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Phosphorus in Organic Synthesis. Acyloxyphosphonium Salts as Chemoselective Acylating Reagents

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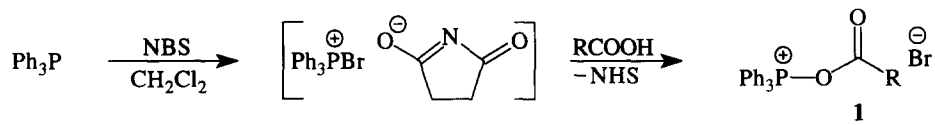
Abstract: Acyloxytriphenylphosphonium salts **1** prepared *in situ* react with a variety of aminophenols to give the corresponding amides in excellent yields. At -25° *N*-acylated products are formed exclusively, whereas at 0° some O-acylated products are observed. **1** is also a convenient trifluoroacetylating reagent.

Reagents which are sufficiently selective to distinguish between functional groups in a multifunctional molecule are very valuable in organic synthesis since they may permit operations that are either impossible or dependent on cumbersome and time-consuming protection and deprotection procedures.

We previously found[1] that treatment of an equimolar mixture of a carboxylic acid and triphenylphosphine with NBS or NCS followed by addition of amines to the acyloxytriphenylphosphonium salt **1** (Scheme **I**) thus generated, afforded the corresponding amides in excellent yield.

Likewise reaction of **1** with an alcohol in the presence of a suitable base, *e.g.*, pyridine, leads to the corresponding ester,[2] and sodium azide[3] reacts with **1** in acetone affording quantitative yields of acyl azides after a few min at 0°.



SCHEME I

The reaction of **1** with aminophenols was thereafter investigated and has been found to constitute a general route to selective acylation of the amino group when the reactions are carried out under mild conditions, *i.e.* at or below -25°.

As trifluoroacetylation is particularly important for the protection or activation of functional groups, some experiments were also performed with **1**; R = CF_3. We found that this reagent in combination with aminophenols, or with primary and secondary amines, afforded good yields of the corresponding trifluoroacetamides (cf. Table **I**).

The recent appearence of a note[4] on trifluoroacetylation of amines and alcohols with a new reagent, 1-(trifluoroacetyl)benzotriazole, has prompted the publication of the above-mentioned results.

The acylbenzotriazole method is reported to give excellent yields under relatively mild conditions, and the by-product benzotriazole can in most cases be removed quite easily. It should be noted, however, that reaction times are longer and the acylbenzotriazole has to be synthesized from the corresponding acid anhydride and benzotriazole, whereas **1** is preferably made *in situ* directly from the carboxylic acid.

This preparation can be performed in a few minutes and the solution of **1** is thereafter applied to the amine or to the aminophenol without any need for isolation or purification.

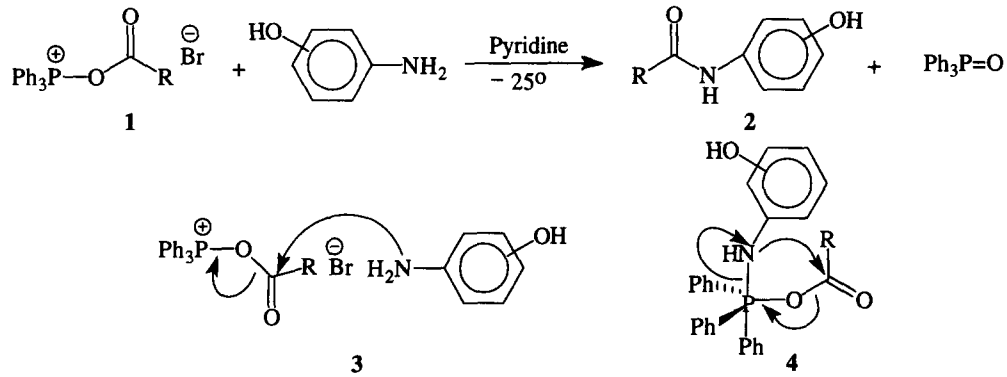
Alternatively, solutions of **1** can be made on a large scale and kept under argon or some other inert gas for a long time without decomposition. Admittedly the knowledge of the properties of **1** is so far very limited, but it appears that solutions of **1** are thermodynamically stable at or below room temperature.

The stored or freshly prepared solutions are chemically very reactive, however, and the acylations are usually completed in a few minutes even at low temperature. Several other agents for trifluoroacetylation are mentioned in the literature, but as pointed out by Katritzky *et al.*[4] they all have drawbacks or limitations. There is also a variety of new general acylating reagents available,[5-7] but many of these agents require prolonged heating, in some cases 12 - 48 h at 80°, in order to react with the amine.[7]

As can be seen from Table **I** aminophenols are acylated exclusively at nitrogen by the present reagent when the reactions are performed at or below - 25°, yielding the corresponding amide in good to excellent yield. When the reactions are carried out at 0°, some ester, usually between 10 and 20 %, is formed together with the amide.

The high reactivity of **1** is also demonstrated by the rapid and quantitative reaction with amines of low nucleophilicity such as *p*-nitroaniline and its reaction at - 50° with the sterically hindered *t*-butylamine.

The formation of amides **2** in the final step of the reaction could proceed either through direct nucleophilic attack of the amine entity at the carbonyl carbon of **1**, as indicated in **3**, or perhaps more likely, via the pentacoordinated species **4** (Scheme **II**).

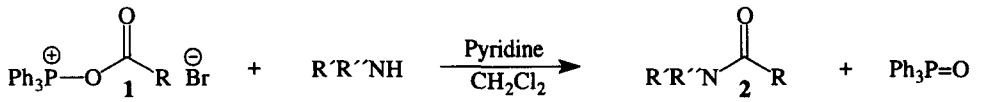


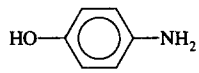
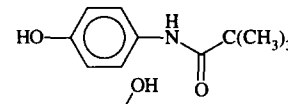
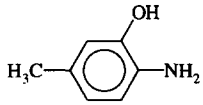
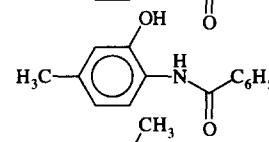
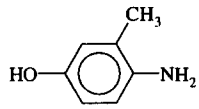
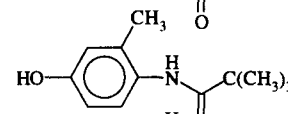
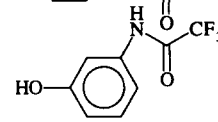
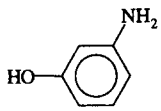
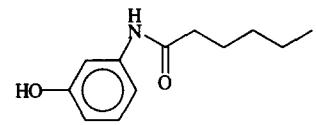
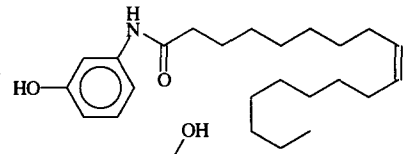
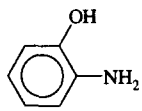
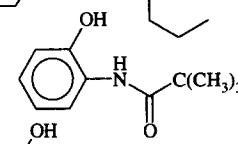
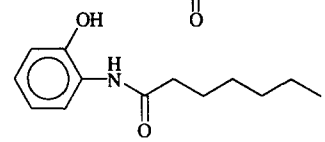
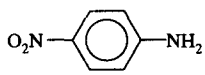
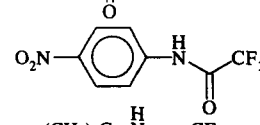
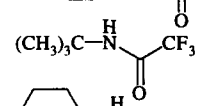
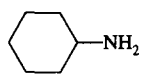
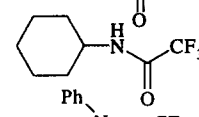
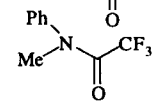
SCHEME II

As to the latter intermediate (**4**), it may appear surprising that nucleophilic attack by nitrogen at phosphorus is preferred in view of the generally greater affinity of phosphorus towards oxygen. Examples are nevertheless known from literature, of comparable attack by nitrogen in preference of oxygen on the phosphorus atom of phosphonium salts.[8,9]

Finally, a few experiments were performed in which **1** was allowed to react with 2-amino alcohols. The attempted acylations of 2-aminoethanol and of 2-amino-2-phenylethanol in dichloromethane failed, however. These negative results point to the pentacoordinated intermediate and suggest that the P-N bond formed in the amino alcohol case is stronger than the corresponding bond to aminophenols (cf. **4**, Scheme **II**), thus impeding the smooth transformation of **4** into **2** and $Ph_3P=O$. It is possible, however, that the use of other solvents or an elevated temperature may extend the scope of the acylating method presented here.

Table I. Acylation of amines and aminophenols using **1** at low temperature



Entry	Substrate (R′R″NH)	R	Product (**2**)	Yield (%)
1		$C(CH_3)_3$		92
2		C_6H_5		82
3		$C(CH_3)_3$		54
4		CF_3		81
5		Pentyl		98
6		8-*cis*-Heptadecenyl		99
7		$C(CH_3)_3$		91
8		Hexyl		99
9		CF_3		99
10	$(CH_3)_3C—NH_2$	CF_3		93[a]
11		CF_3		99[a]
12		CF_3		99

[a] The pyridine was substituted by an extra equivalent of the actual amine to scavenge the HBr formed.

Experimental procedure. The ease and simplicity of the present chemoselective acylation is well illustrated by the preparation of *N*-(3-hydroxyphenyl)-hexanamide (**5**): To a stirred solution of triphenylphosphine (2.55 mmol, 0.67 g) and hexanoic acid (2.5 mmol, 0.29 g) in anhydrous dichloromethane (5 ml) at 0° was added N-bromosuccinimide (NBS, 2.8 mmol, 0.50 g) in one portion. The reaction mixture containing 0.25 mmol of **1** was thereafter set aside at room temperature while a new solution was being prepared: 3-Aminophenol (2.5 mmol, 0.28 g) and pyridine (3.20 mmol, 0.26 g) was dissolved in THF (5 ml). The mixture was cooled to about -25° (ethanol/granular CO_2), and vigorously stirred while the ready-made solution of **1** was added dropwise. The cooling bath was removed after a few min and the temperature allowed to rise towards room temperature. Most of the solvents were removed at reduced pressure and the product purified by flash chromatography on Merck No. 9385 silica gel 60, using ether as eluent. Removal of the solvent gave *N*-(3-hydroxyphenyl)-hexanamide (0.52 g, 98 %) as a colourless solid, m.p. 139-140°. ^{1}H NMR (200 MHz, acetone-d_6): δ 0.90 (m, 3H, CH_3), 1.35 (m, 4H, CH_2), 1.65 (m, 2H, CH_2), 2.35 (t, 2H, CH_2), 6.52 (m, 1H, $H_{arom.}$), 7.0 (m, 2H, $H_{arom.}$), 7.42 (s, 1H, $H_{arom.}$), 8.4 (s, 1H, OH), 9.05 (s, 1H, NH); ^{13}C NMR (50.3 MHz, acetone-d_6): δ 14.18, 23.04, 25.93, 32.09, 37.71, 107.19, 110.94, 110.99, 130.09, 141.47, 158.54, 172.08 (CO). IR (film) cm^{-1}:1595 and 1630 (CO); MS (70 eV): m/z (%) 207 (17, M^+), 151 (6.5), 109 (100).

N-(4-Nitrophenyl)-2,2,2-trifluoroacetamide (**9**): To a stirred solution of triphenylphosphine (2.55 mmol, 0.67 g) and trifluoroacetic acid (2.5 mmol, 0.29 g) in dichloromethane (5 ml) at 0° was added N-bromosuccinimide (NBS, 2.8 mmol, 0.50 g) in one portion. The cooling bath was removed and the reaction mixture stirred for a few min, thereafter a solution of *p*-nitroaniline (2.5 mmol, 0.35 g) and pyridine (3.1 mmol, 0.25 g) in dichloromethane (1ml) was added in one portion. After the exotherm, the reaction mixture was stirred at ambient temperature for 10 min. After removal of most of the solvent, the resulting concentrate was chromatographed as above. Removal of the solvent gave *N* -(4-nitrophenyl)-2,2,2-trifluoroacetamide (**9**) as a yellow solid in quantitative yield. M.p. 154-156°, lit.[10] 151-152°; ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.96 - 8.00 (m, 2H, H_{arom}), 8.30 - 8.35 (m, 2H, $H_{arom.}$), 11.81 (br. s, 1H, NH); ^{13}C NMR (50.3 MHz, DMSO-d_6): δ 115.48 (q, $^1J_{C-F}$ = 288.5 Hz, CF_3), 120.98, 124.85, 142.47, 143.99, 155.02 (q, $^2J_{C-F}$ = 37.8 Hz, C=O); IR (film) cm^{-1}: 1738 (CO) and 1500 (NO_2); MS (70 eV): m/z (%) 234 (100, M^+), 204 (14), 165 (25.6), 102 (13), 91 (22.2), 69 (21.9).

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