Synthesis of α-Arylalkylamines by Addition of Grignard Reagents to *N*-(Diethoxyphosphoryl)aldimines

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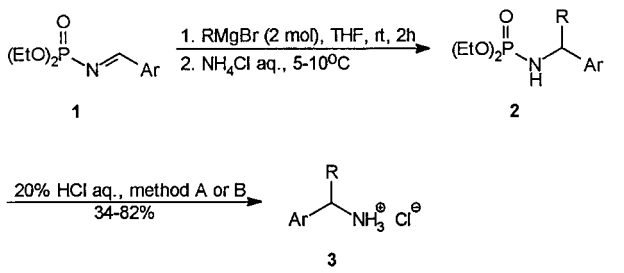
Abstract: Addition of organomagnesium bromides to *N*-(diethoxyphosphoryl) aldimines **1** carried out in tetrahydrofuran at 20–25°C affords diethyl *N*-alkyl-phosphoramidates **2a–w** in high yields and spectroscopic purity. Deprotection of the latent amino groups in **2** results in the formation of α-arylalkylamine hydrochlorides **3a–w**.

Key words: *N*-Phosphorylated imines, nucleophilic addition, dephosphorylation of phosphoramidates, Barbier reaction

The development of methods for the synthesis of primary amines is still an active area of research in organic chemistry.[2,3] Among the various procedures leading to this class of compounds two general approaches have been most widely recommended recently. Nucleophilic ring-opening of *N*-activated aziridines with various copper-modified Grignard reagents usually proceeds regiospecifically at the less hindered carbon atom affording, after deprotection, the respective primary amine with α-branched carbon skeleton.[4] Alternative construction of a primary amine molecule from two different building blocks may also involve nucleophilic addition of organometallic compound to the C=N bond of suitably "masked" imine derivatives,[5] such as sulfenimines,[6] sulfonimines,[7] *N*-(trimethylsilyl)imines,[8] *N*-diphenylphosphinylimines,[9] and recently also resin-immobilized aldimines on Rink resin.[2] Addition followed by the removal of the protecting group leads to a primary amine with a suitably elaborated carbon skeleton. The wide implementation of *N*-activated aziridines into synthetic practice is evidently still hampered by their limited preparative accessibility. The relatively poor electrophilicity of the imine carbon atom and often difficult deprotection of the adducts leading to unsatisfactory yields and/or low purity of the target amines is the notorious drawback of all methods utilizing "masked" imines.

In a search for a simple, effective and economic procedure which could be applicable especially for multigram scale preparation of primary α-arylalkylamines we have focused our attention on *N*-(diethoxyphosphoryl)aldimines **1** recently prepared in our laboratory.[10] These easily available *N*-protected imines can be considered as natural precursors of primary amines because the diethoxyphosphoryl group can function both as C=N bond activator and be easily detached once nucleophilic addition has been attained. *N*-(Diethoxyphosphoryl)aldimines **1** reacted easily and smoothly with organomagnesium bromides in tetrahydrofuran at 20–25°C to give the respective diethyl *N*-alkylphosphoramidates **2a–r** in high yields (85–95%) (Scheme). Crude adducts **2** were spectroscopically pure (^{31}P NMR, see Table 1) and could be used for subsequent dephosphorylation without additional purification. It turned out to be essential to use 1 mole excess of Grignard reagent in order to secure high yields of addition and to avoid the formation of undesirable impurities. A variant of the Barbier procedure[11] was used to effect the addition of an alkyl group to *N*-(diethoxyphosphoryl)aldimines **1**. In our hands the addition of allyl bromide to the solution of imine **1** in tetrahydrofuran containing magnesium at ambient temperature afforded diethyl *N*-aryl-*N*-homoallylphosphoramidates **2s–w** in high yields (83–92%) and excellent purity (^{31}P NMR). The formation of side products was entirely suppressed under such conditions.



2, 3	a	b	c	d	e	f
Ar	Ph	Ph	Ph	Ph	Ph	Ph
R	Me	Et	i-Pr	c-C_6H_{11}	p-Me-C_6H_4	CH_2=CH

2, 3	g	h	i	j	k
Ar	p-Br-C_6H_4	p-Br-C_6H_4	p-Br-C_6H_4	p-Br-C_6H_4	p-Br-C_6H_4
R	Et	i-Pr	c-C_6H_{11}	p-Me-C_6H_4	CH_2=CH

2, 3	l	m	n	o	p
Ar	p-MeO-C_6H_4	p-MeO-C_6H_4	p-MeO-C_6H_4	p-MeO-C_6H_4	2-furyl
R	Et	i-Pr	Bu	Ph	Et

2, 3	q	r	s	t
Ar	2-thienyl	Ph-CH=CH	Ph	p-Me-C_6H_4
R	Et	Et	CH_2=CH-CH_2	CH_2=CH-CH_2

2, 3	u	v	w
Ar	1-naphthyl	Ph-CH=CH	2-thienyl
R	CH_2=CH-CH_2	CH_2=CH-CH_2	CH_2=CH-CH_2

Scheme

The standard removal[4] of the diethoxyphophoryl group from diethyl *N*-substituted phosphoramidates **2** by reflux-

ing them with 20% hydrochloric acid (Method A) was in some cases totally ineffective leading to very poor yields of impure amine hydrochlorides. The use of (1:1, v/v) mixture of 20% hydrochloric acid and tetrahydrofuran at room temperature (Method B) was then found to be the method of choice for deprotection (Scheme) although the reaction times were long (Table 1). The resultant solutions of α-arylalkylamine hydrochlorides **3** were transformed into free amines, isolated by extraction with diethyl ether, and characterized as amine hydrochlorides **3a–w** obtained by saturation of ethereal solutions with dry hydrogen chloride. Crude α-arylalkylamine hydrochlorides **3** delivered analytically pure samples after recrystallization from ethanol/diethyl ether. Yields, melting points, and the relevant spectral assignments of compounds **2** and **3** are compiled in Tables 1 and 2.

The outlined method for the synthesis of α-arylalkylamines represents a versatile and relatively inexpensive approach to these compounds from easily available starting materials.

Table 1 α-Arylalkylamine Hydrochlorides **3** Prepared

Product	^{31}P NMR of 2 δ	Deprotection Method[a]	Yield (%)[b]	mp (°C)	
				found	reported
3a	8.04	A (1 h)	47	156–158	(157–158,[12] 160–162[13])
3b	8.27	A (1 h)	66	192–193	(192–193,[14] 189.5[15])
3c	8.60	A (1 h)	49	265–267 dec	(275–277 dec,[16] 195-196[17])
3d	8.55	A (1 h)	76	310 dec	(310 de,[18] 330[14])
3e	7.75	B (9 d)	56	255–257 dec)	(256–260,[19] 273[20]
3f	7.88	B (6 d)	59	163–165	–
3g	8.03	A (1 h)	63	262–263	(272–273[17])
3h	8.35	A (1 h)	82	273–290 dec	–
3i	8.37	A (1 h)	56	290 dec	–
3j	7.59	B (10 d)	54	269–270 dec	–
3k	7.73	B (7 d)	61	230–232 dec	–
3l	8.28	B (1 d)	58	221–223	(217–218[21])
3m	8.67	B (8 h)[c]	55	217–219 dec	–
3n	8.20	B (2 d)	63	205–207	–
3o	8.39	B (8 d)	42	200–202 dec	(203 dec,[19] 181–182[22])
3p	7.97	B (2 d)	34[d]	142–144 dec	–
3q	7.73	B (3 d)	59	173–175	–
3r	8.50	B (2 d)	54[e]	212–214 dec	–
3s	8.06	B (3 d)	65	223–225 dec	(224–226[14])
3t	8.12	B (4 d)	63	212–214 dec	–
3u	7.96	_f	59	204–205	–
3v	8.34	B (30 h)	47	163–165	–
3w	7.57	B (3 d)	57	194–196 dec	–

[a] Reaction time is given in parentheses.
[b] Overall yields of analytically pure compounds. Satisfactory microanalyses obtained: C ± 0.21, H ± 0.35, N ± 0.25.
[c] Deprotection was carried out at 35–40 °C.
[d] Isolated as amine tosylate.
[e] The compound was identified as pure a-allylcinnamylamine hydrochloride.
[f] Deprotection was carried out by refluxing with ethanolic hydrogen chloride for 2 h.

Table 2 Spectroscopic Data for α-Arylalkylamine Hydrochlorides 3

Product	IR (nujol)[a] (cm^{-1})	^1H NMR (CD_3OD/TMS) δ, J (Hz)	MS–FAB *m*/*z*, MH^+ –HCl (%)
3a	2990, 2570, 1610, 15121458, 1370, 1072	1.64 (d, 3 H, *J* = 7.0, CH3), 4.44 (q, 1 H, *J* = 7.0, CH), 4,87 (s, 3 H, NH3), 7.40–7.45 (m, 5 H, ArH)	122 (51)
3b	2995, 2660, 2000, 1605, 1516, 1480, 1370, 1120, 1079	0.89 (t, 3 H, *J* = 7.5, CH3, 1.92–2.14 (m, 2 H, CH2), 4.16 (dd, 1 H, *J* = 9.3, 6.0, CH), 4.87 (s, 3 H, NH3), 7.41–7,49 (dd, 1 H, *J* = 9.3, 6.0, CH), 4.87 (s, 3 H, NH3), 7.41–7,49	136 (52)
3c	2968, 2672, 2568, 1968, 1604, 1512, 1484, 1460, 1376, 1160, 1096, 1072	0.80, 1.15 (2 d, 6 H, *J* = 6.6, CH_3), 2.10–2.30 (m, 1 H, CH), 3.92 (d, 1 H, *J* = 9.3, C*H*-Ph), 4,87 (s, 3 H, NH_3), 7.38–7.46 (m, 5 H, ArH)	150 (42)
3d	2912, 2696, 2672, 1608, 1568, 1512, 1448	0.83–2.09 (m, 1 H, CH), 3,94 (d, 1 H, *J* = 9.3 C*H*-Ar), 4.87 (s, 3 H, NH_3), 7.36–7.46 (m, 5 H, ArH)	190 (59)
3e	2968, 2656, 2616, 2224, 2040, 1604, 1560, 1516, 1504, 1496, 1448, 1408, 1384, 1192, 1032	2.35 (s,3 H,CH_3), 4.87 (s,3 H,NH_3), 5.59 (s,1 H, CH), 7.24–7.31 (m,4 H,ArH), 7.39–7.49 (m,5 H,ArH)	198 (20)
3f	2864, 2056, 1600, 1512, 1448, 1360	4.55 (s,3 H,NH_3),5.04 (d,1H, *J* = 6.5,CH), 5.44 (dd,1 H, *J* = 17.3, 1.3, =CH), 5.51(dd,1 H, *J* = 10.6, 1.0, =CH), 6.19 (ddd, 1 H, *J* = 17.3, 10.6, 6.5, =CH), 7.43–7.57 (m,5 H,ArH)[b]	134 (32)
3g	3960, 3248, 2872, 2656, 2616, 2288, 2024, 2000, 1592, 1512, 1496, 1484, 1416, 1364, 1304, 1120, 1072, 1008	0.89 (t,3 H, *J* = 7.4,CH_3), 1.88–2.10 (m,2 H,CH_2), 4.18 (dd,1 H, *J* = 9.1, 6.0, CH), 4.89 (s,3 H, NH_3), 7.36–7.65 (m,4 H,ArH)	214 (59), 216 (56)
3h	2896, 2032, 2000, 1596, 1500, 1488, 1424, 1392, 1384, 1376, 1312, 1216, 1072, 1008	0.80, 1.14 (2 d,6 H, *J* = 6.8,CH_3), 2.09–2.83 (m,1 H CH), 3.95 (d,1 H, *J* = 9.3,CH-Ar). 4.87 (s,3 H ,NH_3,), 7.27–7.66 (m,4 H,ArH)	228 (62), 230 (61)
3i	2928, 2000, 1596, 1520, 1504, 1496, 1448, 1424, 1384, 1072, 1008	0.84–2.00 (m,11 H,6 x CH_2,CH), 3.95 (d,1 H, *J* = 9.3, C*H*-Ar), 4.89 (s,3 H,NH_3), 7.30–7.65 (m,4 H,ArH)	268 (64), 270 (60)
3j	2944, 2632, 2600, 2024, 2000, 1604, 1564, 1524, 1500, 1488, 1416, 1380, 1192, 1072	2.26 (s,3 H,CH_3), 4.87 (s,3 H,NH_3), 5.60 (s,1 H,CH), 7.28 (brs,4 H,ArH), 7.29–7.64 (m,4 H,ArH)	274 (8), 276 (8)
3k	2888, 040, 1596, 1512, 1416, 1072	4.84 (s,3 H,NH_3), 4.96 (d,1 H, *J* = 6.5,CH), 5.43 (dd, 1 H, *J* = 17.3, 1.5,=CH), 5.51(dd,1 H, *J* = 10.5, 1.0, =CH), 6.13 (ddd, 1 H, *J* = 17.3, 10.5, 6.5,=CH), 7.36–7.66 (m,4 H,ArH)	212 (32), 214 (31)
3l	2936, 2576, 2544, 2000, 1616, 1592, 1560, 1516, 1464, 1388, 1312, 1248, 1184, 1032	0.88 (t,3 H, *J* = 7.5,CH_3), 1.90–2.07 (m,2 H, CH_2), 3.82 (s,3 H,CH_3O), 4.09 (dd,1 H, *J* = 9.5, 6.0, C*H*-Ar), 4.87 (s,3 H,NH_3), 6.97–7.39 (m,4 H,ArH)	166 (5)
3m	3296, 2968, 2224, 2000, 1592, 1580, 1544, 1500, 1380, 1308, 1296, 1260, 1188, 1080, 1064, 1028	0.79, 1.13 (2 d,6 H, *J* = 6.8,CH_3), 2.09–2.32 (m,1 H, CH), 3.81 (s,3 H,CH_3O) 3.85 (d,1 H, *J* = 9.3,C*H*-Ar), 4.86 (s,3 H, NH_3), 6.96–7.40 (m,4 H,ArH)	180 (4)
3n	2936, 1608, 1512, 1460, 1388, 1252, 1184, 1032	0.91 (t,3 H, *J* = 7.0,CH_3), 1.07–1.46 (m, 4 H, 2 x CH_2), 1.94–2.03 (m, 2 H,CH_2), 3.84 (s,3 H,CH_3O), 4.19 (dd,1 H,J=9.3, *J* = 6.3,C*H*-Ar), 4.88 (s,3 H,NH_3), 6.99–7.41 (m,4 H,ArH)	194 (5)
3o	2968, 2604, 2224, 2000, 1604, 1560, 1505, 1460, 1380, 1184, 1030	3.79 (s,3 H,CH_3O), 4.87 (s,3 H,NH_3) 5.59 (s,1 H, CH), 6.96–7.37 (m,4 H, ArH), 7.39–7.50 (m,5 H,ArH)	214 (15)
3p	–	0.95 (t,3 H, *J* = 7.5,CH_3), 1.96–2.10 (m,2 H, CH_2), 2.39 (s,3 H,CH_3), 4.34(dd,1 H, *J* = 9.0, 6.0,C*H*-Ar), 6.49(dd,1 H, *J* = 3.3, 1.8,=CH), 6.55 (brd, 1 H, *J* = 3.3,=CH), 7.25 (m,2 H,ArH), 7.62 (brd,1 H, *J* = 3.3,=CH), 7.73 (m,2 H,ArH)	126 (78) (MH^+ – TsOH)

Table 2 (continued)

Product	IR (nujol)[a] (cm^{-1})	^1H NMR (CD_3OD/TMS) δ, *J* (Hz)	MS–FAB *m*/z, MH^+ –HCl (%)
3q	2880, 2648, 2624, 2048, 1609, 1512, 1384, 704	0.80 (t,3 H, *J* = 7.4,CH_3), 1.75–2.13 (m,2 H, CH_2), 4.38–4.50 (m,1 H,C*H*-Ar), 7.06(dd,1 H, *J* = 3.6, 5.1,=CH), 7.28 (dd, 1 H, *J* = 3.6, 1.0,=CH). 7.56 (dd,1 H, *J* = 5.1, 1.0,=CH), 8.71 (brs,3 H,NH_3)[c]	142 (55)
3r	2920, 2632, 2576, 2536, 2056, 1600, 1520, 1448, 1384, 968, 696	1.02(t,3 H, *J* = 7.5,CH_3), 1.74–1.92 (m,2 H, CH_2), 3.80 (dt,1 H, *J* = 8.5,5.5,CH), 4.86(s,3 H,NH_3), 6.16 (dd,1 H, *J* = 15.9, 8.5, =CH), 6.80 (d,1 H, *J* = 15.9,=CH), 7.26–7.49 (m,5 H,ArH)	162 (35)
3s	2888, 1600, 1512, 1440	2.71–2.75 (m,2 H,CH_2), 4.35 (t,1 H, *J* = 7.5, CH), 7.26–7.49 (m,5 H,ArH) 4.87 (s,3 H,NH_3), 5.13–5.24 (m,2 H,=CH_2), 5.61–5.79 (m,1 H, =CH), 7.41-7.47 (m,5 H,ArH)	148 (85)
3t	2872, 1596, 1512, 1440	2.36 (s,3 H,CH_3), 2.69–2.76 (m,2 H,CH_2), 4.30 (t,1 H, *J* = 7.6,CH), 4.85 (s,3 H,NH_3), 5.12–5.23 (m, 2 H,=CH_2), 5.61–5.77 (m, 1 H,=CH), 7.25–7.39 (m,4 H,ArH)	162 (37)
3u	2920, 1640, 1592, 1512, 1440	2.72–2.94 (m,2 H,CH_2), 4.95–5.10 (m, 2 H,=CH_2), 5.20–5.28 (m,1 H,CH), 5.60–5.76 (m,1 H,=CH), 7.55–8.22 (m,7 H,ArH), 8.82 (br s. 3 H, NH_3)[c]	198 (22)
3v	2880, 1596, 1512, 1448, 1384	2.59 (t,2 H, *J* = 7.3,CH_2), 3.99 (q,1 H, *J* = 7.3, CH), 4.86 (s,3 H,NH_3), 5.22–5.32 (m,2 H, =CH_2) 5.76–5.92 (m, 1 H,=CH), 6.21 (dd, 1 H, *J* = 8.3,16.0,=CH), 6.78 (d,1 H, *J* = 16.0, =CH), 7.16–7.49 (m,5 H,ArH)	174 (17)
3w	2912, 2640, 2592, 2040, 1604, 1512, 1436, 1384, 1248	2.58–2.87 (m,2 H,CH_2), 4.58–4.64 (m,1 H,CH) 5.01–5.13 (m,2 H,=CH_2), 5.56–5.72 (m,1 H, =CH), 7.04 (dd,1 H, *J* = 3.5,5.0,ArH),7.28 (dd,1 H,*J* = 5.0, 1.0,ArH), 7.55 (dd,1 H, *J* = 5.0, 1.0,ArH), 8.74 (bs,3 H,NH_3)[c]	154 (36)

[a] The strongest absorptions are only given
[b] Measured in D_2O
[c] Measured in DMSO-d6

All solvents and reagents were of reagent grade and were purchased from Fluka. The solution of vinylmagnesium bromide in THF was purchased from Aldrich. All mps (determined in open capillary tubes) are uncorrected. IR spectra (nujol mulls) were measured using a Specord M80 (C.Zeiss). instrument. ^1H NMR spectra were recorded on a Bruker AVANCE DPX-250 spectrometer oparating at 250 MHz, using CD_3OD solutions unless otherwise stated. ^{31}P NMR spectra were recorded at 101.255 MHz with the same spectrometer. Positive chemical shifts are downfield from 85% H_3PO_4. FAB/MS were measured on an APO Electron (Ukraine) Model MI 12001 E mass spectrometer equipped with a FAB ion source (thioglycerol matrix).

All *N*-(diethoxyphosphoryl)aldimines **1** were obtained as described previously.[10]

N-(Diethoxyphosphoryl)-2-thienylideneimine (1, Ar = 2-thienyl)
The synthesis was performed according to the previously described procedure[10] starting from 2-thiophene carboxaldehyde diethyl acetal and diethyl phosphoramidate. Yellow oil; yield: 74%; bp 154°C/0.7 Torr.

^1H NMR ($CDCl_3$): δ = 1.36, 1.37 (2 t, 6 H, *J* = 7.0 Hz, CH_3), 4.13–4.26 (m, 4 H, CH_2), 7.18–7.22 (m, 1 H, ArH), 7.69–7.72 (m, 2 H, ArH), 9.14 (d, 1 H, *J* = 31.3 Hz, =CH).

^{31}P NMR ($CDCl_3$): δ = 8.20.

MS: *m*/z (%) = 248 (M^+ +1, 100).

Anal. calcd for $C_9H_{14}O_3NPS$ (248.1): C, 43.72; H, 5.71; N, 5.67; P, 12.53. Found C, 43.42; H, 5.58; N, 5.92; P, 12.39.

Grignard Addition of Organomagnesium Bromides to *N*-(Diethoxyphosphoryl)aldimines 1; General Procedure
A solution of imine **1** (0.01 mol) in THF (15 mL) was added with stirring at 20–25°C to a solution of organomagnesium bromide prepared from Mg grit (0.49g, 0.02 mol), alkyl or aryl bromide (0.02 mol), and THF (20 mL) at 40–45°C. Stirring was then continued for 2 h at r.t. The resultant mixture was quenched with satd aq NH_4Cl solution (ca 30 mL) below 10°C. The aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic solutions were washed with H_2O (2 × 15 mL), dried ($MgSO_4$), and evaporated under reduced pressure. Crude diethyl *N*-alkylphosphoramidates **2a–r** thus obtained were spectroscopically pure after heating for ca 1 h at 40–50°C/1 Torr. Compound **2a** was obtained by addition of MeMgI to *N*-(diethoxyphosphoryl)benzylideneimine (**1**, Ar = Ph) in Et_2O.

Barbier Addition of Allylmagnesium Bromide to *N*-(Diethoxyphosphoryl)aldimines 1; General Procedure
A solution of allyl bromide (1.33g, 11 mmol) in THF (10 mL) was added with stirring at 0°C to a mixture of imine 1 (10 mmol), Mg grit (0.29 g, 12 mmol), and THF (10 mL). The temperature was then raised to 10°C and stirring was continued at this temperatue for ca 15 min and then at 20–25°C for 1.5 h. The resultant mixture was quenched with satd aq NH_4Cl solution (ca 25 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL) The combined organic solutions were washed with H_2O (2 × 15 mL), dried ($MgSO_4$),

and heated at 40–50°C/1 Torr for ca 1h to give crude **2s–w** in spectroscopically pure state.

Deprotection of Diethyl *N*-Alkylphosphoramidates 2a–w to a-Arylalkylamines 3a–w; General Procedure

Method A: Crude phosphoramidate 2 (5 mmol) was refluxed with 20% HCl (15 mL) for 1 h. The resultant solution was cooled to r.t. and extracted with Et_2O (15 mL). The extract was discarded and the solution was made strongly alkaline with solid NaOH. The amine was extracted with Et_2O (4 × 15 mL), the extract was dried (KOH) and saturated with dry, gaseous HCl at r.t. for ca 15 min. Crystalline α-arylalkylamine hydrochloride **3** was filtered, washed with Et_2O, and dried in vacuo over solid KOH. Recrystallization from EtOH/Et_2O afforded analytically pure samples of **3**.

Method B: To a solution of the crude phosphoramidate **2** (5 mmol) in THF (5 mL) was added 20% HCl (5 mL) and the mixture was left at r.t. (1–10 d, see Table 1). Progress of deprotection was monitored by ^{31}P NMR (disappearance of the signal at $\delta = 7.5 – 8.7$). The resultant mixture was made strongly alkaline with solid NaOH and worked up as in the Method A. Yields, melting points, and spectroscopic data of α-arylalkylamine hydrochlorides **3a–w** obtained by methods A and B are compiled in Tables 1 and 2.

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