1050
3g	3700–2380	2300	1180	1030
3h	3700–2380	2340	1180	1030
3i	3600–2380	2300	1190	1040

TABLE IV

Analytical data for aminobenzylphosphonous acids **3a–3i**. Halog.: Cl (**3d–3f**), Br (**3i**)

Compounds 3a–3i	Found %			Required %		
	N	P	Halog.	N	P	Halog.
3a	8.44	18.02	—	8.19	18.10	—
3b	7.82	16.50	—	7.57	16.73	—
3c	7.77	16.52	—	7.57	16.73	—
3d	7.10	14.95	17.29	6.81	15.06	17.24
3e	7.07	15.29	17.51	6.81	15.06	17.24
3f	7.02	14.85	17.38	6.81	15.06	17.24
3g	7.21	15.12	—	6.96	15.39	—
3h	12.80	14.61	—	12.96	14.33	—
3i	5.88	12.50	32.21	5.60	12.39	31.96

system: going from ortho-Cl (**1d**) via meta-Cl (**1e**) to para-Cl (**1f**) a decrease of δ_H (PCH) is observed: 4.80 ppm, 4.26 ppm and 4.20 ppm. An identical trend holds for $^1J_{PH}$: 526 Hz (**1d**), 522 Hz (**1e**) and 520 Hz (**1f**).

Our work about amidoalkylation of hypophosphorous acid by means of *N,N'*-arylidene bisamides will be continued.

ACKNOWLEDGEMENTS

This work was supported by the Fonds der Chemischen Industrie e.V. and by Henkel KGaA.

EXPERIMENTAL

Melting points were determined using a Boetius apparatus and were not corrected. The IR spectra were taken on a Perkin–Elmer 621 instrument. ^{1}H-NMR spectra were recorded with a Tesla BS 467 instrument operating at 60 MHz using hexamethyldisiloxane as an internal standard.

N,N'-arylidene bisamides **4**. *General procedure.* A mixture of aromatic aldehyde (0.2 mol), acetamide (23.6 g, 0.4 mol), glacial acetic acid (20 ml) and acetic anhydride (20 ml) was refluxed for 1.5 h. After removing the solvents under reduced pressure the product was filtered, washed with alcohol and dried. For other synthetic routes to bisamides see Reference 13.

Aminobenzylphosphonous Acids **3**. *General procedure.* A mixture of arylidene bisamide **4** (0.1 mol), anhydrous hypophosphorus acid[14] (6.6 g, 0.1 mol) and glacial acetic acid (30 ml) was refluxed for 2 h. After removing the solvent under reduced pressure the residue was hydrolized with 20% hydrochloric acid (40 ml) at ambient temperature during 2 h. Volatile products were evaporated in vacuo, the remaining residue was dissolved in ethanol (25–50 ml) and treated with propylene oxide until precipitation ceased. The precipitate was filtered, washed with small amounts of water (to remove NH_4Cl) and with ethanol and dried.

REFERENCES

1. D. Redmore in *Topics in Phosphorus Chemistry*, ed. E. J. Griffith and M. Grayson, Interscience Publishers, New York 1976, Vol. **8**, pp 515.
2. W. P. Kuhar and W. A. Solodenko, *Uspechi Chim.* **8**, 1504 (1987, LVI).
3. L. Maier, *Phosphorus and Sulfur*, **14**, 295 (1983).
4. P. Kafarski and P. Mastalerz in *Beiträge zur Wirkstofforschung*, ed. P. Oehme, H. Loewe, E. Gores, J. Axt, Inst. f. Wirkstofforschung, Berlin (DDR) Vol. **21**, pp. 1–100 (1984).

5. H. Seto, S. Imai, T. Tsuruoka, H. Ogawa, A. Satoh, T. Sasaki and N. Otake, *Biochem. Biophys. Res. Comm.* **111,** 1008 (1983).
6. H. Seto, T. Sasaki, S. Imai, T. Tsuruoka, H. Ogawa, A. Satoh, S. Inouye, T. Niida and N. Otake, *J. Antibiot.* **36,** 96 (1983).
7. H. Schmidt, *Chem. Ber.* **81,** 477 (1948).
8. N. Kreutzkamp, C. Schmipfky and K. Storck, *Arch. Pharm.* **300,** 868 (1967).
9. R. N. Khomutov and T. I. Osipova, *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1978,** 1951.
10. E. K. Baylis, C. D. Campbell, J. G. Dingwall and W. Pickles, ACS Symposium Series No. 171, ed. L. D. Quin and J. Verkade **1981,** 183.
11. E. K. Baylis, C. D. Campbell and J. G. Dingwall, *J. Chem. Soc. Perkin Trans.* I **1984,** 2845
12. (a) L. Maier, *Helv. Chim. Acta,* **50,** 1742 (1967); (b) J. Oleksyszyn, *J. prakt. Chem.* **329,** 19 (1987).
13. (a) H. E. Zaugg and W. B. Martin, *Org. React.* **14,** 52 (1965); (b) H. E. Zaugg, *Synthesis* **85,** 181 (1984).
14. P. J. Fitch, *J. Am. Chem. Soc.* **86,** 61 (1964).