# Regioselective Synthesis of 1-Alkyl-1-phenylhydrazines, 2-Alkyl-1-phenylhydrazines, and 1,2-Dialkyl-1-phenylhydrazines

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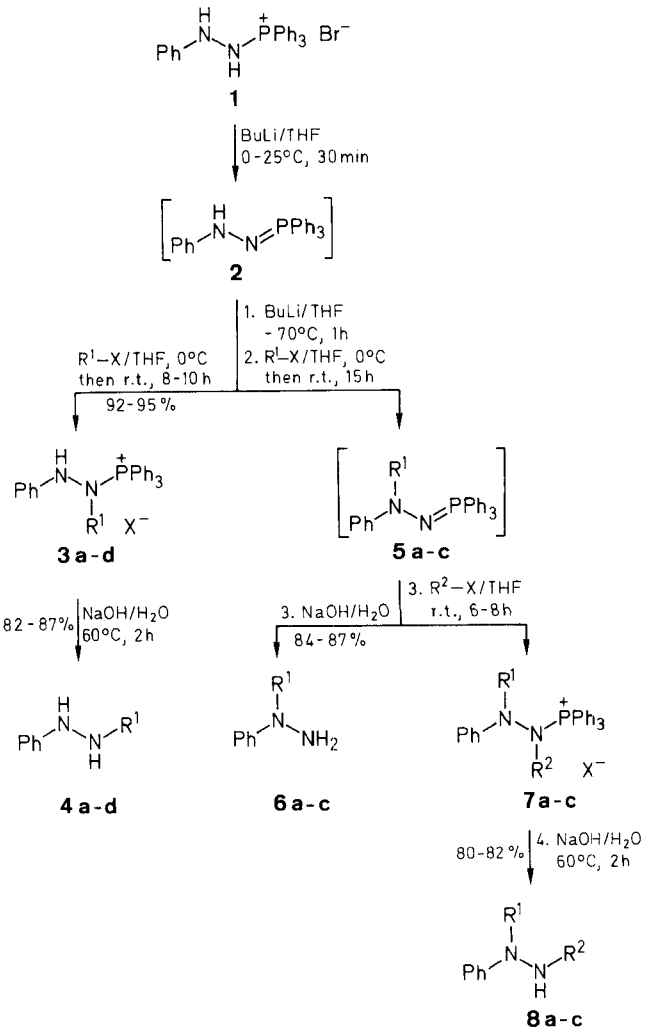
1,2- and 1,1-Disubstituted and 1,1,2-trisubstituted hydrazines are obtained by reaction of (2-phenylhydrazino)triphenylphosphonium bromide with buthyllithium, followed by addition of alkyl halides and alkaline hydrolysis.

Hydrazine derivatives are of interest as building blocks for heterocyclic compounds containing N–N bonds[1] and azapeptides,[2] and because of their pharmaceutical and biological properties.[3] In connection with the synthesis of α,β-unsaturated butyrolactams[4] and *N*-derivatives thereof, we required allylphenylhydrazines with different substitution patterns. A literature search showed that the methods[5,6] most often used for the synthesis of 1,2-and 1,1-alkylphenylhydrazines are the reduction of hydrazones[7] and *N*-nitroso compounds[8] and the alkylation of hydrazine derivatives.[9] However, these methods have some disadvantages: Many *N*-nitrosoamines are carcinogens,[10] the alkylation of phenylhydrazine usually takes place at the more substituted N-atom, and it is difficult to control the number of groups entering the hydrazine molecule as well as the site of alkylation[9] although in some cases the reaction can be stopped after monoalkylation by adding strong bases such as sodium amide.[11]

Our studies on the reactivity of phosphine imide derivatives revealed that these compounds are versatile starting materials for the synthesis of a wide range of acyclic[12] and cyclic[13] compounds. Further, phosphine *N*-arylimides also are convenient intermediates for the monoalkylation of primary aromatic amines.[14] We now report the use of (2-phenylhydrazino)triphenylphosphorane (**2**), a phosphine imide derivative, as a key intermediate in the synthesis of di- and trisubstituted hydrazines **4**, **6**, **8**.

(2-Phenylhydrazino)triphenylphosphonium bromide (**1**), which is very stable in air, is easily prepared, on a multigram scale, from phenylhydrazine and triphenylphosphine dibromide in the presence of triethylamine.[15] Dehydrobromination of **1** with butyllithium in tetrahydrofuran at 0 °C generates the hydrazinophosphorane **2**, which is unstable in air and hence is not isolated; addition of alkyl halides affords the crystalline hydrazino phosphonium salts **3** in nearly quantitative yields, via quaternisation of the P=N linkage of **2** in a selective fashion. The high shift value of the $^{31}$P-NMR signal ($\delta = 45.4$) and the coupling constants $^{3}J_{PH}$ (8.8 Hz) and $^{2}J_{PC}$ (10.1 Hz) of the methyl group observed in the $^{1}$H- and $^{13}$C-NMR spectra of **3a**, which are similar to those described for the *N*-alkylation products of phosphine imide derivatives,[16] are fully consistent with the salt structure **3**. Alkaline hydrolysis of salts **3** affords 2-alkyl-1-phenylhydrazines **4**. It has to be pointed out that the preparation of hydrazines **4** from salts **1** does not require the isolation and purification of the hydrazinophosphinium salts **3**; improved overall yields of **4** are obtained in one-pot reaction when the salts **3** are not isolated but directly submitted to hydrolysis.

The hydrazinophosphonium bromide **1** can also act as starting material for the synthesis of hydrazines **6** and **8** when two equivalents of butyllithium are used. The first equivalent effects dehydrobromination of the salt **1**; the second equivalent then reacts with the acidic NH proton of **2**. Subsequent addition of one equivalent of an alkyl halide followed by alkaline hydrolysis affords 1-alkyl-1-phenylhydrazines **6**. This method also renders possible the *N*-alkylation of both N-atoms to give 1,2-dialkyl-1-phenylhydrazines **8** by the successive addition of two different alkyl halides and alkaline hydrolysis of the salts **7**. Products **8** can be also obtained in one-pot reaction




| 3, 4, 6–8 | $R^1$ | $R^2$ in 7, 8 |
|---|---|---|
| a | Me | Et |
| b | Et | Me |
| c | $CH_2$=$CHCH_2$ | Me |
| d | $PhCH_2$ | |

**Table 1.** Hydrazinophosphonium Salts **3** and **7** Prepared

| Product | X | Yield[a] (%) | mp (°C) (dec) | Molecular Formula[b] | $^1$H-NMR, $CDCl_3$/TMS)[c] $\delta$, $J$(Hz) | $^{13}$C-NMR, $CDCl_3$/TMS)[c] $\delta$, $J$(Hz) | $^{31}$P-NMR[c] $\delta$ |
|---|---|---|---|---|---|---|---|
| **3a** | I | 94 | 177–178 (dec) | $C_{25}H_{24}IN_2P$ (510.5) | 3.31 (d, 3H, $^3J_{PH}$ = 8.8, $CH_3$), 6.7–8.2 (m, 20H$_{arom}$) | 38.4 (d, $^2J_{PC}$ = 10.1, $CH_3$), 114.8–147.8 ($C_{arom}$) | 45.4 |
| **3b** | I | 93 | 160–161 (dec) | $C_{25}H_{24}IN_2P$ (524.4) | 1.14 (t, 3H, $CH_3$), 3.71 (m, 2H, $CH_2$), 6.9–8.3 (m, 20H$_{arom}$) | 14.8 ($CH_3$), 48.2 (d, $^2J_{PC}$ = 9.4, $CH_2$), 113.9–146.5 ($C_{arom}$) | 45.3 |
| **3c** | Br | 92 | 144–145 (dec) | $C_{27}H_{26}BrN_2P$ (489.4) | 4.02 (d, 2H, $CH_2$), 4.86 (d, 1H, $^3J_{PH}$ = 17.3, CH), 4.93 (d, 1H, $^3J_{PH}$ = 10.0, CH=), 6.12 (m, 1H, CH=), 6.7–7.96 (m, 20H$_{arom}$) | 55.9 (d, $^2J_{PC}$ = 10.1, $CH_2$), 114.5–146.5 ($C_{arom}$ + $CH_2$ =, CH=) | 45.5 |
| **3d** | Br | 95 | 144–145 (dec) | $C_{31}H_{28}BrN_2P$ (539.5) | 4.28 (m, 2H, $CH_2$), 6.6–8.1 (m, 25H$_{arom}$) | 54.6 (d, $^2J_{PC}$ = 10.0, $CH_2$), 113.9–147.2 ($C_{arom}$) | 45.3 |
| **7a** | I | 89 | 148–149 (dec) | $C_{27}H_{28}IN_2P$ (538.4) | 1.06 (t, 3H, $CH_3$), 3.62 (s, 3H, $CH_3$), 3.73 (m, 2H, $CH_2$), 6.8–8.2 (m, 20H$_{arom}$) | 14.2 ($CH_3$), 44.3 ($CH_3$), 49.3 (d, $^2J_{PC}$ = 9.6, $CH_2$), 114.6–148.1 ($C_{arom}$) | 46.4 |
| **7b** | I | 87 | 150–151 (dec) | $C_{27}H_{28}IN_2P$ (538.4) | 0.15 (t, 3H, $CH_3$), 3.29 (d, 3H, $^3J_{PH}$ = 8.0, $CH_3$), 3.55 (m, 2H, $CH_2$), 6.61–7.72 (m, 20H$_{arom}$) | 12.9 ($CH_3$), 34.5 (d, $^2J_{PC}$ = 11.5, $CH_3$), 48.0 ($CH_2$), 116.3–144.2 ($C_{arom}$) | 46.3 |
| **7c** | I | 86 | 164–165 (dec) | $C_{28}H_{28}IN_2P$ (550.4) | 3.27 (d, 3H, $^3J_{PH}$ = 8.1, $CH_3$), 3.11 (m, 2H, $CH_2$), 4.87 (m, 2H, $CH_2$), 6.05 (m, 1H, CH=), 6.8–7.8 (m, 20H$_{arom}$) | 35.0 (d, $^2J_{PC}$ = 11.5, $CH_3$), 55.2 ($CH_2$), 113.6–147.2 ($C_{arom}$ + $CH_2$ = + CH=) | 46.5 |

[a] Yield of isolated pure product.
[b] Satisfactory microanalyses: C ±0.30, H ±0.20, N ±0.25.
[c] Recorded on a Varian FT-80A Spectrometer; $^1$H (80 MHz), $^{13}$C (20 MHz), $^{31}$P (30 MHz, $CDCl_3/H_3PO_{4ext}$).

from **1** without isolation of the intermediate phosphonium salts **7**, via an elimination–alkylation–hydrolysis sequence.

**2-Alkyl-1-phenylhydrazines 4; Two-Step Procedure from 1:**

*(2-Alkyl-1-phenylhydrazino)triphenylphosphonium Halides* **3**: In a dried $N_2$-filled flask with addition funnel, a solution of BuLi (10 mmol) in THF (10 mL) is added dropwise to a stirred solution of (2-phenylhydrazino)triphenylphosphonium bromide[15] (**1**; 4.49 g, 10 mmol) in THF (40 mL) at 0 °C and stirring is continued for 30 min. Then, a solution of the alkyl halide (10 mmol) in THF (10 mL) is added and the mixture is allowed to warm to r.t. After 8–10 h, the crystalline salt **6** is isolated by suction, washed with $Et_2O$, and recrystallized from $EtOAc/CH_2Cl_2$. The salts **3** are stable in air.

*2-Alkyl-1-phenylhydrazines* **4**: A mixture of the phosphonium salt **5** (10 mmol) and 2 M aq NaOH (40 mL) is heated at 60 °C for 2 h, then cooled, and with $CH_2Cl_2$ (100 mL). The organic phase is dried ($Na_2SO_4$) and evaporated to afford hydrazines **4** and triphenylphosphine oxide. The product **4** is isolated by distillation under reduced pressure.

**2-Alkyl-1-phenylhydrazines 4; One-Step Procedure from 1:**

A solution of BuLi (10 mmol) in THF (10 mL) is added to a stirred solution of phosphonium salt **1** (10 mmol) in THF (40 mL) under $N_2$. Then, a solution of the alkyl halide (10 mmol) in THF (10 mL) is added and stirring is continued for 8–10 h. A 2 M aq NaOH solution (40 mL) is added and the mixture is heated at 60 °C for 2 h. The organic phase is dried ($Na_2SO_4$) and evaporated to afford the hydrazine **4** and triphenylphosphine oxide. The product **4** is isolated by distillation under reduced pressure.

**1-Alkyl-1-phenylhydrazines 6 from 1; General Procedure:**

A solution of BuLi (10 mmol) in THF (10 mL) is added to a stirred solution of phosphonium salt **1** (10 mmol) in THF (40 mL) und $N_2$ at 0 °C and stirring is continued for min. The mixture is then cooled to −70 °C, a second portion of BuLi (10 mmol) is added, and stirring is continued for 1 h. Then, a solution of the alkyl halide (10 mmol) in THF (10 mL) is added. The mixture is allowed to warm r.t., stirred overnight, and then poured into 3 M aq NaOH (40 mL). The product is extracted with $CH_2Cl_2$ (100 mL), the extract is dried ($Na_2SO_4$) and evaporated, and the hydrazine **6** is isolated by distillation under reduced pressure.

**1,2-Dialkyl-1-phenylhydrazines 8; Two-Step Procedure from 1:**

*(1,2-Dialkyl-1-phenylhydrazino)triphenylphosphonium Halides* **7**: In a dried, $N_2$-filled round-bottomed flask with stirrer and addition funnel, a solution of BuLi (10 mmol) in THF (10 mL) is added dropwise to a stirred solution of phosphonium salt **1** (10 mmol) in THF (40 mL) at 0 °C and stirring is continued for 30 min. Then, a solution of BuLi (10 mmol) in THF (10 mL) is added at −70 °C. The mixture is stirred for 1 h, a solution of the first alkyl halide ($R^1X$; 10 mmol) in THF (10 mL) is added and the reaction is stirred overnight, allowing the temperature to rise to room temperature. Then, a solution of the second alkyl halide ($R^2X$; (10 mmol) in THF (10 mL) is added and stirring is continued for 6–8 h. The crystalline salts **7** is isolated by filtration, washed with $Et_2O$, and recrystallised from $EtOAc/CH_2Cl_2$. The salts **7** are stable in air.

*1,2-Dialkyl-1-phenylhydrazines* **8**: A mixture of the phosphonium salt **7** (10 mmol) and 2 M aq NaOH (40 mL) is heated at 60 °C for 2 h. After workup as described for hydrazines **3**, products **8** are isolated by distillation under reduced pressure.

**Table 2.** Hydrazines **4**, **5**, **8** Prepared

| Product | Yield[a] (%) A | Yield[a] (%) B | bp (°C)/Torr | Molecular Formula[b] or Lit. bp (°C)/Torr | $^1$H-NMR ($CDCl_3$/TMS)[c] $\delta$ | $^{13}$C-NMR ($CDCl_3$/TMS)[c] $\delta$ |
|---|---|---|---|---|---|---|
| **4a** | 85 | 86 | 45–48/0.2 | 110–112/12[d] | 2.60 (s, 3H, $CH_3$), 6.7–7.3 (m, 7$H_{arom}$, 2NH) | 38.7 ($CH_3$), 113.5, 119.3, 129.6, 149.8 ($C_{arom}$) |
| **4b** | 82 | 84 | 50–52/0.2 | 105–107/12[e] | 1.10 (t, 3H, $CH_3$), 2.84 (q, 2H, $CH_2$), 6.7–7.4 (m, 7$H_{arom}$, 2NH) | 14.3 ($CH_3$), 47.2 ($CH_2$), 114.2, 120.0, 130.3, 151.1 ($C_{arom}$) |
| **4c** | 87 | 86 | 70–72/0.2 | $C_9H_{12}N_2$ (148.2) | 3.31 (d, 2H, $CH_2$), 5.16 (m, 2H, $=CH_2$), 5.81 (m, 1H, CH=), 6.7–7.3 (m, 7$H_{arom}$, 2NH) | 53.3 ($CH_2$), 113.0, 118.0 ($=CH_2$), 118.9, 128.8, 134.0 (CH=), 148.7 ($C_{arom}$) |
| **4d** | 84 | 86 | 108–110/0.2 | 290/760[f] | 3.98 (s, 2H, $CH_2$), 6.4–7.6 (m, 12$H_{arom}$, 2NH) | 52.3 ($CH_2$), 114.7, 119.2, 126.2, 126.7, 128.1, 129.6, 144.4, 150.8 ($C_{arom}$) |
| **6a** | | 87 | 50–52/0.2 | 56–57/0.2[10] | 2.84 (s, 3H, $CH_3$), 3.25 (s, 2H, $CH_2$), 6.6–7.3 (m, 5$H_{arom}$) | 45.2 ($CH_3$), 114.7, 119.3, 120.1, 154.1 ($C_{arom}$) |
| **6b** | | 84 | 58–60/0.2 | 63–64/0.3[10] | 1.06 (t, 3H, $CH_3$), 3.33 (q, 2H, $CH_2$), 3.51 (s, 2H, $NH_2$), 6.5–7.4 (m, 5$H_{arom}$) | 11.6 ($CH_3$), 50.5 ($CH_2$), 114.8, 119.3, 130.2, 153.6 ($C_{arom}$) |
| **6c** | | 86 | 65–67/0.2 | 70–71/0.4[10] | 3.25 (m, 2H, $NH_2$), 3.9 (d, 2H, $CH_2$), 5.22 (m, 2H, $CH_2$), 5.82 (m, 1H, CH=), 6.6–7.6 (m, 10$H_{arom}$) | 58.2 ($CH_2$), 114.6, 119.2, 119.8, 128.2, 133.8, 147.2 ($C_{arom}$, CH=, $=CH_2$) |
| **8a** | 80 | 85 | 54–56/0.2 | $C_9H_{14}N_2$ (150.2) | 0.95 (t, 3H, $CH_3$), 2.80 (s, 3H, $CH_3$), 2.92 (q, 2H, $CH_2$), 6.4–7.3 (m, $H_{arom}$, NH) | 13.9 ($CH_3$), 39.5 ($CH_3$), 42.5 ($CH_2$), 113.8, 118.5, 129.3, 151.7 ($C_{arom}$) |
| **8b** | 82 | 83 | 53–55/0.2 | $C_9H_{14}N_2$ (150.2) | 1.05 (t, 3H, $CH_3$), 2.51 (s, 3H, $CH_3$), 3.32 (q, 2H, $CH_2$), 6.3–7.4 (m, $H_{arom}$, NH) | 14.3 ($CH_3$), 36.2 ($CH_3$), 45.7 ($CH_2$), 114.7, 118.0, 130.3, 150.8 ($C_{arom}$) |
| **8c** | 80 | 82 | 70–72/0.2 | $C_{10}H_{14}N_2$ (162.2) | 2.46 (s, 3H, $CH_3$), 3.95 (m, 2H, $CH_2$), 5.25 (m, 2H, $=CH_2$), 5.87 (m, 1H, $=CH_2$), 5.87 (m, 1H, CH=), 6.6–7.6 (m, 10$H_{arom}$) | 36.6 ($CH_3$), 58.9 ($CH_2$), 113.4, 118.2, 118.7, 128.7, 132.4, 146.1 ($C_{arom}$, $=CH_2$, CH=) |

[a] A: Yields from salts **3** or **7**; B: yields from **1**.
[b] Satisfactory mycroanalyses: C ±0.40, H ±0.25, N ±0.30.
[c] Recorded in a Varian FT-80A spectrometer; $^1$H (80 MHz), $^{13}$C (20 MHz).
[d] Ref. 5, p. 313.
[e] Ref. 5, p. 405.
[f] Ref. 5, p. 408.

**1,2-Dialkyl-1-phenylhydrazines 8; One-Step Procedure from 1:**
The reaction is carried out as described for the preparation of phosphonium salts **7** but these compounds are not isolated; instead, they are directly heated at 60 °C for 2 h with 2 M aq NaOH (40 mL). Hydrazines **8** are isolated by distillation under reduced pressure.

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