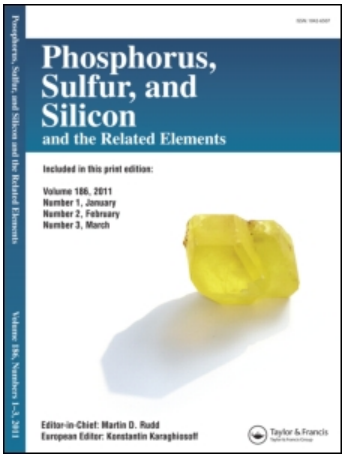

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THE REACTION OF ETHYL-[*N*-(DIETHOXYPHOSPHORYL)]FORMIMIDATE WITH GRIGNARD REAGENTS: A NEW APPROACH TO ELECTROPHILIC AMINATION

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Addition of Grignard reagents to ethyl-[*N*-(diethoxyphosphoryl)]formimidate, **3** followed by aqueous workup and treatment of the resultant diethyl phosphoramidates with *p*-toluenesulfonic acid in ethanol gives, depending upon the organomagnesium reagent used, the corresponding tosylates of primary or secondary amines in moderate to good yields. The diethoxyphosphoryl moiety remains unchanged upon treatment of **3** with Grignard reagents.

Key words: Diethyl-(*N*-alkylphosphoramidates); Grignard reagents; ammonium tosylates; substitution–addition; substitution–reduction; electrophilic amination.

INTRODUCTION

There are several reports in the literature[1–6] which demonstrate the possible application of some "masked" imine derivatives of ammonia in the synthesis of hindered secondary and tertiary carbinamines. The C–N double bond in *N*-substituted imines **1** is an efficient Michael acceptor for variety of organometallic reagents. Removal of the protecting group *Y* in the resultant adducts **2** affords the free amine (Equation 1).

$$\underset{\mathbf{1}}{Y\text{-}N{=}CR^1R^2} \xrightarrow[2.\ H_3O^+]{1.\ R^3M} \underset{\mathbf{2}}{Y\text{-}HN\text{-}CR^1R^2R^3} \longrightarrow H_2NCR^1R^2R^3 \qquad (1)$$

$Y = ArS,\ SiMe_3,\ SO_2R,\ (C_6H_5)_2P(O)$;

$R^1, R^2 = H,$ alkyl, aryl; $R^3 =$ alkyl, aryl; $M = Li, MgX$

Several *N*-substituted imines, like *N*-alkylidenearenesulfenamides ($Y = SAr$),[2] nonenolizable *N*-trimethylsilyl imines ($Y = SiMe_3$),[3] *N*-arylidenesulfonamides ($Y = SO_2Ph$),[4] *N,N*-diarylidenesulfamides ($Y = SO_2N{=}CHAr$)[5], and ethyl-[*N*-diphenylphosphinyl]formimidate ($Y = Ph_2PO$, $R^1 = H$, $R^2 = OEt$)[6] have been mentioned, according to the sequence outlined above (Equation 1), as potential precursors of primary amines. However, due to the high cost and limited availability of the respective starting materials and/or some other serious preparative restrictions none of the reported procedures have become widely applicable, especially for large scale preparations. Looking for a more convenient approach to the synthesis of primary amines, based on electrophilic amination, it

seemed reasonable to try ethyl-[*N*-diethoxyphosphoryl] formimidate, **3** as an inexpensive and easily available "masked" imine derivative.

RESULTS AND DISCUSSION

Ethyl-[*N*-diethoxyphosphoryl]formimidate, **3** is readily available and can easily be prepared in bulk by thermal condensation of diethyl phosphoramidate with a slight excess of ethyl orthoformate (Equation 2). Compound **3** was first prepared by Moskva *et al.*[7] but it was not spectroscopically characterized and its structure was not proved. It is a stable liquid which can be stored at ambient temperature for several months without any signs of decomposition.

$$(C_2H_5O)_2\overset{\overset{O}{\|}}{P}\text{-}NH_2 \bullet HC(OC_2H_5)_3 \xrightarrow[80\ \%]{\Delta} (C_2H_5O)_2\overset{\overset{O}{\|}}{P}\text{-}N{=}CHOC_2H_5 + 2C_2H_5OH \qquad (2)$$

3

It was now found that **3** reacts smoothly with an excess of primary Grignard reagent at room temperature in ether to form the corresponding substitution–addition, **5** or substitution–reduction products, **6**. The typical splitting patterns observed in the ^{1}H-NMR spectra of the crude substitution–addition products, for example **5a–5c**, unequivocally prove the presence of the diethoxyphosphoryl group in their structures. These signals consist of the six-proton triplets in the range of δ 1.00–1.30 ppm and the four-proton quintets ($^3J_{HH} = {}^3J_{PH}$) in the range of δ 3.60–3.84 ppm, for the methyl and methylene protons of the CH_3CH_2OP groupings, respectively. Thus, it is evident that the diethoxyphosphoryl group remains unaffected during treatment of **3** with Grignard reagents. It is neither necessary nor advisable to isolate and purify the phosphoramidates **5** or **6** before their cleavage to the appropriate ammonium tosylates **7** or **8** by refluxing them with equimolar amount of *p*-toluenesulfonic acid monohydrate in ethanol for 8*h*[8] (Scheme 1).

$$3 \xrightarrow[\text{ether, r.t.}]{RMgBr} \left[(C_2H_5O)_2\overset{\overset{O}{\|}}{P}\text{-}N{=}CHR\right] \xrightarrow[\text{2. 5\% aq. } H_2SO_4,\ 0\text{-}5^\circ]{\text{1. } RMgBr} (C_2H_5O)_2\overset{\overset{O}{\|}}{P}\text{-}NHCHR_2 \text{ or}$$

4 **5 a–d**

$$(C_2H_5O)_2\overset{\overset{O}{\|}}{P}\ NHCH_2R \xrightarrow[\text{reflux, 8h}]{TsOH\cdot H_2O/C_2H_5OH} TsO^{(-)}[H_3\overset{(+)}{N}CHR_2] \text{ or } TsO^{(-)}[H_3\overset{(+)}{N}CH_2R] +$$

6 e–i **7 a–d** **8 e–i**

$$+ (C_2H_5O)_3PO$$

Ts = 4-$CH_3C_6H_4SO_2$

5–8	R	5–8	R
a	CH_3	f	i-C_3H_7
b	C_2H_5	g	n-C_4H_9
c	C_6H_5	h	i-C_4H_9
d	$C_6H_5CH_2$	i	$C_6H_5CH_2CH_2$
e	n-C_3H_7	j	s-C_4H_9

SCHEME 1

Evaporation of the solvent, followed by precipitation of the products with ether, furnishes the crystalline ammonium tosylates, **7** and **8**, in moderate to good overall yields. Analytically pure samples could be obtained by dissolving the crude ammonium tosylates in hot ethanol and reprecipitation with ether. The results presented in Table I illustrate the synthetic scope of the procedure.

The identify of the ammonium tosylates, **7** and **8**, was proved by ^{1}H-NMR spectroscopy (Table II) and, in some cases, also by comparing their melting points with those of authentic specimens.

From these results it is clear that the method works well with primary alkyl- and aryl-magnesium bromides. Attempted application of sec-alkylmagnesium bromides in the reaction with **3** was, however, totally unsuccessful. It is also evident that the structures of the phosphoramidates **5** and **6** and hence those of the compounds **7** and **8** are strongly dependent upon the structure of the alkyl moiety present in the Grignard reagent. This finding is in contrast to the previously observed[6] direction of Grignard substitution-addition to ethyl-[*N*-diphenylphosphinyl]-formimidate where only one product of type **5** was always formed. In the case of **3**, substitution, followed by addition of Grignard reagent to the phosphorylated imine intermediate **4**, competes with its reduction. The reaction sequence presented in Scheme 2 may provide a possible explanation for the observed reactions.

TABLE I

Preparation of the ammonium tosylates **7** and **8**

Entry	R	Product	Yield (%)[a]	m.p. (°C)[b]	Molecular formula	Calc./Found (%) C	H	N
1	CH_3	7a	60	121–123[c]	$C_{10}H_{17}NO_3S$ (231.3)	51.93 52.21	7.41 7.41	6.06 6.03
2	C_2H_5	7b	58	118–120	$C_{12}H_{21}NO_3S$ (259.4)	55.57 55.18	8.16 7.97	5.40 5.38
3	C_6H_5	7c	56	231–233	$C_{20}H_{21}NO_3S$ (355.6)	67.58 67.18	5.95 6.10	3.94 4.05
4	$C_6H_5CH_2$	7d	43	173–174	$C_{22}H_{25}NO_3S$ (383.5)	68.90 68.68	6.57 6.12	3.65 3.65
5	*n*-C_3H_7	8e	33	115–117	$C_{11}H_{19}NO_3S$ (245.3)	53.85 54.06	7.80 7.97	5.71 5.85
6	*i*-C_3H_7	8f	51	112–114	$C_{11}H_{19}NO_3S$ (245.3)	53.85 54.11	7.80 7.68	5.71 5.71
7	*n*-C_4H_9	8g	52[d]	103–106[e]	$C_{12}H_{21}NO_3S$ (259.4)	55.57 55.87	8.16 8.04	5.40 5.21
8	*i*-C_4H_9	8h	60	94–96	$C_{12}H_{21}NO_3S$ (259.4)	55.57 55.24	8.16 8.14	5.40 5.69
9	$C_6H_5CH_2CH_2$	8i	67[d]	165–166	$C_{16}H_{21}NO_3S$ (307.4)	62.53 62.52	6.89 7.17	4.56 4.54
10	*s*-C_4H_9	8j	0	—				

[a] Yield of isolated product, based on **3**.

[b] Uncorrected, after crystallization from ethanol/ether.

[c] Lit.[11] m.p. 126.5–127.5°C.

[d] From the mother liquor after crystallization the products of type **7** ($R = n$-C_4H_9 and $R = C_6H_5CH_2CH_2$) were isolated in about 7% yield, m.p. 125–158°C and m.p. 196–201°C, respectively. The elemental analyses and ^{1}H-NMR spectra of these compounds were consistent with the anticipated structures.

[e] Lit.[11] m.p. 119–120°C.

TABLE II

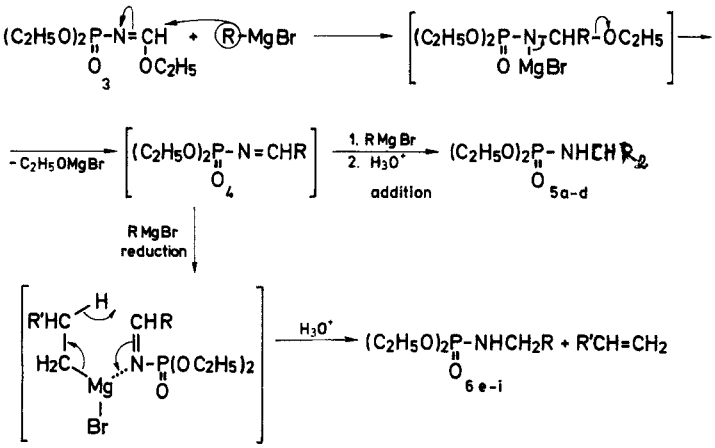
Spectroscopic data of the Ammonium *p*-Toluenesulfonates **7** and **8**

Compound	IR(KBr)[a] $\nu(cm^{-1})$	^{1}H-NMR[b](D_2O/TMS_{ext})[c] δ(ppm), J(Hz)
7a	3020(NH), 2980, 2940, 1640(NH_3^+), 1527, 1470, 1190, 1120, 1035, 1010, 815, 680	1.27(d, 6H, J = 6, 5, CH_3); 2.32(s, 3H, $\underline{CH_3}$-Ar); 3.44(hep, 1H, J = 6.5, CH); 7.18–7.94(AA'XX' of *p*-C_6H_4, 4H)
7b	3040(NH), 2960, 1630(NH_3^+), 1530, 1460, 1230, 1150, 1030, 1005, 817, 682	0.95(t, 6H, J = 7.2, CH_3); 1.64(qu, 4H, J = 7.2, CH_2); 2.36(s, 3H, CH_3-Ar); 3.11(qu, 1H, J = 7.2, CH); 7.25–7.98(AA'XX' of *p*-C_6H_4, 4H)
7c	3040(NNH), 2940, 1645(NH_3^+), 1590, 1513, 1220, 1178, 1120, 1035, 1012, 815, 737, 680	2.29(s, 3H, CH_3–Ar); 4.86(bs, NH_3^+); 5.58(s, 1H, CHN); 7.00–7.88 (AA'XX' of *p*-C_6H_4, 4H)
7d	3000(NH), 2910;1600(NH_3^+), 1525, 1498, 1455, 1230, 1170, 1125, 1035, 1012, 815, 750, 700, 680	2.25(s, 3H, CH_3-Ar); 2.84(d, 4H, J = 7.0, $\underline{CH_2}$Ph); 3.38–3.80(m, 1H, CHN); 4.75(s, NH_3^+); 7.02–7.90(AA'XX' of *p*-C_6H_4, 4H); 7.38(s, 10H, C_6H_5)
8e	3060(NH), 2930, 1635(NH_3^+), 1500, 1180, 1123, 1037, 1015, 815, 685	0.94(t, 3H, J = 7.0, CH_3); 1.10–1.93(m, 4H, CH_2CH_2); 2.40(s, 3H, CH_3Ar); 3.02(t, 2H, J = 7.0, CH_2N); 7.30–7.93(AA'XX' of *p*-C_6H_4, 4H)
8f	3040(NH), 2940, 1635(NH_3^+), 1520, 1470, 1210, 1178, 1125, 1037, 1012, 818, 685	0.94(d, 6H, J = 6.5, CH_3); 1.90(hep, 1H, J = 6.5, CH); 2.33(s, 3H, CH_3Ar); 2.80(d, 2H, J = 7.0, CH_2N); 7.30–7.93(AA'XX' of *p*-C_6H_4, 4H)
8g	3040(NH), 2940, 1620(NH_3^+), 1505, 1190, 1127, 1140, 1015, 820, 685	0.62–1.80(m, 9H, $CH_3(CH_2)_3$); 2.31(s, 3H, CH_3Ar); 2.92(t, 2H, J = 7.0, CH_2N); 7.12–8.10(AA'XX' of *p*-C_6H_4, 4H)
8h	3100(NH), 2980, 1630(NH_3^+), 1480, 1180, 1125, 1038, 1005, 905, 805, 680	0.91(d, 6H, J = 6.0, CH_3); 2.55–3.00(m, 3H, CH_2CH); 2.38(s, 3H, CH_3Ar); 2.85–3.15(m, 2H, CH_2N); 7.20–7.95(AA'XX' of *p*-C_6H_4, 4H)
8i	3150(NH), 2980, 1620(NH_3^+), 1480, 1170, 1122, 1040, 1007, 808, 760, 685	1.85(qu, 2H, J = 8.0, CH_2); 2.29(s, 3H, CH_3Ar); 2.61(t, 2H, J = 8.0, CH_2Ar); 2.85(t, 2H, J = 8.0, CH_2N); 6.98–7.85(AA'XX' of *p*-C_6H_4, 4H); 7.23(s, 5H, C_6H_5)

[a] Recorded on a Specord 71 IR (C. Zeiss) spectrophotometer.

[b] Measured at 80 MHz with a Tesla BS 487C spectrometer. Reported multiplicity: s—singlet, d—doublet, t—triplet, qu—quintet, hep—heptet, m—multiplet.

[c] ^{1}H-NMR spectra of the compounds **7c** and **7d** were measured on CD_3OD solutions, using TMS as internal standard.



SCHEME 2

Similarly to the behaviour of the *N*-diphenylphosphinyl analog of **3**, the reaction probably proceeds stepwise. The first, relatively slow step involving nucleophilic displacement at sp^2 carbon results in the formation of the very reactive *N*-phosphorylated imine derivative **4**. The further fate of this intermediate depends upon the structure of the alkyl group present in the Grignard reagent.

When an alkene, stabilized by hyperconjugation, can be formed from the alkyl moiety of the Grignard reagent (entry no. 5–9; Table I) intermolecular hydride transfer takes place and reduction of the imine **4** with an excess of alkylmagnesium bromide leading to the phosphoramidates **6e–6i** is observed. When such a possibility is excluded (entry no. 1–4; Table I), the imine **4** undergoes rapid subsequent addition to give the diethyl *N*-alkylphosphoramidate **5a–5d** as the final product. Such a mechanism, accounting for the "anomalous" reaction, i.e. reduction observed in Grignard additions, was previously postulated for carbonyl compounds.[9,10]

Finally, the high selectivity of addition versus reduction and vice versa observed in the reactions of **3** with Grignard reagents should be emphasized. In most cases the crude ammonium tosylates **7a–7d** and **8e–8i** were not contaminated with each other. The electrophilic amination of Grignard reagents with **3** described can, therefore be utilized for preparative purposes when aminomethylation of alkyl halides and, in some cases, the preparation of symmetrical secondary carbinamines is desired.

EXPERIMENTAL

Diethyl-phosphoramidate was prepared in 92% yield, according to the previously described procedure.[12]

Ethyl-[*N*-(diethoxyphosphoryl)]-formimidate, **3**. The diethyl-phosphoramidate (0.2 mol) is refluxed with freshly distilled triethyl-orthoformate (0.22 mol) in a distillation apparatus. Ethanol is distilled off slowly while it is formed over a period of about 1 h. When the temperature of the mixture reaches 120°C excess triethyl orthoformate is evaporated under reduced pressure and the residue is distilled in vacuo to give **3** as a colorless liquid. Yield: 33.4 g (80%); b.p. 88–89°C/0.8 Torr; n_D^{20} 1.4340 (lit.[7] yield

83%, b.p. 68–69°C/0.04 Torr; n_D^{20} 1.4348). IR (film): 2980, 1640 (C=N), 1480, 1450, 1395, 1370, 1240, (P=O), 1165, 1040, 970, 820, 755 cm^{-1}.

^{1}H-NMR (CCl_4/TMS): δ 1.20 (*t*, 6H, J = 7.1 Hz, $\underline{CH_3}COP$), 1.25 (*t*, 3H, J = 7.3 Hz, $\underline{CH_3}COC$), 3.93 (qu, 4H, J = 7.1 Hz, $^3J_{PH}$ = 7.1 Hz, $\underline{CH_2}OP$), 4.21 (q, 2H, J = 7.3 Hz, $\underline{CH_2}OC$), 8.09 ppm (d, 1H, $^3J_{PH}$ = 15.5 Hz, CH=NP).

^{31}P-NMR (100%/H_3PO_4): δ 5.91, 5.97 ppm (possibly E and Z isomers).

Ammonium tosylates, **7,8a–j** (general procedure). To a solution of the Grignard reagent freshly prepared from magnesium (0.06 mol) and the corresponding alkyl or aryl bromide (0.06 mol) in ether (40 mol) a solution of ethyl-[*N*(diethoxyphosphoryl)]-formimidate (**3**; 4.18 g, 0.02 mol) in ether (20 ml) is added dropwise at room temperature. The resultant mixture is stirred for an additional 2 h, then cooled to 0–5°, and 5% aqueous sulfuric acid (50 ml) is added dropwise. The mixture is allowed to warm to room temperature, diluted with ether (20 ml) and separated. The organic layer is dried with anhydrous magnesium sulfate and evaporated to give the crude amide, **5** or **6**. The resultant amide is dissolved in ethanol (20 ml), an equivalent amount of *p*-toluenesulfonic acid monohydrate is added and the mixture is refluxed gently for 8h. After removal of the solvent ether (40 ml) is added to the residue and the crystalline precipitate of ammonium tosylate **7** or **8** is filtered off, washed with ether and recrystallized by dissolving it in hot ethanol and reprecipitation with an excess of ether.

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