A New Approach to the Atherton-Todd Reaction

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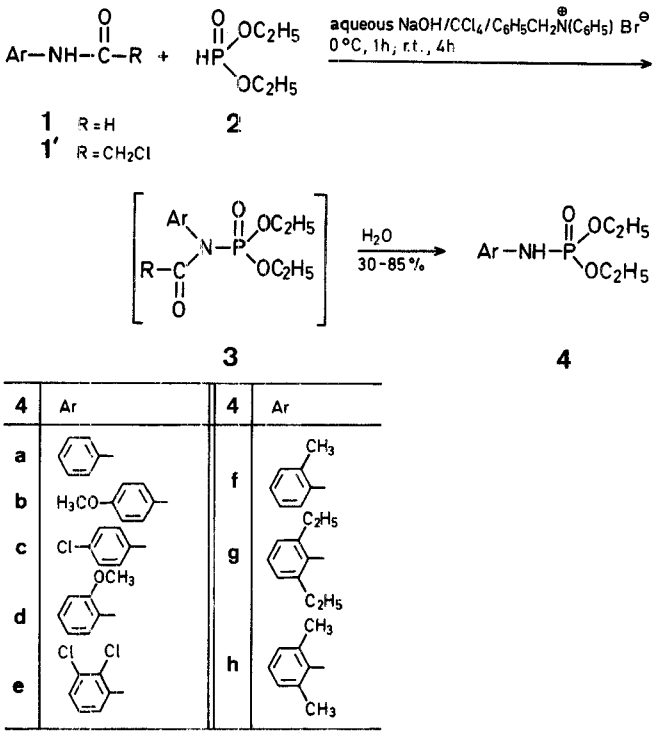
N-Arylphosphoramidates **4** are prepared by reacting formanilides **1** and chloroacetanilides **1'** with diethyl phosphite under phase-transfer conditions.

Phosphorylation of amines by the conventional Atherton-Todd procedure[1,2] is the most convenient method for the synthesis of phosphoramidates. The phase-transfer-

catalysed version[3,4] of this reaction is apparently more convenient and versatile as compared to the conventional approach. However, there are only few examples of *N*-arylphosphoramidates synthesised by both procedures. The interest in *N*-arylphosphoramidates was based on their importance as intermediates in organic synthesis[5,6] as well as their potential biological activity[7]. Our attempts to apply the conventional Atherton-Todd procedure and its phase-transfer-catalysed version for the synthesis of phosphoramidates of *ortho*-substituted anilines were unsuccessful, despite variation of the reaction conditions and the catalyst.

In search of an alternative approach for the synthesis of *N*-arylphosphoramidates, we found that formanilides **1** and chloroacetanilides **1'**, including the *ortho*-substituted derivatives, are sufficiently stable and nucleophilic under the conditions of the phase-transfer-catalysed version of the Atherton-Todd reaction. They can be used as substrates for phosphorylation with diethyl phosphite **(2)** to give *N*-arylphosphoramidates **4**.

Diethyl *N*-aryl phosphoramidates **4** are prepared by dropwise addition of diethyl phosphite **(2)** to a cold solution of formanilide **1** or chloroacetanilide **1'** in tetrachloromethane and 30% sodium hydroxide in the presence of catalytic amounts of benzyl triethylammonium bromide (Table). The results show that the outlined procedure of using **1** and **1'** for introduction of diethoxyphosphinyl group in *ortho*-substituted anilines seems to be a useful extension of the Atherton-Todd reaction. The reaction proceeds probably because of the stronger NH-acidity of **1** and **1'** and smaller steric hindrance problems in amide anions in comparison with the corresponding anilines. The reaction can proceed



4	Ar	4	Ar
a		f	
b	H_3CO	g	
c	Cl		
d	OCH_3		
e	Cl Cl	h	

either as a transacylation or the formation of the intermediate **3** can be envisaged, which undergoes fast hydrolysis under the reaction conditions.

The solid-liquid variant of the two phase reaction for the phosphorylation of **1** and **1'** can also be applied successfully when potassium hydroxide is used as the base. The yields of **4**

Table. Phosphoramidates **4a–h** prepared

Product	Yield [%] from 1	Yield [%] from 1'	m.p. [°C]	Molecular Formula[a] or Lit. m.p. [°C]	I.R. ($CHCl_3$)[b] [cm^{-1}] ν_{NH}	I.R. ($CHCl_3$)[b] [cm^{-1}] $\nu_{P=O}$	^{1}H-N.M.R. ($CDCl_3$/TMS)[c] δ [ppm]	M.S.[d] *m/e* (M^+)
4a	60	70	96–97	94–95°[4]	3200	1240	1.32 (t, 6H, J = 10 Hz); 4.16 (q, 4H, J = 10 Hz), 6.90–7.20 (m, 5H)	229
4b	30	60	65–65.5°	$C_{11}H_{18}NO_4P$ (259.3)	3200	1240	1.30 (t, 6H, J = 10 Hz); 3.78 (s, 3H); 4.10 (q, 4H, J = 10 Hz); 6.65–7.05 (m, 4H)	259
4c	70	60	75–77°	75–77°[4]	3200	1250	1.35 (t, 6H, J = 10 Hz); 4.10 (q, 4H, J = 11 Hz); 7.06 (d, 2H, J = 8 Hz); 7.70 (d, 2H, J = 16 Hz)	263
4d	30	80	oil	$C_{11}H_{18}NO_4P$ (259.3)	3400	1240	1.30 (t, 6H, J = 10 Hz); 3.85 (s, 3H); 4.10 (q, 4H, J = 11 Hz); 6.85–7.30 (m, 4H)	259
4e	50	85	oil	$C_{10}H_{14}Cl_2NO_3P$ (298.1)	3300	1240	1.35 (t, 6H, J = 10 Hz); 4.15 (q, 4H, J = 10 Hz); 7.08–7.35 (m, 3H)	298
4f	45	80	83–84°	$C_{11}H_{18}NO_3P$ (243.3)	3430	1250	1.34 (t, 6H, J = 10 Hz); 2.28 (s, 3H); 4.05 (q, 4H, J = 11 Hz); 7.10–7.40 (m, 4H)	243
4g	70	62	113°	$C_{14}H_{24}NO_3P$ (285.3)	3390	1220	1.20 (t, 6H, J = 11 Hz); 1.25 (t, 6H, J = 10 Hz); 2.30 (q, 4H, J = 11 Hz); 4.00 (q, 4H, J = 10 Hz); 7.02 (s, 3H)	285
4h	75	70	94–95°	$C_{12}H_{20}NO_3P$ (257.3)	3380	1240	1.28 (t, 6H, J = 11 Hz); 2.40 (s, 3H); 4.00 (q, 4H, J = 11 Hz); 6.98 (s, 3H)	257

[a] Satisfactory microanalyses obtained: C ± 0.35, H ± 0.20, N ± 0.30.
[b] The I.R. spectra were recorded on a C. Zeiss Specord I.R. spectrophotometer.
[c] The ^{1}H-N.M.R. spectra were measured at 60 MHz using a Perkin-Elmer R-24B spectrometer.
[d] The mass spectra were recorded on a MS-D300 spectrometer.

are comparable with the above results. This variant cannot be applied when potassium hydrogen carbonate/potassium carbonate is used as the solid phase.

Diethyl *N*-Arylphosphoramidates *4*; General Procedure:
To a stirred suspension of **1** or **1'** (5 mmol) in tetrachloromethane (25 ml), 30% aqueous sodium hydroxide (10 ml) and benzyltriethylammonium bromide (0.2 g) cooled in an ice/water bath, is added dropwise diethyl phosphite (**2**; 0.828 g, 6 mmol) in tetrachloromethane (5 ml). Stirring is then continued for 1 h at ice bath temperature and 4 h at room temperature. The separated organic layer is dried with anhydrous sodium sulphate and the solvent is removed by evaporation in vacuo to give the crude *N*-arylphosphoramidate **4** which is purified by recrystallisation or column chromatography.

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