Phase-Transfer-Catalysed Phosphorylation of Amines in an Aqueous System[1]

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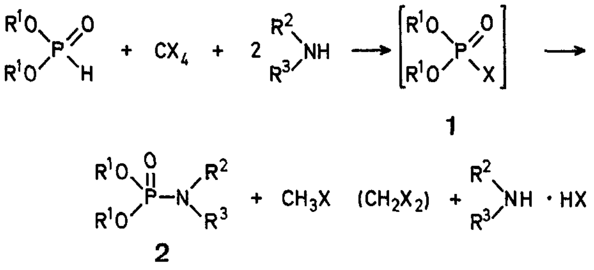
Great interest has developed in recent years in phase-transfer processes, especially liquid-liquid phase-transfer catalysed two-phase reactions[2,3] in which anionic reactants are transferred from an aqueous to an organic phase by suitable quaternary aminium or phosphonium salts acting as specific catalysts[4,5]. Owing to the formation of relatively loose ion-pairs with various anionic intermediates, phase-transfer catalysts simplify and accelerate numerous reactions traditionally performed in non-aqueous media. Several examples reported recently[4,6–12] evidently show how this technique may be used as a routine synthetic tool.

The generally accepted procedure developed by Atherton and Todd[13,14], which can be utilised for the phosphorylation of ammonia as well as primary and secondary amines, involves the application of the dialkyl phosphite/tetrahalomethane system as a source of a dialkyl phosphorohalidate (1)—intermediately formed as a reactive phosphorylating agent.



R², R³ = alkyl, aryl, H;
X = Cl or Br

This procedure, which is the method of choice for the phosphorylation of ammonia, has, however, several drawbacks in the case of amines: (i) from the two mol of amine used for phosphorylation one mol is inevitably lost as the corresponding hydrohalide, unless it is substituted by one mol of sufficiently strong tertiary base, e.g. triethylamine, 2,6-lutidine, etc.; (ii) separation of an amine salt from phosphoroamidate (**2**) is sometimes laborious and ineffective; (iii) partial monodebenzylation[15] can occur when dibenzyl phosphite in the presence of strong tertiary amine is used as phosphorylating agent; (iv) when weakly basic amines (e.g. aniline) are phosphorylated in the presence of tetrachloromethane as a source of "positive" halogen, the addition of a strong base is necessary to induce reaction; (v) considerable amounts of dark-brown, tarry contaminants are formed when the phosphorylation is carried out in the presence of tetrabromomethane and tertiary amines (e.g. triethylamine).

It was now found that phosphorylation of amines by the Atherton-Todd method can be accomplished conveniently in a two-phase system in the presence of catalytic (about 5 mol-%) amounts of triethylbenzylaminium chloride (TEBA). The use of standard, 50% aqueous sodium hydroxide is not recommended due to the possibility of concurrent dihalocarbene formation (from CHX_3) followed by its subsequent reaction with primary[16] or secondary[17] amine. It was established, however; that these possible side-reactions become negligible when the concentration of sodium hydroxide solution is reduced to 20–30%. Moreover, no undesired hydrolysis of dialkyl phosphites[18] occurs under such conditions providing that the temperature of the reaction mixture is kept sufficiently low (0–25°).

Application of tetrabromomethane as a polyhalogen reactant is advisable for phosphorylation of weakly basic aromatic amines (general procedure B). It is, however, necessary when the less reactive, sterically hindered di-*t*-butyl phosphite is

Table. Phosphorylation of Amines in a Two-Phase System

R^1	R^2	R^3	Procedure	Yield (%)	M.p. or [n_D^{20}]	^{31}P-N.M.R.[a] δ (ppm)	Literature Data or Elemental Analysis
C_2H_5	H	C_6H_5	A[b]	77	96–97°[d]	− 3.1	M.p. 93–94.5°[14]; 96.5°[19]
C_2H_5	H	C_6H_5	B	84	96–97°		
C_2H_5	H	C_6H_5	C[b]	35	95–97°		
C_2H_5	H	c-C_6H_{11}	A[b]	89	75–76°[d]	− 8.75	M.p. 71–72°[20]
C_2H_5	H	$C_6H_5—CH_2$	A[b]	85	[1.4968]	− 9.75	$C_{11}H_{18}NO_3P$ calc. C 54.4 H 7.45 P 12.75 (243.2) found 54.4 7.3 13.1
C_2H_5	C_2H_5	C_2H_5	A[b]	86	[1.4238]	− 9.75	n_D^{25} = 1.4212[21]; n_D^{27} = 1.4212[22]
C_2H_5	C_2H_5	C_2H_5	C[b]	85	[1.4238]	− 9.75	
C_2H_5	H	C_2H_5	C[b]	81	[1.4248]	− 10.2	$C_6H_{16}NO_3P$ calc. C 39.8 H 8.8 P 17.1 (181.2) found 39.7 8.9 17.0
$C_6H_5—CH_2$	H	C_6H_5	A	40[c]	90–92°[d]		M.p. 91–92.5°[13]
$C_6H_5—CH_2$	H	C_6H_5	B	78	90–92°	− 3.5	
$C_6H_5—CH_2$	H	c-C_6H_{11}	A	93	84–86°[d]	− 9.75	M.p. 79–80°[13,14]
$C_6H_5—CH_2$	H	$C_6H_5—CH_2$	A	83	82–84°[d]	− 10.1	M.p. 81–83°[23]; 84–85°[24]
$C_6H_5—CH_2$	C_2H_5	C_2H_5	A	91	[1.5317]	− 10.7	$C_{18}H_{24}NO_3P$ calc. C 64.8 H 7.2 P 9.3 (333.4) found 64.9 7.3 9.2
t-C_4H_9	H	c-C_6H_{11}	B	90	81–83°[e]	+ 0.3	$C_{14}H_{30}NO_3P$ calc. C 57.7 H 10.3 P 10.6 (291.4) found 57.5 10.1 10.2
t-C_4H_9	H	$C_6H_5—CH_2$	B	92	97–99°[e]	+ 0.3	M.p. 96–98°[25]

[a] ^{31}P-N.M.R. spectra were measured in CCl_4 solution at 24.3 MHz with a Jeol JNM-C-60HL spectrometer using 85% H_3PO_4 as external standard. A Heteronuclear Spin Decoupler, JNM-SD-HC, was used for precise ^{31}P chemical shift determinations.

[b] 25% excess of diethyl phosphite was used.

[c] Crystallised product.

[d] From hexane/benzene (1 : 1).

[e] From ethanol/water (1 : 1).

used as phosphorylating agent. Phosphorylation of more basic aliphatic amines proceeds readily in the presence of tetrachloromethane (general procedure A). Amine hydrochlorides can be also phosphorylated conveniently by a slightly modified procedure (general procedure C).

The specific catalytic action of triethylbenzylaminium chloride in the reactions considered was confirmed by two blank experiments which were carried out under standard conditions (general procedure A), but without a catalyst. Attempted phosphorylation of aniline by means of diethyl phosphite failed completely, and the same procedure applied for cyclohexylamine afforded the corresponding phosphoroamidate in a very low yield (32% as compared with 89% achieved in the presence of the catalyst).

The outlined synthetic procedure is particularly convenient for phosphorylation of a wide range of amines on account of its simplicity, relatively short reaction time, and effectiveness. It is worth emphasising that almost all the phosphoroamidates **2**, especially those prepared according to the procedure A, are formed in high yields (Table) and are analytically pure in crude state.

Phosphorylation of Amines; General Procedures:

Method A: A solution of dialkyl phosphite (0.1–0.125 mol) and the corresponding amine (0.1 mol) in dichloromethane (30 ml) was added drop-wise to a stirred two-phase system consisting of dichloromethane (30 ml), tetrachloromethane (30 ml), 20% aqueous sodium hydroxide (40 ml), and benzyltriethylaminium chloride (1.0 g). The temperature of the strongly exothermic reaction was kept at 0–5° by external cooling (ice-salt bath). After the addition had been completed, stirring was continued for 1 h at 0–5° and then for another 1 h at room temperature. The mixture was then diluted with dichloromethane (25 ml), the organic layer was separated, washed with 5% hydrochloric acid (50 ml), and water (2 × 50 ml), and dried over anhydrous magnesium sulphate. Evaporation of solvent, followed by heating of the residue at 30–40°/0.1–0.5 torr (1 h) or its recrystallisation afforded an analytically pure sample of the corresponding phosphoroamidate **2**.

Method B: A solution of dialkyl phosphite (0.05 mol) and the corresponding amine (0.05 mol) in dichloromethane (15 ml) was added at room temperature to a stirred two-phase system consisting of dichloromethane (30 ml), tetrabromomethane (8.3 g, 0.025 mol), 20% aqueous sodium hydroxide (20 ml), and triethylbenzylaminium chloride (0.5 g). Stirring was continued for 3 h at room temperature. Dichloromethane (25 ml) was then added, the organic layer was separated, washed with water (3 × 25 ml), and dried over anhydrous magnesium sulphate. On evaporation of solvent and one recrystallisation of the residue, a sample of phosphoroamidate **2** thus obtained was analytically pure.

Method C: A solution of 30% aqueous sodium hydroxide (40 ml) was added drop-wise at 0–5° with efficient stirring and external cooling (ice-salt bath) to the mixture of diethyl phosphite (17.25 g, 0.125 mol), amine hydrochloride (0.1 mol), tetrachloromethane (40 ml), dichloromethane (40 ml), and triethylbenzylaminium chloride (1.0 g). The resulting two-phase system was stirred for 2 h at room temperature, then diluted with dichloromethane (50 ml), and separated. The organic layer was washed with 5% hydrochloric acid (25 ml) and water (2 × 50 ml), dried over anhydrous magnesium sulphate, and evaporated. The residue was analytically pure phosphoroamidate **2** when heated at 30–40°/0.1–0.5 torr (1 h) or recrystallised from an appropriate solvent.

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