Pergamon

Tetrahedron, Vol. 52, No. 26, pp. 8789-8794, 1996

0040-4020/96 $15.00 + 0.00

PII: S0040-4020(96)00420-6

THE THERMALLY INDUCED SYNTHESIS OF N-(DIETHOXYPHOSPHORYL)ALDIMINES[1]

Andrzej Zwierzak and Anna Napieraj

Institute of Organic Chemistry, Technical University (Politechnika),
Żwirki 36, 90-924 Łódź 40, Poland.

Abstract: The reaction of diethyl phosphoroamidate (**2**) with aromatic aldehyde diethyl acetals (**1**) carried out at 120 - 160°C provides a simple, one-step preparation of N-(diethoxyphosphoryl)aldimines (**3a-b**). The extension of this reaction to aliphatic aldehyde diethyl acetals failed to give the expected imines.

INTRODUCTION

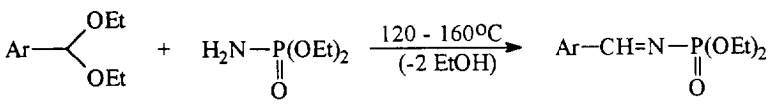
N-Sulphonylaldimines have proven to be useful intermediates in organic synthesis and their use as reagents continues to expand in recent years[2,3]. Addition of Grignard and organolithium compounds to electrophilic N-tosylimines (produced in situ by the Kresze procedure[4]) described by Weinreb and Sisko[5] offered the first general solution to the longstanding problem of addition of organometallics to imines. The N-tosyl group is, however, one of the most stable protecting groups for an amino function, and only the reduction with sodium in liquid ammonia is practically the useful deprotection method[6,7]. Many serious side reactions have been, however, reported for such desulphonylation[8]. Recently several new methods for the deprotection of tosyl group have appeared in the literature. These methods include the use of 30% hydrogen bromide in acetic acid in the presence of phenol at room temperature[9], utilization of sodium naphthalene anion radical in dimethoxyethane solution[10], or photodesulphonylation in the presence of 1,5-dimethoxynaphthalene and sodium borohydride[11]. All the aforementioned detosylation protocols are neither convenient nor economic, especially for large scale preparations. Looking for stable, nonbasic and electron-deficient imine derivatives bearing easily deprotectable groups at nitrogen we turned recently our attention to N-(diethoxyphosphoryl)aldimines which were not so far reported in the literature[1]. Compounds of similar structure, N-(diphenylphosphinyl)imines, are known[12] and used *inter alia* for enantio-[13] and diastereo-selective[14] syntheses of primary amines, but they cannot be easily and inexpensively prepared by simple and reliable procedures.

RESULTS AND DISCUSSION

Kresze *et al.*[4] have shown that aromatic aldehyde diethyl acetals easily condense with arylsulphonamides at 150-160°C to give N-sulphonylaldimines in high yield. In view of these results, it was envisaged that a similar reaction might be possible between diethyl phosphoroamidate and aromatic aldehyde diethyl acetals. Indeed, it was found that brief heating of diethyl phosphoroamidate (**2**) with an excess of the respective diethyl acetal (**1**) at 120-160°C and removal of ethanol formed by distillation gave the N-(diethoxyphosphoryl)aldimines (**3a-h**) in good yield (Table).

In spite of the results of our initial experimentation[1] the use of stoichiometric amounts of (**1**) and (**2**) for condensation did not guarantee the reported yields of (**3**). Washing the product with water in benzene solution, which was previously deemed to remove the unreacted diethyl phosphoroamidate (**2**), was now found detrimental to the purity of crude (**3**) producing even more of (**2**) by rapid hydrolysis. An excess of diethyl acetal (**1**) and small amounts (usually below 5%) of unreacted (**2**) could be easily separated by distillation *in vacuo* affording analytically pure samples of N-(diethoxyphosphoryl)aldimines (**3**).

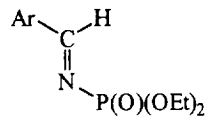
All these compounds were characterised by ^{1}H and ^{31}P NMR spectroscopy, molecular weight determinations and elemental analysis.



(**1**) (**2**) (**3**)

N-(Diethoxyphosphoryl)aldimines (**3a-h**) are colourless, yellow or orange syrupy oils or low melting solids (**3d** and **3f**), easily soluble in common organic solvents. They are hydrolytically unstable but under strictly anhydrous conditions can be stored at low temperature (0-5°C) for long periods of time without any appreciable change. Compound (**3c**) is distinctly less stable and tends to decompose after 2 weeks of storage at 0-5°C.

The most informative and diagnostic structural feature in the ^{1}H NMR spectra of compounds (**3a-h**) is the imino proton doublet usually at $\delta=8.8$ - 9.1 ppm split by a large three-bond coupling of ca. 32-33Hz to phosphorus[12]. Compound (**3g**) is anomalous in this respect. The signal of the imino proton is shifted downfield to $\delta=9.70$ ppm, which may be attributed to the position of the imine proton in the deshielding region of an aromatic ring. Such phenomenon has been previously observed and similarly explained for N-(diphenylphosphinyl)-1-naphthylideneimine[12]. All phosphorylated imines (**3a-h**) exhibit only one signal in their ^{31}P NMR spectra. We tentatively ascribe the structure of (E)-diastereoisomers (**4**) to all of them.



(4)

Table. N-(Diethoxyphosphoryl)aldimines (3)

Compound	Ar	Yield (%)[a]	δ_H[b]	$^3J_{PH}$/Hz	δ_p	$\nu_{C=N}$/cm^{-1}
3a	Ph	68	9.10	32.4	8.30	1626
3b	4-MeC_6H_4	88	9.05	32.4	8.68	1624
3c	4-BrC_6H_4	73	9.03	32.1	7.92	1632
3d	4-MeOC_6H_4	82	9.00	32.3	9.07	1624
3e	2-MeOC_6H_4	77	9.55,9.56[c]	32.8	9.34	1620
3f	2-Furyl	79	8.81	33.3	8.79	1622
3g	1-Naphthyl	73	9.70	33.5	8.10	1632
3h	Ph-CH=CH	69	8.81	31.9	8.09	1626

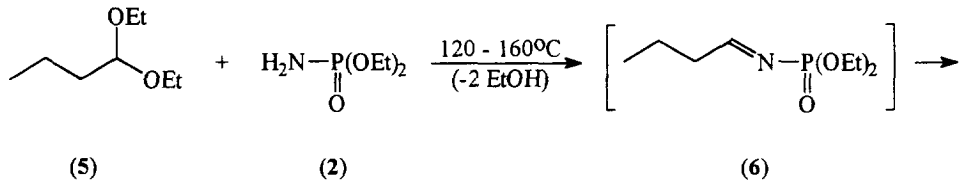
[a] Isolated yields of analytically pure imines.

[b] Chemical shift of the imino proton.

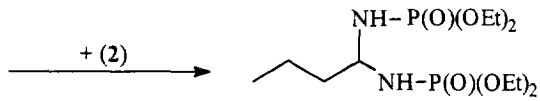
[c] Two doublets of almost equal intensities. The reason of such pattern is unclear.

Such configuration, which is thermodynamically favoured[15], has been recently undoubtedly established by NOE studies for a series of N-sulphonylimines[3].

Attempted preparation of N-(diethoxyphosphoryl)butylideneimine (**6**) from butyraldehyde diethyl acetal (**4**) and diethyl phosphoroamidate (**2**) by the procedure used for aromatic aldehydes was totally unsuccessful. The evolution of ethanol at 120-160°C was observed but the residue obtained on removal of an excess of acetal (**5**) *in vacuo* did not contain the expected imine (**6**). It was identified (^{1}H NMR, ^{31}P NMR, MS) as 1,1-bis-(diethoxyphosphorylamino)butane (**7**) contaminated with minor amounts of other unidentified products.



(5) (2) (6)

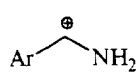


(7)

It seems feasible that (**7**) is produced by addition of (**2**) to the initially formed, strongly electrophilic imine (**6**). Similar reaction pattern was observed also for other aliphatic aldehyde diethyl acetals.

CONCLUSION

The thermally induced preparation of N-(diethoxyphosphoryl)aldimines evidently works well for aromatic aldehyde diethyl acetals but cannot be extended to aliphatic aldehydes. The procedure outlined in this paper is probably the method of choice for the preparation of N-(diethoxyphosphoryl)aldimines derived from aromatic aldehydes. These compounds are potential synthetic equivalents of a^1 type synthons (**8**) and convenient precursors of primary arylalkylamines owing to easy deprotection of an amino function[16] after addition of organometallics to an activated C=N bond.



(**8**)

Application of N-(diethoxyphosphoryl)aldimines for the synthesis of amines is currently under investigation.

EXPERIMENTAL

Reagents and solvents were purified in the usual way. Boiling points are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AC 200 spectrometer operating at 200 MHz, using $CDCl_3$ solutions and TMS as internal standard. ^{31}P NMR spectra were taken on a Bruker AC 200 spectrometer at 81 MHz.
Positive chemical shifts are downfield from 85% H_3PO_4 used as external reference. IR spectra were measured

in liquid films using a Specord M 80 (C.Zeiss) instrument. FAB/MS were recorded on a PO Electron (Ukraine) Modell MI 1200E mass spectrometer equipped with a FAB ion source (thioglycerol matrix). Xenon was used as ionizing gas. The beam energy was set to 5keV.

Diethyl phosphoroamidate (2) was prepared as described previously[17].

Aromatic aldehyde diethyl acetals (1) were obtained by a modified literature procedure[18]. A mixture of aromatic aldehyde (0.1 mol), triethyl orthoformate (16.3 g, 0.11 mol), ethanol (13.8 g, 0.3 mol), and ammonium chloride (0.25 g) was refluxed for 45 min. Ethanol was then distilled off. The residue was dissolved in CH_2Cl_2 (30 mL), washed with water (20 mL), dried over $MgSO_4$, evaporated, and distilled under reduced pressure to give pure diethyl acetal (**1**) in 75-85 % yield.

Preparation of N-(diethoxyphosphoryl)aldimines (3a-h). General procedure.

A mixture of diethyl phosphoroamidate (**2**,6.12 g, 40 mmol) and aromatic aldehyde diethyl acetal (**1**, 52 mmol) was placed in a distillation flask and heated gently up to 160°C in the reacting mixture until ethanol distilled off (at the end under slightly reduced pressure). The total time of heating was ca.45 min. The residue was distilled *in vacuo* to give the forerun consisting of an acetal (**1**) used in excess, and small amounts (up to 5 %) of unreacted amide (**2**). The high boiling fraction was analytically pure N-(diethoxyphosphoroyl)aldimine (**3a-h**).

N-(Diethoxyphosphoryl)-benzylideneimine (3a).

Colourless oil; b.p.140-141°C/0.7 mm Hg; n_D^{20}-1.5175; IR: υ=1626, 1580, 1256, 1024, 972, 864 cm^{-1}; ^1H NMR: δ 1.35, 1.36 (2t, J=7.1Hz, 6H), 4.12-4.24 (m, 4H), 7.43-7.96 (m, 5H), 9.10 (d, J=32.4Hz, 1H); ^{31}P NMR: δ 8.30; MS (m/z): 242 (M+1, 100). Anal. Calcd for $C_{11}H_{16}NO_3P$ (241.2): C, 54.77; H, 6.69: N, 5.81; P, 12.84. Found: C, 54.68; H, 6.80; N, 6.02; P, 12.79.

N-(Diethoxyphosphoryl)-4-methylbenzylideneimine (3b).

Colourless oil; b.p. 147-148°C/0.8 mm Hg; n_D^{20}-1.5900; IR: υ=1624, 1606, 1572, 1256, 1032, 972, 874 cm^{-1}; ^1H NMR: δ 1.34, 1.35 (2t, J=7.1Hz, 6H), 2.41 (s, 3H), 4.11-4.26 (m, 4H), 7.25-7.83 (m, 4H), 9.05 (d, J=32.4Hz, 1H); ^{31}P NMR: δ 8.68; MS (m/z): 256 (M+1, 100). Anal. Calcd for $C_{12}H_{18}NO_3P$ (255.2): C, 56.46; H, 7.11; N, 5.49; P, 12.14. Found: C, 56.25; H, 7.20; N, 5.52; P, 12.22.

N-(Diethoxyphosphoryl)-4-bromobenzylideneimine (3c).

Colourless oil; b.p. 168-169°C/0.8 mm Hg; n_D^{20}-1.5582; IR: υ=2980, 1632, 1588, 1568, 1256, 1032, 972, 874 cm^{-1}; ^1H NMR: δ 1.35, 1.36 (2t, J=7.1Hz, 6H), 4.12-4.28 (m, 4H), 7.59-7.82 (m, 4H), 9.03 (d, J=32.1Hz, 1H); ^{31}P NMR: δ 7.92; MS (m/z): 320, 322 (M+1, 100, 99) (^{79}Br and ^{81}Br isotope peaks). Anal. Calcd for $C_{11}H_{15}BrNO_3P$ (320.1): C, 41.27; H, 4.72; N, 4.38; P, 9.68. Found: C, 41.15; H, 4.80; N, 4.45; P, 9.80.

N-(Diethoxyphosphoryl)-4-methoxybenzylideneimine (3d).

Colourless solid; b.p. 157-159°C/0.3 mm Hg; IR: υ=2980, 1624, 1602, 1572, 1512, 1258, 1164, 1030, 972, 878 cm-^{1}; ^1H NMR: δ 1.34, 1.35 (2t, J=7.1Hz, 6H), 3.87 (s, 3H), 4.14-4.26 (m, 4H), 6.49-7.91 (m, 4H), 9.00 (d, J=32.3Hz, 1H); ^{31}P NMR: δ 9.07; MS (m/z); 272 (M+1, 100). Anal. Calcd for $C_{12}H_{18}NO_4P$ (271.2): C, 53.13; H, 6.69; N, 5.16; P, 11.42. Found: C, 53.30; H, 6.72; N, 5.25; P, 11.50.

N-(Diethoxyphosphoryl)-2-methoxybenzylideneimine (3e).

Colourless oil; b.p. 158-160°C/0.4 mm Hg; n_D^{20}-1.5372; IR: υ=2980, 1620, 1598, 1252, 1032, 972, 874 cm^{-1}; ^1H NMR: δ 1.34, 1.35 (2t, J=7.1Hz, 6H), 3.88 (s, 3H), 4.10-4.22 (m, 4H), 6.92-8.11 (m, 4H), 9.55, 9.56 (2d, J=32.8Hz, 1H); ^{31}P NMR: δ 9.34; MS (m/z): 272 (M+1, 100). Anal. Calcd for $C_{12}H_{18}NO_4P$: (271.2): C, 53.13; H, 6.69; N, 5.16; P, 11.42. Found: C, 53.33; H, 6.70; N, 5.20; P, 11.30.

N-(Diethoxyphosphoryl)-2-furylideneimine (3f).

Dark yellow solid; b.p. 126-128°C/0.4 mm Hg; IR: υ=2984, 2908, 1622, 1556, 1396, 1246, 1030, 972, 864 cm^{-1}; ^1H NMR: δ 1.32, 1.33 (2t, J=7.1Hz, 6H), 4.08-4.24 (m, 4H), 6.59 (dd, J=3.6, 1.7Hz, 1H), 7.20 (d, J=3.6Hz, 1H), 7.68 (dd, J=1.7, 0.7Hz, 1H), 8.81 (d, J=33.3Hz, 1H); ^{31}P NMR: δ 8.79; MS (m/z): 232 (M+1, 100). Anal. Calcd for $C_9H_{14}NO_4P$ (231.1): C, 46.76; H, 6.10; N, 6.06; P, 13.40. Found: C, 46.81; H, 6.25; N, 6.15; P, 13.52.

N-(Diethoxyphosphoryl)-1-naphthylideneimine (3g).

Yellow oil; b.p. 180-182°C/0.4 mm Hg; n_D^{20}-1.5918; IR: υ=1632, 1612, 1256, 1032, 972, 868, 776 cm^{-1}; ^1H NMR: δ 1.39, 1.40 (2t, J=7.1Hz, 6H), 4.18-4.34 (m, 4H), 7.53-.9.13 (m, 7H), 9.7 (d, J=33.5Hz, 1H); ^{31}P NMR: δ 8.10; MS (m/z): 292 (M+1, 100). Anal. Calcd for $C_{15}H_{18}NO_3P$ (291.2): C, 61.85; H, 6.23; N, 4.81; P, 10.63. Found: C, 61.95; H, 6.30; N, 4.90; P, 10.40.

N-(Diethoxyphosphoryl)cinnamylideneimine (3h).
Orange oil; b.p. 165-170°C/0.4 mm Hg; n_D^{20}-1.5774; IR: υ=2984, 1626, 1606, 1254, 1164, 1030, 972, 886, 754 cm^{-1}; ^1H NMR: δ 1.34, 1.35 (2t, J=7.1Hz, 6H), 4.09-4.24 (m, 4H), 6.94 (ddd, J=15.9, 9.0, 2.2Hz, 1H), 7.34-7.57 (m, 6H), 8.81 (dd, J=31.9, 9.0Hz, 1H); ^{31}P NMR: δ 8.09; MS (m/z): 268 (M+1) . Anal. Calcd for $C_{13}H_{18}NO_3P$ (267.2): C, 58.42; H, 6.79; N, 5.24; H, 6.79; N, 5.24: P, 11.59. Found: C, 58.30; H, 6.85: N, 5.40: P, 11.70.

Attempted preparation of N-(diethoxyphosphoryl)butylideneimine (6).
A mixture of diethyl phosphoramidate (**2**, 3.06 g, 20 mmol) and butyraldehyde diethyl acetal (**5**, 3.8 g, 26 mmol) was placed in a distillation flask and heated up to 160°C in the reacting mixture for ca.45 min. Ethanol started to distil at 140°. When the evolution of ethanol had ceased the excess of acetal (**5**) was removed in vacuo to give yellow, syrupy oil (3.4 g, 94 %), partially crystallizing on refrigeration. This material was identified as 1,1-bis-(diethoxyphosphorylamino)butane (**7**), contaminated with small amounts of other unidentified products. ^1H NMR: δ 1.04 (dist.t., J=7.5Hz, 3H), 1.34 (t, J=7.1Hz, 12H), 1.63-2.29 (m, 5H), 3.04 (s, 2H), 4.12(qt, J=7.1Hz, 8H); ^{31}P NMR: δ 10.43; MS (m/z): 361 (M+1, 26), 208.

ACKNOWLEDGEMENTS

The authors are indebted to Dr.A.Koziara for valuable help and constant interest in this investigation. Financial support by a grant 3T-09A/095/08 from the Polish Committee of Scientific Researches (KBN) is gratefully acknowledged.

REFERENCES

1. Preliminary publication: Zwierzak, A. and Osowska-Pacewicka, K., *Polish J.Chem.* **1993**, 67, 2085.
2. Love, B.E., Raje, P.S. and Williams II, T.C., *Synlett* **1994**, 493 and references cited therein.
3. Georg, G.I., Harriman, G.C.B. and Peterson, S.A. *J.Org.Chem.* **1995**, 60, 7366 and references cited therein.
4. Albrecht, R., Kresze, G. and Mlakar, B. *Chem.Ber.* **1964**, 97, 483.
5. Sisko, J. and Weinreb, S.M. *J.Org.Chem.* **1990**, 55, 393.
6. Green, T.W. and Wuts, G.M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley, New York 1991; p.379.
7. Kovacs, J. and Ghatak, U.R. *J.Org.Chem.* **1966**, 31, 119 and references cited therein.
8. Schön, I. *Chem.Rev.* **1984**, 84, 287.
9. Weisblat, D.I., Magerlein, B.J. and Myers, D.R. *J.Am.Chem.Soc.* **1953**, 75, 3630.
10. Ji, S., Gortler, R.B., Waring, A., Battisti, A., Bank, S., Closson, W.D. and Wriede, P. *J.Am.Chem.Soc.* **1967**, 89, 5311.
11. Hamada, T., Nishida, A. and Yonemitsu, O. *J.Am.Chem.Soc.* **1986**, 108, 140.
12. Jennings, W.B. and Lovely, C.J. *Tetrahedron* **1991**, 47, 5561 and references cited therein.
13. Hutchins, R.O., Abdel-Magid, A.F., Stercho, Y.P. and Wambsgans, A. *J.Org.Chem.* **1987**, 52, 702.
14. Hutchins, R.O., Adams, J. and Rutledge, M.C. *J.Org.Chem.* **1995**,60, 7396.
15. Fraser, R.R. and Banville, J. *J.Chem.Soc., Chem.Commun.* **1979**, 47.
16. Koziara, A. and Zwierzak, A. *Synthesis* **1992**, 1063.
17. Osowska-Pacewicka, K. and Zwierzak, A. *Tetrahedron* **1985**, 41, 4717.
18. Claisen, L. *Ber.dtsch.Chem.Ges.* **1907**, 40, 3903.

(*Received in UK* 21 *March* 1996; *revised* 30 *April* 1996; *accepted* 2 *May* 1996)