Synthesis of 1,2-Dialkylhydrazines by Stepwise Phase-Transfer-Catalysed *N*-Alkylation of Diphenylphosphinic Hydrazide

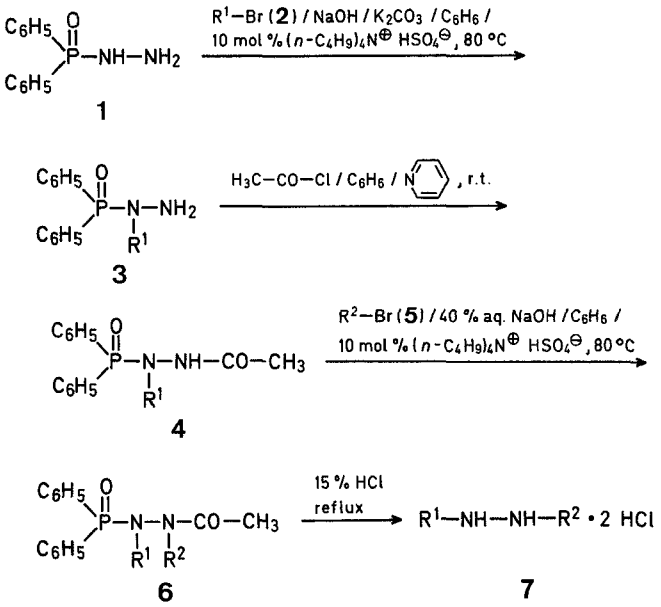
Maria KLUBA, Andrzej ZWIERZAK*

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

1,2-Dialkylhydrazines have attracted considerable interest as potential building blocks for some heterocyclic systems or starting materials for the preparation of azoalkanes - known progenitors of alkyl radicals by photolytic, radiolytic, and pyrolytic reactions[1]. Reductive procedures applied to 1-acyl-2-alkylidenehydrazines (acylhydrazones) permit the preparation of a wide variety of 1,2-dialkylhydrazines[1], however, a general and reliable alkylative approach to these compounds is still lacking. Methods applicable to symmetrically substituted hydrazines having identical alkyl groups, e.g. those based on the alkylation of 1,2-diacylhydrazides (with subsequent hydrolysis)[2], are not convenient for stepwise insertion of differing substituents, although this was essentially the method used[3] for the preparation of *N*-methyl-*N'*-isopropylhydrazine.

We have recently found that diphenylphosphinic hydrazide **(1)** is regioselectively monoalkylated under solid-liquid PTC conditions[4] to give the corresponding *N*-alkyl derivatives **(3)** in good yields[5]. *N*-Alkyldiphenylphosphinic hydrazides **(3)** can be considered as potential starting materials for the preparation of *N,N'*-dialkyldiphenylphosphinic hydrazides. Direct alkylation of **3** is, however, inefficient because of the difficulty in controlling the number of alkyl groups introduced. Nevertheless, this inconvenience can be easily overcome by employing removable protecting groups at the terminal nitrogen atom. Diphenylphosphinyl as well as diethoxyphosphoryl residues were found to be unsuitable because of poor yields of phosphorylation, possibly due to relatively low nucleophilicity of the amino group in close vicinity to an electron-attracting substituent. In contrast to this, acetylation of **3** with an excess of acetyl chloride in benzene/pyridine solution can be accomplished effectively. The resulting *N'*-acetyl derivatives of *N*-alkyldiphenylphosphinic hydrazides **(4)**, formed in high yields are easily purifiable by crystallization.

No difficulties have been encountered when alkylation of **4** was performed under conventional liquid-liquid PTC conditions[4]. The reaction of **4** with alkyl halides **(5)** in a two-phase system consisting of 40% aqueous sodium hydroxide and benzene in the presence of 10 mol-% of tetra-*n*-butylaminium hydrogen sulfate as catalyst proceeded smoothly at reflux temperature to afford the corresponding *N,N'*-dialkyl derivative **(6)** in high yield.



1 **3** **4** **6** **7**

Alkyl bromides and dimethyl sulfate used in 100% excess appear to be the alkylating agents of choice. Crude **6** can be satisfactorily analysed and directly used for deprotection without purification. Yields and physical constants of the acetyl derivatives of monoalkyl **(4)** and *N,N'*-dialkyldiphenylphosphinic hydrazides **(6)** are compiled in Table 1. All compounds are analytically pure and their spectra are in accord with the assigned structures. The removal of both diphenylphosphinyl and acetyl protecting groups can be easily and almost quantitatively achieved by refluxing with 15% hydrochloric acid for 5 h. Separation of the insoluble diphenylphosphinic acid by filtration and evaporation of the residue to dryness afforded 1,2-dialkylhydrazine dihydrochlorides **(7)** as crystalline solids. Analytically pure samples of **7** were obtained by dissolving the crude dihydrochlorides in warm ethanol, adding two drops of concentrated hydrochloric acid, and precipitation with ether. Yields, melting points, analysis, and ^{1}H-N.M.R. data of 1,2-dialkylhydrazine dihydrochlorides **7** are summarised in Table 2.

The reported procedure offers several advantages over the previously described synthetic methods leading to 1,2-dialkylhydrazines: (1) it seems to be generally applicable at least when primary alkyl halides are employed; (2) all intermediate products can be easily purified or do not need purification; (3) the deprotection step is clean and leads to pure 1,2-dialkylhydrazine dihydrochlorides **(7)**, easily separable from contaminating by-products.

N-Alkyldiphenylphosphinic Hydrazides (3):

The compounds were prepared according to the previously described procedure[5] by solid-liquid phase-transfer-catalysed *N*-alkylation of diphenylphosphinic hydrazide **(1)**[6].

***N'*-Acetyl-*N*-alkyldiphenylphosphinic Hydrazides (4); General Procedure:**

Acetyl chloride (2.36 g, 0.03 mol) in benzene (5 ml) is added dropwise with stirring to a suspension of the corresponding *N*-alkyldiphenylphosphinic hydrazide (**3**; 0.02 mol) in benzene (40 ml) containing pyridine (5 ml). The addition is carried out at such a rate as to maintain the temperature of the slightly exothermic reaction below 30 °C. Stirring is then continued for 2 h at room temperature. The resultant mixture is diluted with chloroform (30 ml) and treated successively with water (10 ml) and 2% hydrochloric acid until slightly acidic (pH = 4). The organic layer is separated, washed with water (3 × 10 ml) until neutral, dried with magnesium sulfate, and evaporated to give **4**, which quickly solidifies to a crystalline mass. Recrystallisation from benzene/hexane (1 : 1) affords analytically pure samples.

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N'-Acetyl-N,N'-dialkyldiphenylphosphinic Hydrazides (6); General Procedure:

N'-Acetyl-N-alkyldiphenylphosphinic hydrazide (**4**, 0.02 mol), alkyl bromide (**5**) or dimethyl sulfate (0.04 mol), tetra-*n*-butylaminium hydrogen sulfate (0.6 g, 0.002 mol), benzene (30 ml), and 40% aqueous sodium hydroxide (20 ml) are stirred efficiently and refluxed for 3 h. The resultant mixture is cooled to room temperature. The organic layer is separated and washed successively with saturated ammonium chloride solution (20 ml) and water (3 × 10 ml) until neutral. It is then dried with magnesium sulfate and evaporated to give analytically pure **6** as a thick oil or crystalline mass. Solids **6** can be recrystallised from benzene/hexane (1:2).

1,2-Dialkylhydrazine Dihydrochlorides (7); General Procedure:

The suspension of N'-acetyl-N,N'-dialkyldiphenylphosphinic hydrazide (**6**; 0.02 mol) in 15% hydrochloric acid (50 ml) is refluxed gently with stirring for 5 h, and then cooled to room temperature. The precipitated diphenylphosphinic acid is filtered off, the filtrate evaporated to dryness under reduced pressure, and carefully dried in vacuo over phosphorus pentoxide. Crude 1,2-dialkylhydrazine dihydrochlorides (**7**) thus obtained can be purified by dissolving in warm anhydrous ethanol, cooling to room temperature, adding 1–2 drops of concentrated hydrochloric acid, and precipitation with ether.

Table 1. N'-Acetyl-N-alkyldiphenylphosphinic Hydrazides **4** and N'-Acetyl-N,N'-dialkyldiphenylphosphinic Hydrazides **6**

Product No.	R^1	R^2	Yield[a] [%]	m.p. [°C] or n_D^{18}	Molecular formula[b]	I.R. (KBr or film)[c] ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS)[d] δ [ppm]	^{31}P-N.M.R. ($CHCl_3$)[e] δ [ppm]
4a	C_2H_5	—	85	163–165°	$C_{16}H_{19}N_2O_2P$ (302.3)	3195, 1540 (NH); 1680 (C=O); 1200, 1180 (P=O)	1.17 (t, 3H, J=7.5 Hz); 1.85 (s, 3H); 3.17 (qt, 2H, J=7.5 Hz); 7.3–7.8 (m, 6H); 7.9–8.2 (m, 4H); 10.25 (s, 1H)	+31.0
4b	$C_6H_5CH_2$	—	85	194–196°	$C_{21}H_{21}N_2O_2P$ (364.4)	3200, 1540 (NH); 1680 (C=O); 1180 (P=O)	1.64 (s, 3H); 4.30 (d, 2H, J=8.0 Hz); 7.27 (s, 5H); 7.2–7.6 (m, 6H); 7.9–8.3 (m, 4H); 9.55 (s, 1H)	+31.0
4c	H_2C=CH—CH_2	—	78	145–147°	$C_{17}H_{19}N_2O_2P$ (314.3)	3195, 1540 (NH); 1700 (C=O); 1190 (P=O)	1.84 (s, 3H); 3.72 (t, 2H, J=7.0 Hz); 5.07 (d, 1H, J=11 Hz); 5.11 (d, 1H, J=16 Hz); 5.8–6.3 (m, 1H); 7.2–7.6 (m, 6H); 7.8–8.2 (m, 4H); 10.24 (s, 1H)	+31.4
6a	C_2H_5	CH_3	67	78–79°	$C_{17}H_{21}N_2O_2P$ (316.3)	1660 (C=O); 1190, 1160 (P=O)	1.06 (t, 3H, J=7.0 Hz); 1.66, 1.98 (2s, 3H); 3.00, 3.14 (2s, 3H); 3.1–3.5 (m, 2H); 7.3–7.7 (m, 6H); 7.7–8.1 (m, 4H)	+31.4, +32.6[f]
6b	C_2H_5	n-C_3H_7	71	96–97°	$C_{19}H_{25}N_2O_2P$ (344.4)	1655 (C=O); 1200, 1170 (P=O)	0.83 (t, 3H, J=7.5 Hz); 1.14 (t, 3H, J=7.5 Hz); 1.75, 2.02 (2s, 3H); 1.5–1.9 (m, 2H); 3.1–3.8 (m, 4H); 7.3–7.7 (m, 6H); 7.7–8.2 (m, 4H)	+30.8, +32.5[f]
6c	C_2H_5	n-C_4H_9	88	112–113°	$C_{20}H_{27}N_2O_2P$ (358.4)	1660 (C=O); 1205, 1170 (P=O)	0.84 (dist. t, 3H, J=7.0 Hz); 1.10 (t, 3H, J=7.0 Hz); 1.2–1.9 (m, 4H); 1.74, 2.02 (2s, 3H); 3.1–3.7 (m, 4H); 7.2–7.7 (m, 6H); 7.7–8.1 (m, 4H)	+29.5, +31.2[f]
6d	$C_6H_5CH_2$	CH_3	84	150–151°	$C_{22}H_{23}N_2O_2P$ (378.4)	1665 (C=O); 1195 (P=O)	1.30, 1.58 (2s, 3H); 2.55, 3.25 (2s, 3H); 4.24, 4.35 (2d, 2H, J=3.0 Hz, 5.5 Hz); 7.1–7.7 (m, 11H); 7.8–8.3 (m, 4H)	+29.7, +32.7[f]
6e	$C_6H_5CH_2$	n-C_3H_7	71	82–84°	$C_{24}H_{27}N_2O_2P$ (406.6)	1660 (C=O); 1200 (P=O)	0.81 (t, 3H, J=7.0 Hz); 1.46, 1.71 (2s, 3H); 1.5–1.9 (m, 2H); 3.55 (t, 2H, J=7.0 Hz); 4.32, 4.40 (2d, 2H, J=3.0 Hz, 5.5 Hz); 7.1–7.7 (m, 11H); 7.8–8.3 (m, 4H)	+30.4, +31.4[f]
6f	$C_6H_5CH_2$	n-C_4H_9	86	150–152°	$C_{25}H_{29}N_2O_2P$ (420.5)	1660 (C=O); 1205 (P=O)	0.83 (dist. t, 3H, J=7.0 Hz); 1.0–1.8 (m, 4H); 1.44, 1.67 (2s, 3H); 3.55 (t, 2H, J=7.0 Hz); 4.30, 4.38 (2d, 2H, J=3.0 Hz, 5.5 Hz); 7.1–7.7 (m, 11H); 7.8–8.2 (m, 4H)	+29.5, +30.6[f]
6g	H_2C=CH—CH_2	CH_3	72	1.5810	$C_{18}H_{21}N_2O_2P$ (328.4)	1660 (C=O); 1200 (P=O)	1.65, 1.97 (2s, 3H); 3.10, 3.18 (2s, 3H); 3.6–3.9 (m, 2H); 5.17 (d, 1H, J=17.5 Hz); 5.21 (d, 1H, J=9.5 Hz); 5.6–6.2 (m, 1H); 7.2–7.7 (m, 6H); 7.8–8.2 (m, 4H)	+29.3, +30.6[f]

Table 1. (Continued)

Product No.	R^1	R^2	Yield[a] [%]	m.p. [°C] or n_D^{18}	Molecular formula[b]	I.R. (KBr or film)[c] ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS)[d] δ [ppm]	^{31}P-N.M.R. ($CHCl_3$)[e] δ [ppm]
6h	$H_2C{=}CH{-}CH_2$	n-C_3H_7	75	1.6980	$C_{20}H_{25}N_2O_2P$ (356.4)	1665 (C=O); 1200 (P=O)	0.81 (t, 3H, J=7.5 Hz); 1.4-1.9 (m, 2H); 1.73, 2.00 (2s, 3H); 3.58 (t, 2H, J=7.5 Hz); 3.7-4.0 (m, 2H); 5.14 (d, 1H, J=17.0 Hz); 5.21 (d, 1H, J=9.0 Hz); 5.6-6.2 (m, 1H); 7.2-7.7 (m, 6H); 7.7-8.2 (m, 4H)	+29.5, +30.8[f]
6i	$H_2C{=}CH{-}CH_2$	n-C_4H_9	95	1.5675	$C_{21}H_{27}N_2O_2P$ (370.4)	1670 (C=O); 1205 (P=O)	0.81 (dist. t, 3H, J=7.0 Hz); 1.0-1.7 (m, 4H); 1.65, 1.98 (2s, 3H); 3.57 (t, 2H, J=7.0 Hz); 3.8-4.0 (m, 2H); 5.15 (d, 1H, J=17.0 Hz); 5.22 (d, 1H, J=9.0 Hz); 5.6-6.2 (m, 1H); 7.3-7.6 (m, 6H); 7.7-8.1 (m, 4H)	+30.3, +31.8[f]

[a] Yield of crude product.
[b] Satisfactory microanalyses obtained: C ±0.4, H ±0.2, N ±0.3, P ±0.2.
[c] The I.R. spectra were recorded on a Specord 71 IR C. Zeiss spectrophotometer.
[d] The ^{1}H-N.M.R. spectra were measured at 80 MHz with a Tesla BS 487C spectrometer.
[e] The ^{31}P-N.M.R. spectra were measured at 24.3 MHz with a Jeol JNM-C-60HL spectrometer using 85% H_3PO_4 as external reference. A Heteronuclear Spin Decoupler, JNM-SD-HC, was used for precise ^{31}P chemical shift determinations. A positive sign indicates downfield shifts from H_3PO_4.
[f] The two signals coalesce to a singlet at ~70°C. The signals may be associated with two preferred conformations arising from relatively high torsional barrier to rotation about the N—N bond. A similar phenomenon was observed previously for several *N,N'*-dialkyl-*N,N'*-diacylhydrazines[7].

Table 2. *N,N'*-Dialkylhydrazine Dihydrochlorides **7** from Compounds **6**

Product[a]	Yield [%][b]	m.p. [°C]	Molecular formula[c]	^{1}H-N.M.R. (D_2O/DSS) δ [ppm][d]
7a	98	150-152°	$C_3H_{12}Cl_2N_2$ (147.0)	1.68 (t, 3H, J=7.0 Hz); 3.25 (s, 3H); 3.25 (q, 2H, J=7.0 Hz)
7b	99	156-158°	$C_5H_{16}Cl_2N_2$ (175.1)	1.06 (t, 3H, J=7.0 Hz); 1.33 (t, 3H); 1.75 (sext, 2H); 3.15 (t, 2H); 3.25 (q, 2H)
7c	96	145-146°	$C_6H_{18}Cl_2N_2$ (189.1)	1.35 (dist. t, 3H); 1.66 (t, 3H, J=7.0 Hz); 1.8-2.2 (m, 4H); 3.55 (t, 3H); 3.57 (q, 2H)
7d	85	122-124°	$C_8H_{14}Cl_2N_2$ (209.1)	3.25 (s, 3H); 4.60 (s, 2H); 7.85 (s, 5H)
7e	92	138-141°	$C_{10}H_{18}Cl_2N_2$ (237.2)	1.35 (t, 3H, J=7.0 Hz); 2.07 (sext, 2H); 3.50 (t, 2H, J=7.0 Hz); 4.53 (s, 2H); 7.70 (s, 5H)
7f	77	148-150°	$C_{11}H_{20}Cl_2N_2$ (251.2)	1.33 (dist. t, 3H); 1.6-2.2 (m, 4H); 3.56 (t, 2H, J=7.0 Hz); 4.55 (s, 2H); 7.75 (s, 5H)
7g	93	142-144°	$C_4H_{12}Cl_2N_2$ (159.1)	3.31 (s, 3H); 4.20 (d, 2H, J=6.0 Hz); ABC system: 5.8-6.1, 6.2-6.7 (2m, 3H)
7h	95	149-152°	$C_6H_{16}Cl_2N_2$ (187.1)	1.47 (t, 3H, J=7.0 Hz); 2.20 (sext, 2H); 3.65 (t, 2H, J=7.0 Hz); 4.22 (d, 2H, J=6.0 Hz); ABC system: 5.8-6.1, 6.2-6.7 (2m, 3H)
7i	80	133-135°	$C_7H_{18}Cl_2N_2$ (201.1)	1.40 (dist. t, 3H); 1.6-2.4 (m, 4H); 3.67 (t, 2H, J=7.0 Hz); 4.20 (d, 2H, J=6.0 Hz); ABC system: 5.8-6.1, 6.2-6.7 (2m, 3H)

[a] For R^1, R^2 see compounds **6**, Table 1.
[b] Yield for the deprotection step **6**→**7**.
[c] Satisfactory microanalyses obtained: C ±0.5, H ±0.5, N ±0.4.
[d] Recorded at 80 MHz on a Tesla BS 487C spectrometer.

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* Author to whom correspondence should be addressed.

[1] L. Spialter, D. H. O'Brien, G. L. Untereiner, W. A. Rush, *J. Org. Chem.* **30**, 3278 (1965) and references cited therein.
[2] H. H. Hatt, *Org. Synth. Coll. Vol.* **2**, 208 (1943).
[3] H. C. Ramsperger, *J. Am. Chem. Soc.* **51**, 918 (1929).
H. L. Lochte, W. A. Noyes, J. R. Bailey, *J. Am. Chem. Soc.* **44**, 2556 (1922).
[4] For review see: E. V. Dehmlow, S. S. Dehmlow, *Phase Transfer Catalysis*, Verlag Chemie, Weinheim 1980.
[5] B. Młotkowska, A. Zwierzak, *Tetrahedron Lett.* **1978**, 4731.
[6] E. Steininger, *Monatsh. Chem.* **97**, 383 (1966).
[7] G. J. Bishop, B. J. Price, I. O. Sutherland, *J. Chem. Soc. Chem. Commun.* **1967**, 672.