A General Synthesis of Unsymmetrical Azines via *N*-(Diethoxyphosphinyl)-hydrazones

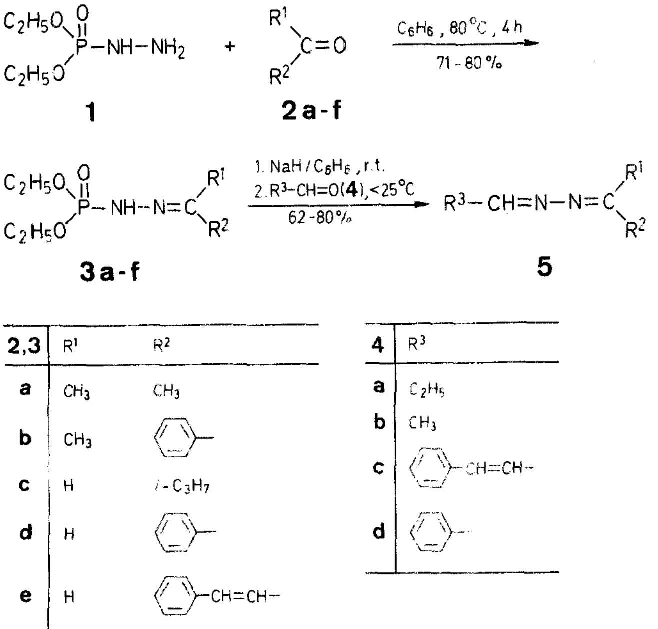
Anna Koziara, Krzysztof Turski, Andrzej Zwierzak*

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

A new synthesis of unsymmetrical azines utilizing diethyl phosphorohydrazidate as starting material and based on Wadsworth-Emmons type phosphoramidate approach is described.

Among the various conjugated systems, 2,3-diazabuta-1,3-dienes (commonly known as azines) are well defined and have been thoroughly studied in recent years, mainly as potential substrates for cycloaddition reactions[1]. Symmetrically substituted aldazines and ketazines are readily accessible in good yields (60-90%) from the reaction of an aldehyde or ketone with an excess of hydrazine hydrate in aqueous alcoholic solution, or in some cases with anhydrous hydrazine in the absence of solvent[2]. Since azine formation under these conditions is a two-step process involving an intermediate hydrazone, isolation of the latter followed by subsequent condensation with a second carbonyl component should lead to the corresponding unsymmetrical azine. Such a simple approach fails, however, totally or partially, except for hydrazones of diaryl ketones, because unsymmetrical azines exhibit a pronounced tendency for disproportionation and the desired compounds are always contaminated with considerable amounts of the respective symmetrical azines[3]. Several different routes, e.g. alkylidene group exchange between azines and imines[4], have been proposed for the preparation of pure unsymmetrical azines, none of them, however, meets the demand of simplicity, convenience, and general character. It was claimed[3] that the disproportionation of unsymmetrical azines is accelerated by contact with air, traces of moisture, and elevated temperature. In the light of these findings, the Wittig-like reaction of aldehydes with triphenylphosphinazines[5], which takes place under relatively mild conditions, constitutes a potential general route to unsymmetrical azines. The method suffers, however, from limited accessibility of the starting materials and difficulties usually encountered during separation of the azine from triphenylphosphine oxide.

Very often a useful and experimentally more convenient alternative to the phosphinimine route to unsaturated organic nitrogen compounds is the phosphoramidate approach devised by Wadsworth and Emmons[6]. As a further development of synthetic utility of this reaction, we now report on its successful application for the synthesis of unsymmetrical azines. Previous studies from this laboratory established that diethyl phosphorohydrazidate (**1**) can be easily prepared in high yield[7]. On refluxing in benzene with azeotropic removal of water diethyl phosphorohydrazidate (**1**) reacts easily with aldehydes and ketones **2** affording the corresponding *N*-(diethoxyphosphinyl)-hydrazones **3**.



The latter react smoothly with sodium hydride in benzene to form stable anions which add easily to aldehydes **4**. The reaction is quite rapid and takes place at room temperature with a slight exothermic effect. Similarly to the behaviour of phosphoroamidate anions[6] the synthesis probably proceeds stepwise and is based on the excellence of diethyl phosphate as a leaving group. The sodium diethyl phosphate precipitates from the reaction medium after the reaction is complete and, in contrast to triphenylphosphine oxide formed via the phosphinimine route, can be conveniently removed at that time. As proven by ¹H-N.M.R. spectroscopy crude unsymmetrical azines **5** obtained on evaporation of solvent are pure

Table 1. Preparation of *N*-(Diethoxyphosphinyl)-hydrazones **3** and Unsymmetrical Azines **5**

Product	Yield[a] [%]	m.p. [°C] or n_D^{20}	b.p. [°C]/torr	Molecular Formula[b]
3a	71	43-45°	–	$C_7H_{17}N_2O_3P$ (208.2)
3b	85	62-64°	–	$C_{12}H_{19}N_2O_3P$ (270.2)
3c	84	47-49°	–	$C_8H_{19}N_2O_3P$ (222.2)
3d	87	84-85,5°	–	$C_{11}H_{17}N_2O_3P$ (256.1)
3e	83	99.5-101.5°	–	$C_{13}H_{19}N_2O_3P$ (282.3)
3f	80	42-44°	–	$C_{10}H_{22}N_2O_3P$ (249.3)
5ad	78	1.5776	54-55.5°/0.01	$C_{10}H_{12}N_2$ (160.2)
5ba	64	1.5638	68-69°/0.15	$C_{11}H_{14}N_2$ (174.25)
5bb	62	1.5787	61-63°/0.1	$C_{10}H_{12}N_2$ (160.2)
5bd	69	52-55°[c]	123.5°/0.04	$C_{15}H_{14}N_2$ (222.3)
5ca	80	1.4460	41-42°/10	$C_7H_{14}N_2$ (126.2)
5cc	78	1.6178	90-91°/0.025	$C_{13}H_{16}N_2$ (200.3)
5da	77	1.5743	50.5-51.5°/0.05	$C_{10}H_{12}N_2$ (160.2)
5db	–[d]	–	–	–
5eb	75	1.6529	85-86.5°/0.15	$C_{11}H_{12}N_2$ (172.2)
5fb	–[d]	–	–	–
5fd	73	39-42°	107-108°/0.3	$C_{13}H_{16}N_2$ (200.3)

[a] Yield of analytically pure products.
[b] Satisfactory microanalysis obtained: C ±0.40, H ±0.20, N ±0.25, P ±0.35.
[c] Lit. [8], m.p. – 59°C.
[d] Crude products as well as distilled samples were contaminated with ~30% of the symmetrical azines.

and free from contamination with disproportionation products. Contrary to the earlier statements[3], most of them can be distilled in vacuo in order to obtain analytically pure samples. No disproportionation was encountered during such treatment. Distilled specimens are yellow oils or low melting, pale-yellow solids. Usually they can be stored at − 10 °C for 4 weeks without any signs of decomposition. Some compounds exhibit, however, extremely high tendency for disproportionation and decompose at − 10 °C after 24 h (compound **5fd**) or cannot be obtained at all in pure state (compounds **5db** and **5fb**).

Yields and physical constants of *N*-(diethoxyphosphinyl)-hydrazones **3** and unsymmetrical azines **5** are compiled in the Table 1. All compounds listed, except **5db** and **5fb**, are analytically pure and their spectroscopic data (Table 2) are fully consistent with the anticipated structures. The stereochemistry of the reaction was not investigated but the inspection of some ^{1}H-N.M.R. spectra (e. g. for compounds **5bb** and **5ba**) reveal the formation of diastereomeric mixtures.

N-(Diethoxyphosphinyl)-hydrazones 3; General Procedure:

A mixture of crude diethyl phosphorohydrazidate[7] (**1**; 25.2 g, 0.15 mol), the respective carbonyl compound **2** (0.15 mol), and benzene (110 ml) is refluxed gently for 4 h with azeotropic removal of water. Evaporation of solvent gives crude **3** as a crystalline solid Recrystallisation from hexane/benzene (2:1) affords analytically pure samples.

The synthesis of **3a** is carried out be refluxing **1** (0.15 mol) with acetone (70 ml) for 4 h without removal of water. Evaporation of solvent gives crude **2a** as a crystalline solid. Recrystallisation from hexane/benzene (2:1) affords analytically pure samples.

Table 2. Spectroscopic Data for *N*-(Diethoxyphosphinyl)-hydrazones 3 and Unsymmetrical Azines 5

Product	I.R.[a] ν[cm^{-1}]	^{1}H-N.M.R.[b] ($TMS_{int.}$) δ[ppm], J[Hz]
3a	3190 (NH), 1645 (C=N), 1240 (P=O), 1165, 1035, 970	1.73 (t, 6H, J = 7.05); 2.27 (s, 3H); 2.31 (s, 3H); 4.46 (qt, 4H, $J_{HH} \approx {}^3J_{PH}$ = 7.05); 8.86 (d, 1H, J_{PH} = 24.8)
3b	3150 (NH), 1610 (C=N), 1250 (P=O), 1160, 1035, 970	1.73 (t, 6H, J = 7.1); 2.66 (s, 3H); 4.53 (qt, 4H, $J_{HH} \approx {}^3J_{PH}$ = 7.1); 7.53–7.82 (m, 3H); 7.92–8.20 (m, 2H); 9.43 (d, 1H, J_{PH} = 27.0)
3c	3140 (NH), 1640 (C=N), 1245 (P=O), 1165, 1030, 980	1.46 (d, 6H, J = 6.8); 1.73 (t, 6H, J = 7.0); 2.78 (d, sep., 1H, J = 5.0, J = 6.8); 4.46 (qt, 4H, $J_{HH} \approx {}^3J_{PH}$ = 7.0); 7.48 (d, 1H, J = 5.0); 9.42 (d, 1H, J_{PH} = 27.5)
3d	3120 (NH), 1600 (C=N), 1235 (P=O), 1160, 1025, 970	1.78 (t, 6H, J = 7.1); 4.57 (qt, 4H, $J_{HH} \approx {}^3J_{PH}$ = 7.1); 7.55–7.82 (m, 3H); 7.86–8.15 (m, 2H); 8.31 (s, 1H); 10.03 (d, 1H, J_{PH} = 29.0)
3e	3100 (NH), 1625 (C=N), 1235 (P=O), 1160, 1035, 975	1.79 (t, 6H, J = 7.1); 4.55 (qt, 4H, $J_{HH} \approx {}^3J_{PH}$ = 7.1); 7.20 (d, 1H, J = 3.5); 7.23 (d, 1H, J = 5.8); 7.50–7.93 (m, 5H); 8.03–8.27 (m, 1H); 9.95 (d, 1H, J_{PH} = 29.2)
3f	3160 (NH), 1630 (C=N), 1240 (P=O), 1160, 1030, 980	1.76 (t, 6H, J = 7.0); 1.93–2.30 (m, 6H); 2.45–3.00 (m, 4H); 4.48 (qt, 4H, $J_{HH} \approx {}^3J_{PH}$ = 7.0); 8.95 (d, 1H, J_{PH} = 25.5)
5ad	1635 (C=N)	2.00 (s, 3H); 2.03 (s, 3H); 7.20–7.50 (m, 3H); 7.60–7.90 (m, 2H); 8.24 (s, 1H)
5ba	1633 (C=N)	1.07, 1.18 (2t, 3H, J = 7.5); 2.21, 2.38 (2s, 3H); 2.43 (dq, 2H, J = 5.0, J = 7.5); 7.30–7.50 (m, 3H); 7.70–7.90 (m, 3H)
5bb	1640 (C=N)	1.75, 1.95 (2d, 3H, J = 5.0); 2.13, 2.30 (2s, 3H); 7.01–7.46 (m, 3H); 7.62–8.03 (m, 3H)
5bd	1615 (C=N)	2.48 (s, 3H); 7.25–7.55 (m, 6H); 7.70–8.05 (m, 4H); 8.39 (s, 1H)
5ca	1645 (C=N)	1.13 (d, 6H, J = 7.0); 1.14 (t, 3H, J = 7.2); 2.36 (dq, 2H, J = 5.0, J = 7.2); 2.54 (d, sep, 1H, J = 5.5, J = 7.0); 7.72 (d, 1H, J = 5.5); 7.85 (t, 1H, J = 5.0)
5cc	1637 (C=N)	1.16 (d, 6H, J = 6.7); 2.61 (d. sep, 1H, J = 5.5, J = 6.7); 7.00 (dd, 2H, J = 3.5, J = 5.2); 7.26–7.68 (m, 5H); 7.83 (d, 1H, J = 5.5); 8.27 (dd, 1H, J = 3.5, J = 5.2)
5da	1645 (C=N)	1.19 (t, 3H, J = 7.5); 2.43 (dq, 2H, J = 5.3, J = 7.5); 7.25–7.50 (m, 3H); 7.70–7.85 (m, 2H); 8.03 (t, 1H, J = 5.3); 8.48 (s, 1H)
5eb	1650 (C=N)	2.08 (d, 3H, J = 5.5); 7.00 (dd, 2H, J = 3.6, J = 5.3); 7.20–7.85 (m, 5H); 7.98 (q, 1H, J = 5.5); 8.26 (dd, 1H, J = 3.6, J = 5.3)
5fd	1625 (C=N)	1.44–1.98 (m, 6H); 2.18–2.51 (m, 2H); 2.58–2.86 (m, 2H); 7.11–7.49 (m, 3H); 7.53–7.87 (m, 2H); 8.31 (s, 1H)

[a] The I.R. spectra were recorded on a Specord 71 IR (C. Zeiss) spectrophotometer for CCl_4 solutions (compounds **5**) or KBr discs (compounds **3a–f**, **5bd**, **5fd**). The most characteristic absorptions are given.

[b] The ^{1}H-N.M.R. spectra were measured for $CDCl_3$ solutions at 80 MHz with a Tesla BS 487C spectrometer (compounds **3a–f**) and at 90 MHz with a Bruker HFX 90 spectrometer (compounds **5ba**, **5ca**, **5cc**, **5da**, **5eb**, **5fd**). The spectra of compounds **5ad**, **5bb**, **5bd** were taken for CCl_4 solutions at 80 MHz.

Unsymmetrical Azines 5; General Procedure:

A solution of *N*-(diethoxyphosphinyl)-hydrazone (0.03 mol) in benzene (35 ml) is added dropwise with stirring to a suspension of sodium hydride (0.72 g, 0.03 mol; freshly separated from paraffin oil by washing with hexane) in benzene (30 ml) during 30 min at 15–20 °C. After evolution of hydrogen has ceased, a solution of aldehyde **4** (0.03 mol) in benzene (10 ml) is added at such a rate as to maintain the temperature of an exothermic reaction below 25 °C. For acetaldehyde, 50% excess of this reagent is used and the addition is carried out at 10–15 °C with external cooling (ice/water bath). After the addition has been completed, stirring is continued at room temperature for 2 h. The resultant solution is decanted, diluted with benzene (150 ml), rapidly washed with cold water (3 × 30 ml) until neutral, dried with magnesium sulfate, and evaporated under reduced pressure. Crude azines **5** are purified by distillation in vacuo.

The authors acknowledge financial support of this work by grant MR-I.12.1.3.1/2 from the Polish Academy of Sciences.

Received: March 1, 1985

---

* Address for correspondence.

[1] Tennant, G. in: *Comprehensive Organic Chemistry*, Barton, D. H. R., Ollis. W. D., Ed., Vol. 2, Pergamon Press, Oxford, 1979, pp. 459–465.

[2] Kolbach, D., Koruncev, D. in: Houben-Weyl, *Methoden der Organischen Chemie*, 4th. Edn., Müller, E., Ed., Vol. X/2, Georg Thieme Verlag, Stuttgart, 1967, pp. 89–120.

[3] Ugriumov, P.G. *Zh. Obshch. Khim.* **1959**, *29*, 4091.

[4] Barluenga, J., Fustero, S., Gómez, N., Gotor, V. *Synthesis* **1982**, 966.

[5] Bestmann, H.J., Fritzsche, H. *Chem. Ber.* **1961**, *94*, 2477.

[6] Wadsworth, Jr., W.S., Emmons, W.D. *J. Org. Chem.* **1964**, *29*, 2816; **1967**, *32*, 1279.

[7] Zwierzak, A., Sulewska, A. *Synthesis* **1976**, 835.

[8] Curtius, T., Pflug, L. *J. Prakt. Chem.* **1891**, *44*, 541.