Phosphoramidomercuration-Demercuration: A Simple, Two-Step Conversion of Alkenes into Alkanamines

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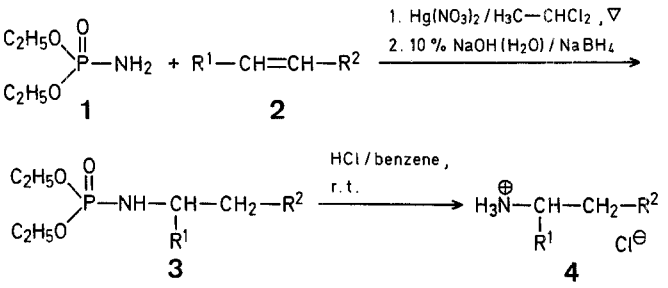
Among the various synthetic methods employing the intermediate formation of organomercurials, solvomercuration-demercuration of alkenes is probably the most widely applicable[1] one. This procedure is capable of wide variation and can serve as a general technique for the regiospecific introduction of a variety of nucleophiles at C=C double bonds in the Markovnikov direction[2]. Amidomercuration-demercuration of alkenes in the presence of acetonitrile provides a convenient technique for the Markovnikov amination of double bonds via the corresponding *N*-alkylacetamides[3]. This reaction appears to possess wide synthetic applicability but it obviously has certain drawbacks, e.g., the necessity of deprotecting an amino function which sometimes requires rather drastic conditions.

In a search for an alternative approach free from this limitation we have found that diethyl phosphoramidate (**1**) is sufficiently nucleophilic to be used for the mercuration of olefins in the presence of mercury(II) nitrate. Similarly to previous statements[3], neither mercury(II) acetate nor mercury(II) trifluoroacetate gave satisfactory results in this reaction. Apparently, these mercury(II) salts compete with the weakly nucleophilic diethyl phosphoroamidate (**1**) for the organomercury intermediate. However, dry mercury(II) nitrate proved to work satisfactorily in the reaction. Thus, when 3 mol of diethyl phosphoramidate (**1**) were refluxed in 1,1-dichloroethane with 1 mol of olefin (**2**) and 1 mol of mercury nitrate for 4 h, followed by *in situ* demercuration of the mercurial intermediate with aqueous alkaline sodium borohydride, the corresponding diethyl *N*-alkylphosphoramidates (**3**) were formed in moderate yields. They could be easily separated from excess diethyl phosphoramidate (**1**) by washing the solution in 1,1-dichloroethane with water. Additional purification was neither necessary nor desirable because the crude products **3** gave satisfactory analyses and could be directly used for the preparation of the amine hydrochlorides **4**.



In an attempt to optimise the conditions of the mercuration step, we found that increasing the reaction temperature to 80 °C as well as prolonged refluxing in 1,1-dichloroethane lead to evidently inferior results. The latter variant is advisable only in the case of less reactive alkenes, e.g., norbornene (**2i**). A substantial excess of diethyl phosphoramidate (**1**) is essential for the relatively high conversions of alkenes (**2**) into the desired organomercurial. The use of molar ratios of 1.5 : 1 : 1 [for **1** : **2** : mercury(II) nitrate] instead of the recommended 3 : 1 : 1 leads to drastically reduced yields of amidates **3**.

The regioisomeric purity of all crude products **3** derived from unsymmetrical alkenes **2** is evident from their ^{31}P-N.M.R. spectra. Careful inspection of the mass spectra of diethyl *N*-alkylphosphoramidates (**3**) leads to the conclusion that, in accord with expectation, they are all Markovnikov derivatives of **2**. No intramolecular rearrangement of the Wagner-Meerwein type was observed for 3,3-dimethyl-1-butene which was converted into diethyl *N*-(3,3-dimethyl-2-butyl)-phosphoramidate (**3d**) in 55% yield. Similarly to previous observations involving amination of olefins via hydroboration[4,5,6], stereospecific

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functionalisation of norbornene affording diethyl *N-exo*-norbornylphosphoramidate **(3i)** in 60% yield was also possible by using our approach. The only serious limitation of the procedure stems from its inapplicability to tertiary olefins, i.e. 2-methyl-1-butene, α- and β-pinene, and limonene which do not react with diethyl phosphoramidate **(1)** in the presence of mercury(II) nitrate according to the general pattern. Crude reaction products obtained from such olefins do not exhibit characteristic P=O absorptions in their I.R. spectra and do not display the respective ^{31}P-N.M.R. signals. Similar behavior of branched alkenes in amidomercuration-demercuration has previously been reported[3]. All crude diethyl *N*-alkylphosphoramidates **(3)** obtained by phosphoramidomercuration-demercuration of **2** could be easily and effectively cleaved to the corresponding amine hydrochlorides **(4)** by means of gaseous hydrogen chloride in benzene at room temperature. Some amine hydrochlorides **(4)** could be precipitated from the solution after cleavage of **3** by simply adding ether (Procedure A). When difficulties with the direct precipitation of **4** were encountered, the hydrochlorides were transformed into

Table 1. Diethyl *N*-Alkylphosphoramidates **(3)** and Amine Hydrochlorides **(4)**

	R^1	R^2	*Diethyl N-Alkylphosphoramidate* **3**				Amine Hydrochloride **4**			
			Duration [h]	Yield [%]	m.p. [°C]	Molecular formula[a]	Procedure	Yield[b] [%]	m.p. [°C] found	m.p. [°C] reported
a	*n*-C_3H_7	H	4	71	oil	$C_9H_{22}NO_3P$ (223.25)	A	86 (61)	147–148°	147.5–148°[8]
b	*n*-C_4H_9	H	4 8	75 68	oil	$C_{10}H_{24}NO_3P$ (237.3)	B	82 (62)	104–106°	102–104°[9]
c	C_2H_5	C_2H_5	4 8	43 34	oil	$C_{10}H_{24}NO_3P$ (237.3)	B	78 (34)	234–236°	227–229°[10]
d	*t*-C_4H_9	H	4 8	55 36	oil	$C_{10}H_{24}NO_3P$ (237.3)	B	87 (48)	275–280° (dec)	>245°[11]
e	*n*-C_6H_{13}	H	4	79	oil	$C_{12}H_{28}NO_3P$ (265.3)	B	63 (50)	90–90.5°	90–91°[12]
f	C_6H_5	H	8	33.5[c]	48–49.5°	$C_{12}H_{20}NO_3P$ (257.3)			—	
g	C_6H_5—CH_2—	H	4	70	65–67°	$C_{13}H_{22}NO_3P$ (271.3)	B	64 (45)	147–148°	147°[13]
h	—$(CH_2)_4$—		4 8 24[d]	76.5 60 70	79–80°	$C_{10}H_{22}NO_3P$ (235.3)	A	78 (60)	208–210°	204–205°[14]
i			4 15	20 60	oil	$C_{11}H_{22}NO_3P$ (247.3)	A	83 (50)	142–144°[e]	143–144°[5]

[a] Satisfactory microanalyses obtained: C, ±0.41; H, ±0.23; N, ±0.20; P, ±0.35.
[b] Yield of the two-step transformation **2**→**3**→**4** is given in brackets.
[c] Yield of pure **3f**. The crude product is contaminated with ~40% of styrene oligomers as estimated by inspection of the ^{1}H-N.M.R. spectrum.
[d] The reaction was carried out in boiling dichloromethane.
[e] *N*-Acetyl derivative of 2-*exo*-aminonorbornane (m.p. of the *endo* isomer: 132 °C[5]).

Table 2. Spectrometric Data of Diethyl *N*-Alkylphosphoramidates **(3)**

3	M.S. (70 eV)[a] *m/e* (rel. int.)	I.R. (film)[b] ν_{NH}	$\nu_{P=O}$ [cm^{-1}]	^{31}P-N.M.R. (CCl_4/85% H_3PO_{4ext})[c] δ [ppm]
a	223 (M, 0.13); 180 (M−C_3H_7, 4.13)	3220	1240	8.9
b	237 (M, 0.36); 180 (M−C_4H_9, 100)	3200	1240	9.0
c	238 (M+1, 6.6); 194 (M−C_3H_7; 40.0)	3200	1235	8.6
d	237 (M, 1.17); 180 (M−C_4H_9, 100)	3210	1235	9.2
e	250 (M−CH_3, 5.6); 180 (M−C_6H_{13}, 100)	3200	1225	8.8
f[d]	257 (M, 33.6); 242 (M−CH_3, 100) 180 (M−C_6H_5, 9.3)	3190	1222	8.0
g[e]	271 (M, 3.4); 180 (M−C_6H_5−CH_2, 100)	3200	1225	8.35
h	—	3200	1220	8.9
i	247 (M, 2.4)	3230	1230	8.5

[a] Recorded on a LKB-9000 mass spectrometer.
[b] Recorded on a Specord 71 IR (C. Zeiss) spectrophotometer.
[c] Measured at 36.43 MHz with a Bruker HFX 90 spectrometer.
[d] ^{1}H-N.M.R. (CCl_4/TMS_{int}): δ = 0.92 (t, J_{HH} = 7.0 Hz, 3H); 1.31 (t, J_{HH} = 7.0 Hz, 3H); 1.41 (d, J_{HH} = 7.25 Hz, 3H); 2.56–4.35 (m, 1H); 4.05 (qt, $J_{HH} \approx {}^3J_{PH} \approx 7.0$ Hz, 4H); 5.80 (dd, J_{HH} = 10.0 Hz, J_{PH} = 13.0 Hz, 1H); 6.98–7.53 ppm (m, 5H).
[e] ^{1}H-N.M.R. (CCl_4/TMS_{int}): δ = 1.08 (d, J_{HH} = 6.25 Hz, 3H); 1.14 (t, J_{HH} = 7.0 Hz, 3H); 1.27 (t, J_{HH} = 7.0 Hz, 3H); 2.37–3.25 (m, 3H); 3.98 (qt, $J_{HH} \approx {}^3J_{PH} \approx 7.0$ Hz, 4H); 4.87 (br. t, $J_{HH} \approx J_{PH} \approx 10.5$ Hz, 1H); 7.05 ppm (s, 5H).

the free amines which were purified by steam-distillation and then reconverted to the hydrochlorides **4** or *N*-acetylated (Procedure B).

Thus, phosphoroamidomercuration-demercuration followed by acidolysis may be regarded as a convenient route from alkenes to alkanamines which in our opinion compares favorably with a conventional alternative approach involving hydroboration followed by amination with hydroxylamine-*O*-sulfonic acid[4,5] or *O*-mesitylenesulfonylhydroxylamine[6] owing to its simplicity and for economical reasons.

Diethyl phosphoramidate (**1**) was obtained from diethyl phosphite and gaseous ammonia in tetrachloromethane according to the known procedure[7].

Mercury(II) Nitrate: Commercial mercury(II) nitrate hemihydrate, strongly hygroscopic and containing varying amounts of water, is ground in a mortar and dried in vacuo over phosphorus pentoxide for several days. The dry material is stored over phosphorus pentoxide.

Diethyl *N*-Alkylphosphoramidates (3); General Procedure:
A mixture of diethyl phosphoramidate (**1**; 9.2 g, 60 mmol), dry mercury(II) nitrate (6.67 g, 20 mmol), the alkene (**2**; 20 mmol), and 1,1-dichloroethane (60 ml) is refluxed gently with stirring for 4 h. The resultant yellow-orange solution is cooled to 0 °C and then aqueous 10% sodium hydroxide (60 ml), and a solution of sodium borohydride (0.8 g, 20 mmol) in aqueous 10% sodium hydroxide (20 ml) are added. Stirring is continued for 1 h at room temperature. The precipitated mercury is filtered off and washed with dichloromethane (30 ml). The organic layer is thoroughly washed with water (3 × 20 ml), dried with magnesium sulfate, and evaporated. The residual crude phosphoramidates **3** mostly are analytically pure when heated at 40–50 °C/0.2 torr for 1 h to remove traces of volatile impurities.

Cleavage of Diethyl Phosphoramidates 3 to give the Amine Hydrochlorides 4; General Procedures:
Dry hydrogen chloride gas is passed for 1.5 h at room temperature through a solution of the crude diethyl phosphoramidate **3** (10 mmol) in benzene (30 ml). The solution saturated with hydrogen chloride is left overnight at room temperature. The excess of gas and some solvent (~20 ml) are then removed in vacuo.

Work-up Procedure A: Anhydrous ether (50 ml) is added to the residue. The crystalline precipitate of amine hydrochloride **4** is isolated by suction and washed with ether. Analytically pure samples are obtained by dissolving **4** in a small amount of ethanol and reprecipitation with an excess of dry ether.

Work-up Procedure B: Water (50 ml) and sodium hydroxide (40 g) are added to the residue and the liberated amine is steam-distilled. The distillate (~300 ml) is made alkaline (pH: 12–14), saturated with solid sodium chloride, and extracted with ether (3 × 50 ml). The extract is dried with magnesium sulfate, concentrated to ~50 ml, and saturated with gaseous hydrogen chloride (or ketene if the *N*-acetylamine is desired). Evaporation to dryness followed by addition of hexane (10 ml) affords crude **4** which can be recrystallised if necessary.

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