PO-Activated Olefination and Conversion of Aldehydes and Ketones to Higher Amines; II. Synthesis of Arylethylamines

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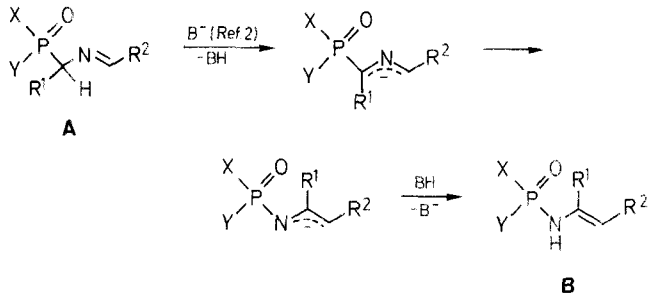
The transformation of arylcarboxaldehydes and/or – ketones **2** by three different routes into arylethylamines **3** and/or **4** is reported. According to the first route, the intermediate iminophosphonates **9** react through a classical PO-activated olefination. The second and the third involve the rearrangement of the iminophosphonates **9** into the vinylphosphoramidates **12**.

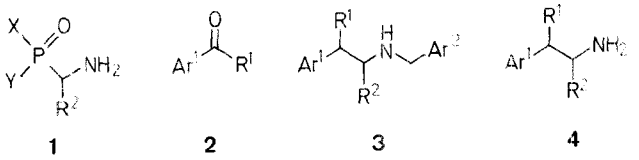
In the first part of this series,[2] we reported the rearrangement **A** → **B** under basic conditions, for which we suggested possible mechanisms.



A **B**

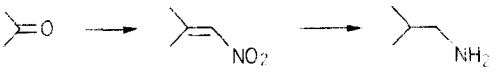
We were able to determine the scope of this transformation, notably by demonstrating that it is favoured by higher temperature, that it does not occur if the substituent R is other than hydrogen and, with regard to substituents X and Y studied (alkoxy and phenyl), that the presence of at least one alkoxy group appears essential.

In the present paper, we report the use of aminomethyl phosphonates **1** in the PO-activated olefination, enabling conversion of aldehydes and/or ketones **2** to higher amines **3** and/or **4**, by two different routes, in a limited number of steps and in satisfactory overall yields.



1 **2** **3** **4**

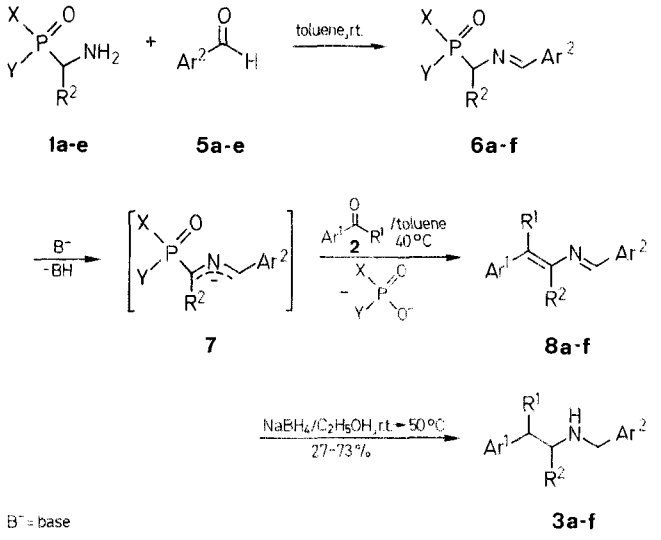
If is noteworthy that the literature[3] relating to this transformation emphasizes the lack of satisfactory alternatives to the classical two-step procedure involving condensation of the carbonyl derivative with nitromethane and subsequent reduction.



Moreover, the latter suffer from incompatibility in the presence of numerous functional groups as a result of frequent use of vigorous reagents such as lithium aluminium hydride.

The reactions carried out with **1** and carbonyl compounds are illustrated in Schemes **A**–**C**. According to Method A, (Schema **A**), conversion of **2** to **3** is effected without rearrangement of the intermediate 2-aza-allyl anion **7**. Compound **1**, when reacted at ambient temperature with aromatic aldehydes **5** in a solvent such as toluene, quantitatively afforded imines **6** (Table 1). Anion **7**, generated from **6**, either at ambient temperature under phase transfer catalysis conditions, or at low temperature by means of a base, such as *n*-butyllithium, did not rearrange and yielded 2-aza-1,3-diene **8** (Table 2) after addition of carbonyl compound **2** to the reaction mixture under the same conditions. Sodium borohydride reduction of **8** in ethanol finally provided **3** in satisfactory overall yield (Table 3).

According to Method B, see (Scheme **B**), conversion of aldehydes **2** (R^1 = H) to amines **3** (R^1 = R^2 = H) was carried out by intermediary rearrangement of 2-aza-allyl anion **10** to vinylphosphoramidate anion **11**.



Scheme A (Method A)

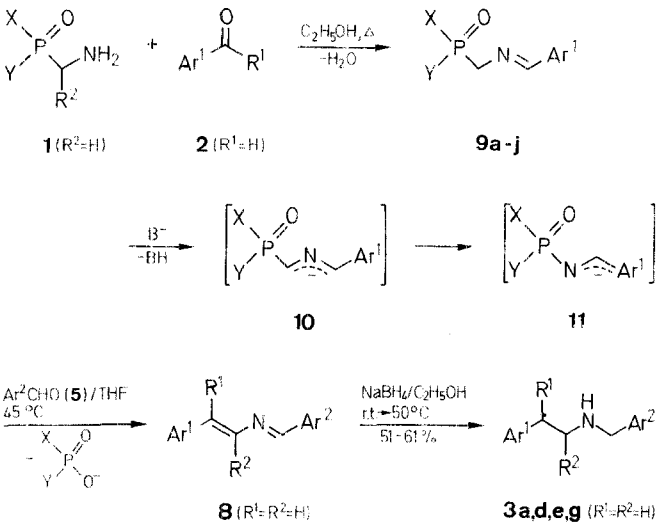
1	R^2	X	Y
a	H	C_2H_5O	C_2H_5O
b	C_6H_5	C_2H_5O	C_2H_5O
c	H	*i*-C_3H_7O	*i*-C_3H_7O
d	H	*i*-C_3H_7O	C_6H_5
e	H	C_6H_5	C_6H_5

2	Ar^1	R^1	2	Ar^1	R^1
a	2-thienyl	H	e	5-bromo-2-thienyl	H
b	2-thienyl	CH_3	f	α-naphthyl	H
c	C_6H_5	H	g	4-pyridyl	H
d	4-$CH_3OC_6H_4$	H	h	2-furyl	H

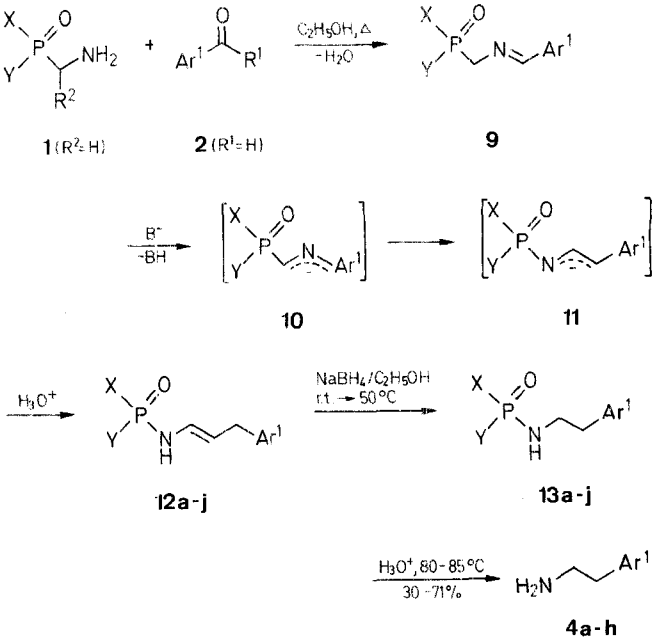
3, 8	Ar^1	R^1	Ar^2	R^2
a	2-thienyl	H	2-ClC_6H_4	H
b	2-thienyl	CH_3	2-ClC_6H_4	H
c	2-thienyl	H	2-ClC_6H_4	C_6H_5
d	2-thienyl	H	2-thienyl	H
e	2-thienyl	H	2-furyl	H
f	2-thienyl	H	4-pyridyl	H
g	2-thienyl	H	2-$O_2NC_6H_4$	H

5	Ar^2	5	Ar^2
a	2-ClC_6H_4	d	4-pyridyl
b	2-thienyl	e	2-$O_2NC_6H_4$
c	2-furyl		

In the above manner, aldehyde **2** (R^1 = H) and compound **1** (R^2 = H) afforded imine **9** (Table 1). The latter was subsequently reacted, at ambient temperature, in e.g. tetrahydrofuran, with a base e.g. *n*-butyllithium, sodium hydride or potassium *t*-butoxide. Anion **10** thus generated was converted as it was formed into anion **11** to which aldehyde **5** was in turn



Scheme B (Method B)



Scheme C (Method C)

12, 13	Ar^1	X	Y
a	2-thienyl	C_2H_5O	C_2H_5O
b	C_6H_5	C_2H_5O	C_2H_5O
c	C_6H_5	*i*-C_3H_7	*i*-C_3H_7
d	5-bromo-2-thienyl	C_2H_5O	C_2H_5O
e	α-naphthyl	C_2H_5O	C_2H_5O
f	4-$CH_3OC_6H_4$	C_2H_5O	C_2H_5O
g	4-pyridyl	C_2H_5O	C_2H_5O
h	2-furyl	C_2H_5O	C_2H_5O
i	2-ClC_6H_4	C_2H_5O	C_2H_5O
j	2-thienyl	*i*-C_3H_7O	C_6H_5

added to yield 2-aza-1,3-diene **8** (R^1 = R^2 = H). Upon reduction as before, the latter afforded amine **3** (R^1 = R^2 = H), again in satisfactory overall yield (Table 3).

Finally, the third route (Method C, Scheme C) provides a more direct means of converting an aromatic aldehyde **2** (R^1 = H) into a primary arylethylamine **4**, thereby avoiding the need to hydrogenolyse the *N*-substituted amine **3** (R^1 = R^2 = H).

Table 1. ^{1}H-NMR Data of Compounds **6a–f** and **9a–j**

Product(s) No.	X	Y	Ar^2/Ar^1	R^2	^{1}H-NMR ($CDCl_3$/TMS) δ (ppm)
6a/9a	C_2H_5O	C_2H_5O	2-ClC_6H_4	H	1.35 (t, 6H); 4.2 (m, 6H); 7.1–7.8 (m, 3H); 8.0 (m, 1H); 8.7 (d, 1H)
6b/9b	C_2H_5O	C_2H_5O	2-thienyl	H	1.35 (t, 6H); 3.9–4.45 (m, 6H); 7.0–7.8 (m, 3H); 8.5 (d, 1H)[a]
6c	C_2H_5O	C_2H_5O	2-ClC_6H_4	C_6H_5	1.2 (t, 6H); 3.9 (m, 4H); 4.8 (d, 1H); 7.0–7.8 (m, 8H); 8.1 (m, 1H); 8.85 (d, 1H)
6d/9c	C_2H_5O	C_2H_5O	2-furyl	H	1.3 (t, 6H); 4.0 (m, 6H); 7.0–7.5 (m, 3H); 8.3 (d, 1H
6e	*i*-C_3H_7O	C_6H_5	4-pyridyl	H	1.4 (dd, 6H); 4.15 (d, 2H); 4.7 (m, 1H); 7.0–7.8 (m, 7H); 8.25 (d, 1H); 8.55 (d, 2H)
6f	*i*-C_3H_7O	C_6H_5	2-$NO_2C_6H_4$	H	1.5 (dd, 6H); 4.25 (d, 1H); 7.5–8.3 (m, 9H); 8.6 (d, 1H)
9d	C_2H_5O	C_2H_5O	C_6H_5	H	1.3 (t, 6H); 4 (m, 6H); 7.2–7.8 (m, 5H); 8.2 (d, 1H)
9e	*i*-C_3H_7O	*i*-C_3H_7O	C_6H_5	H	1.35 (d, 12H); 3.95 (d, 2H); 4.5 (m, 2H); 7.2–7.8 (m, 5H); 8.2 (d, 1H)
9f	C_2H_5O	C_2H_5O	5-bromo-	H	1.3 (t, 6H); 4.1 (m, 6H); 7.0–7.15 (m, 2H); 8.2 (d, 1H)
9g	C_2H_5O	C_2H_5O	2-thienyl 2-naphthyl	H	1.3 (t, 6H); 4.0 (m, 6H); 6.9–8.1 (m, 7H); 8.3 (d, 1H)
9h	C_2H_5O	C_2H_5O	4-$CH_3OC_6H_4$	H	1.3 (t, 6H); 3.75 (s, 3H); 4.15 (m, 6H); 5.90 (d, 2H), 7.75 (d, 2H); 8.30 (d, 1H)
9i	C_2H_5O	C_2H_5O	4-pyridyl	H	1.3 (t, 6H); 4.10 (m, 6H); 7.7 (d, 2H); 8.4 (d, 2H); 8.75 (d, 2H)
9j	*i*-C_3H_7O	C_6H_5	2-thienyl	H	1.4 (dd, 6H); 4.15 (d, 2H); 4.75 (m, 1H); 7.8 (m, 8H); 8.25 (d, 1H)

[a] Solvent for **6b**: DMSO-d_6.

Table 2. Physical and Spectral Data for Compounds **8a–g**

Product No.	Yield (%)	m.p. (°C)	Molecular Formula	^{1}H-NMR ($CDCl_3$/TMS) δ (ppm)
8a	72	oil	$C_{13}H_{10}ClNS$ (247.7)	8.6 (s, 1H); 8.0 (m, 1H); 6.9–7.9 (m, 8H)
8b	63	102	$C_{14}H_{12}ClNS$ (261.8)	2.2 (s, 3H); 6.9–8.1 (m, 8H); 8.75 (d, 1H)
8c	52	118	$C_{19}H_{14}ClNS$ (323.8)	8.85 (s, 1H); 6.95–8.1 (m, 13H)
8d	85	163	$C_{11}H_9NS_2$ (219.3)	8.35 (s, 1H); 6.9–7.5 (m, 8H)
8e	100	oil	$C_{11}H_9NOS$ (203.4)	–
8f	85	165	$C_{12}H_{10}N_2S$ (214.3)	6.5–7.5 (m, 7H); 8.4 (s, 1H); 8.45 (d, 2H)
8g	85	oil	$C_{13}H_{10}N_2O_2S$ (258.3)	1.65 (s, 1H); 2.9 (t, 4H); 4.0 (s, 2H); 6.7–7.9 (m, 7H)

As in the previous case the procedure involves initial formation of anion **11**. The vinylphosphoramidate **12** (Table 4), obtained by acid hydrolysis of the reaction mixture, was reduced by sodium borohydride in ethanol to the phosphoramidate **13** (Table 5). Treatment of **13** with hot 6 normal hydrochloric acid afforded arylethylamine **4** with a single exception, the overall yield of **4** from **1** (R^2 = H) lies in the range 45–71% (Table 6). In conclusion, we wish to emphasise the compatibility of this new method with a wider range of functional groups when compared with existing procedures.

Amines 3 from 1 and 2; Typical Procedures:

Method A: ***N*-*o*-Chlorobenzyl-2-(2-thienyl)ethylamine Hydrochloride (3a):**

Diethyl N-o-Chlorobenzylideneaminomethylphosphonate (**6a**): A solution of **1a** (16.7 g, 0.1 mol) and **5a** (14.0 g, 0.1 mol) in toluene (200 ml) is stirred for 0.5 h at ambient temperature. The water formed is separated, the organic layer washed with saturated brine (50 ml), dried with sodium sulfate and evaporated to give **6a** as an oil (single spot in TLC silica gel, ethyl acetate, R_f = 0.45); yield: 29.0 g (~ 100%).

1-o-Chlorophenyl-2-aza-4-(2-thienyl)-1,3-butadiene (**8a**): To a vigorously stirred mixture of 50% aqueous sodium hydroxide (80 ml), toluene (80 ml) and tetra-*n*-butylammonium iodide (1.47 g, 0.004 mol) at ambient temperature is added dropwise a solution of **6a** (28.95 g, 0.1 mol) and **2a** (11.2 g, 0.1 mol) in toluene (20 ml). The mixture is stirred at 40 °C for 0.5 h and cooled. The aqueous phase is extracted with toluene (2 × 50 ml), the combined organic phase is washed with water (50 ml), dried with sodium sulfate and evaporated to afford **8a** as a yellow oil showing essentially a single peak in GC; yield: 19.8 g (80%).

Conversion of **8a** *to* **3a**: To a solution of sodium borohydride (6.08 g, 0.16 mol) in ethanol (150 ml) is added at ambient temperature a solution of **8a** (19.8 g, 0.08 mol) in ethanol (50 ml). The mixture is slowly heated to 50 °C, held at this temperature for 1 h, then evaporated to dryness and the residue is taken up in diisopropyl ether (200 ml). The solution is washed with 1 normal aqueous sodium hydroxide (2 × 20 ml) dried with sodium sulfate and evaporated to give the free base of **3a** as a pale yellow oil; yield: 20.0 g (~ 100%). Treatment of the oil with hot 6 normal hydrochloric acid (8.3 ml) followed by cooling, filtration and drying affords **3a** as colourless crystals; yield: 20.4 g (71% overall).

***N*-2-Furfuryl-2-(2-thienyl) Ethylamine Oxalate (3e):**

Diethyl N-2-Furfurylideneaminomethylphosphonate (**6d**): Compound **6d** is prepared analogous to **6a** as given above in quantitative yield.

1-(2-Furyl)-2-aza-4-(2-thienyl)-1,3-butadiene (**8e**): To a solution of **6d** (27.4 g, 0.1 mol) in anhydrous tetrahydrofuran (100 ml) is aded at −78 °C under nitrogen a 2.8 molar solution of *n*-butyllithium in hexane (35.7 ml, 0.1 mol). After stirring at −78 °C for 0.5 h, a solution of **2b** (11.2 g, 0.1 mol) in anhydrous tetrahydrofuran (20 ml) is added at

Table 3. Preparation of Amines **3a–g** from **1a–e**, **2a–b** and **5a–e**

Substrate No.	Reaction Conditions		Product No.	Yield[a] (%)	m.p. (°C)	Molecular Formula[b]	Ref.
	Method	Base					
1a	A	NaOH	**3a**	71	143	$C_{13}H_{14}ClNS \cdot HCl$ (288.2)	4, 5
1e	A	NaOH	**3a**	45	143	–	4, 5
1a	B	t-C_4H_9OK	**3a**	55	143	–	4, 6
1d	B	NaH	**3a**	51	143	–	4, 6, 7
1a	A	n-C_4H_9Li	**3b**	44	120	$C_{14}H_{16}ClNS \cdot HCl$ (302.3)	5
1a	A	n-C_4H_9Li	**3c**	27	214	$C_{19}H_{20}ClNS \cdot HCl$ (366.4)	5
1a	A	NaOH	**3d**	73	230 (dec.)	$C_{11}H_{13}NS_2 \cdot HCl$ (259.8)	5
1c	B	t-C_4H_9OK	**3d**	53	230 (dec.)	–	6
1a	A	n-C_4H_9Li	**3e**	58	215	$C_{11}H_{13}NOS \cdot C_2H_4O_4$ (297.3)	5
1a	B	NaH	**3e**	59	215	–	6
1d	A	n-C_4H_9Li	**3f**	42	oil	$C_{12}H_{14}N_2S \cdot HCl$[c] (254.8)	
1a	B	n-C_4H_9Li	**3g**	61	168	$C_{13}H_{14}N_2O_2S \cdot HCl$ (298.8)	6

[a] Yields are calculated based on compound **1** and are not optimized.
[b] Satisfactory microanalyses obtained: C ±0.3, H ±0.3, N ±0.3
[c] Not analysed.

Table 4. Physical and Spectral Data for compounds **12a–j**

Product No.	Yield[a] (%)	m.p. (°C)	Molecular Formula[b]	^{1}H-NMR ($CDCl_3$/TMS) δ (ppm)
12a	75	oil	–	1.3 (t, 6H); 3.95 (q, 4H); 5.35 (m, 1H); 6.9–7.5 (m, 5H)
12b	70	60	$C_{12}H_{18}NO_3P$ (255.2)	1.3 (t, 6H); 4.05 (m, 4H); 5.85 (d, 1H); 6.65 (m, 2H); 7.15 (s, 5H)
12c	75	98	$C_{14}H_{22}NO_3P$ (283.3)	1.35 (d, 12H); 4.5 (m, 2H); 5.80 (d, 1H); 6.65 (m, 2H); 7.15 (s, 5H)
12d	88	oil	–	–
12e	73	oil	–	1.3 (t, 6H); 4.1 (qd, 4H); 6.7–8.9 (m, 2H); 7.0–8.2 (m, 8H)
12f	70	oil	–	–
12g	51	75	$C_{11}H_{17}N_2O_3P$ (256.2)	1.35 (t, 6H); 4.15 (dq, 4H); 5.80 (d, 1H); 6.95 (c, 2H); 7.0 (dd, 1H); 8.25 (d, 2H)
12h	73	oil	–	–
12i	75	98	$C_{12}H_{17}ClNO_3P$ (289.7)	1.3 (t, 6H); 4.1 (d, q, 4H); 6.0–6.5 (m, 2H); 6.8–7.5 (m, 5H)
12j	60	125	$C_{15}H_{13}NO_2PS$ (307.3)	1.35 (d, 6H); 4.8 (m, 1H); 6.9 (m, 1H); 6.2–7.0 (m, 4H); 7.0–8.0 (m, 6H)

[a] Yield based on **1**.
[b] Satisfactory microanalyses obtained: C ±0.3, H ±0.3, N ±0.3.

– 78 °C. The mixture is stirred at ambient temperature for 1 h and then evaporated under reduced pressure. The residue is taken up in water (100 ml) and extracted with diisopropyl ether (2 × 100 ml). The combined organic phase is dried with sodium sulfate and evaporated to afford **8e** as a yellow oil; yield: 22 g (~ 100%).

Conversion of **8e** *to* **3e**: The preparation is carried out as given for the conversion of **8a** to **3a**. The purification of the crude amine product *via* the oxalate, gives **3e** as colourless crystals; yield: 17.3 g (58% overall).

Method B: ***N*-*o*-Chlorobenzyl-2-(2-thienyl)ethylamine Hydrochloride (3a):**

Diethyl N-2-Thienylideneaminomethylphosphonate **(9b)**: To a solution of **1a** (16.7 g, 0.1 mol) in absolute ethanol (200 ml) is added **2a** (11.2 g, 0.1 mol) and the mixture is heated at reflux for 1 h. Evaporation of the solvent under reduced pressure affords **9b** as an oil (single spot in TLC, silica gel, ethyl acetate); yield: 28.0 g (~ 100%).

1-(o-Chlorophenyl)-2-aza-4-(2-thienyl)-1,3-butadiene **(8a)**: To a suspension of potassium t-butoxide (11.2 g, 0.1 mol) in tetrahydrofuran (160 ml) is added dropwise at 30–35 °C a solution of **9b** (27.9 g, 0.1 mol) in tetrahydrofuran (40 ml). The mixture is heated at 45 °C for 0.5 h and a solution of **5a** (14.05 g, 0.1 mol) in tetrahydrofuran (10 ml) slowly added. The mixture is held at 45 °C for 1 h, and then evaporated under reduced pressure. The residue is taken up in diisopropyl ether (100 ml) and water (100 ml) and the aqueous phase is re-extracted with diisopropyl ether (2 × 50 ml). The combined organic phase is washed with water (50 ml), dried with sodium sulfate and evaporated to give **8a** as an orange oil; yield: 17.8 g (72%).

Conversion of **8a** *to* **3a**: This is carried out as given under Method A; colorless crystals; yield: 15.9 g (55% overall).

Amines **4a–h** from **1a, c–d** and **5a, c–g**; Typical Procedure:
Method C: **2-*o*-Chlorophenylethylamine Hydrochloride (4c):**

Diethyl N-o-Chlorobenzylideneaminomethylphosphonate **(9a)**: A similar experimental procedure given under **6a** is used.

Diethyl N-[β-(o-Chlorophenyl)-vinyl]phosphoramidate **(12i)**: To a suspension of sodium hydride (50% in oil, 4.8 g, 0.1 mol) in tetrahydrofuran (100 ml) is added at 25 °C a solution of **9a** (28.95 g, 0.1 mol) in tetrahydrofuran (40 ml). The mixture is heated at 45 °C for 2 h and, after cooling to 25 °C, poured into saturated aqueous ammonium chloride solution (600 ml) and extracted with diisopropyl ether (2 × 100 ml). The combined organic phase is washed with saturated brine (50 ml), dried with sodium sulfate and evaporated to an oil which is crystallized from hexane to give **12i**; yield: 21.7 g (75% from **1a**).

Diethyl N-(2-o-chlorophenylethyl)phosphoramidate, **(13i)**: Reduction of **12i** (14.5 g, 0.05 mol) with sodium borohydride (1.9 g, 0.05 mol) following the example given earlier affords **13i**; yield: 14.6 g (~ 100%).

Conversion of **13i** *to* **4c**: An efficiently stirred mixture of **13i** (14.6 g, 0.05 mol) and 6 normal hydrochloric acid (100 ml) is heated at 80–85 °C for 1.5 h. After extraction of the cooled mixture with dichloromethane (2 × 50 ml), the separated aqueous phase is basified with aqueous sodium hydroxide and extracted with diisopropyl ether (2 × 50 ml). The com-

Table 5. Physical and Spectral Data of Compounds **13a–j**

Product No.	Yield[a] (%)	m.p.	^{1}H-NMR ($CDCl_3$/TMS) δ (ppm)
13a	75	oil	1.3 (t, 6H); 3.1 (m, 5H); 4.05 (q, 4H); 6.75–7.2 (m, 3H)
13b	70	oil	1.33 (t, 6H); 3.0 (m, 5H); 4.0 (qd, 4H); 7.2 (s, 5H)
13c	75	oil	1.35 (d, 12H); 4.5 (m, 2H); 5.80 (d, 1H); 6.65 (m, 2H); 7.15 (s, 5H)
13d	50	oil	1.33 (t, 6H); 3.0 (m, 5H); 4.0 (dq, 4H); 5.55 (d, 1H); 6.80 (d, 1H)
13e	71	oil	1.3 (t, 6H); 3.2 (m, 5H); 3.95 (qd, 4H); 7.2–8.0 (m, 7H)
13f	69	oil	3.15 (m, 4H); 3.8 (s, 3H); 6.85 (d, 2H); 7.3 (d, 2H)
13g	50	oil	1.3 (t, 6H); 3.2 (m, 5H); 4.15 (qd, 4H); 7.9 (d, 2H); 8.85 (d, 2H)
13h	57	oil	1.3 (t, 8H); 3.0 (m, 5H); 4.0 (dq, 4H); 6.0 (d, 1H); 6.2 (d, 1H); 7.2 (d, 1H)
13i	75	oil	1.3 (t, 6H); 3.0 (m, 5H); 4.0 (qd, 4H); 7.2 (m, 4H)
13j	60	oil	1.3 (d, 6H); 3.0 (m, 5H); 4.85 (m, 1H); 6.7–7.9 (m, 8H)

[a] Yield based on **1**.

bined organic extract is dried with sodium sulfate and evaporated to an oily residue which is treated with ethanolic hydrogen chloride to give **4c**; as colourless crystals; yield: 8.65 g (90%).

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Table 6. Preparation of Amines **4a–h** from **1a**, **c–d**

Substrate No.	Ar[1]	Base	Product No.	Yield (%)	m.p. (°C)	Lit. m.p. (°C)
1a	2-thienyl	t-C_4H_9OK	**4a**	54	202	202[8], 200-2[9]
1d	2-thienyl	t-C_4H_9OK	**4a**	55	202	
1a	C_6H_5	t-C_4H_9OK	**4b**	66	222	222[8,10]
1c	C_6H_5	n-C_4H_9Li	**4b**	71	222	
1a	2-ClC_6H_4	NaH	**4c**	67	145	145[8], 149[11]
1a	4-$CH_3OC_6H_4$	t-C_4H_9OK	**4d**	53	217	217[8], 207[13]
1a	5-bromo-2-thienyl	t-C_4H_9OK	**4e**	30	220 (dec.)	220[8] (dec.)
1a	α-naphthyl	t-C_4H_9OK	**4f**	61	260 (dec.)	260[8], 251-3[12] (dec.) (dec.)
1a	4-pyridyl	t-C_4H_9OK	**4g**	47	oil	[8,14]
1a	2-furyl	t-C_4H_9OK	**4h**	45	204	204[8], 190[15]

[a] Yields based on compound **1** and not optimized.

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