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P-Triazinylphosphonium chlorides as a new group of coupling reagents

Research Article

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Abstract: Tertiary phosphines in reaction with 2-chloro-4,6-dialkoxy-1,3,5-triazines gave unstable quaternary *P*-triazinylphosphonium chlorides, which readily decomposed with a departure of the alkyl group of the triazine ring substituent. Stable quaternary *P*-triazinylphosphonium chlorides were obtained only in reaction of 2-chloro-4,6-diphenoxy-1,3,5-triazine. Both, stable quaternary *P*-triazinylphosphonium chlorides as well unstable analogues prepared *in situ* activated carboxylic acid yielding "superactive" triazine esters, useful as highly efficient reagents in peptide bond synthesis.

Keywords: *P-triazinylphosphonium chlorides • Dealkylation • Coupling Reagents • 1,3,5-Triazine • Phosphine*

1. Introduction

The arsenal of recently available reagents and coupling strategies suffices for the successful incorporation of 20 proteinogenic amino acids into the peptide chain in solution and on a solid support [1]. However, in the case of their unnatural analogues, or so-called difficult sequences, the known reagents are often found insufficient or even fail completely. The most demanding in this respect is the coincidence of poor reactivity and steric hindrance in one building block, because the application of stronger activation and prolonged coupling time may severely deteriorate the yield and purity of the final peptide. At present, the main reasons for practicing this frustrating approach are an expected increase in the resistance of the unnatural structures to metabolic degradation, prolonged activity, reduced dosage, and a more convenient application of peptides showing a broad range of activity. Many of those employed as insecticides, contraceptives, growth promoters, metabolism regulators, agents combating various diseases, etc. are prepared using unnatural building blocks such as non-coded amino acids. In most cases, these advantageous effects of the incorporation of unnatural moieties into the peptide chain entail the impossibility of the application of biological approaches for their preparation, which need to be replaced with successful chemical synthetic strategies. Consequently, there is a strong need for the development of new coupling reagents and more advanced synthetic strategies. The most promising approach to rational design of new reagents is based on reducing size of the fragment participating in the rate determining step. So far, only a few reagents have been designed in line with this idea. One of the first and most promising responses to this problem was the design of coupling reagents based on the compact, strongly electron-withdrawing 1,3,5-triazine nucleus. Due to the presence of a hydrogen bond acceptor fragment favoring the formation of a cyclic transition state, the transfer of the acyl group on the amino component is greatly facilitated even in the case of extremely sterically hindered substrates. This spectacular increase of the

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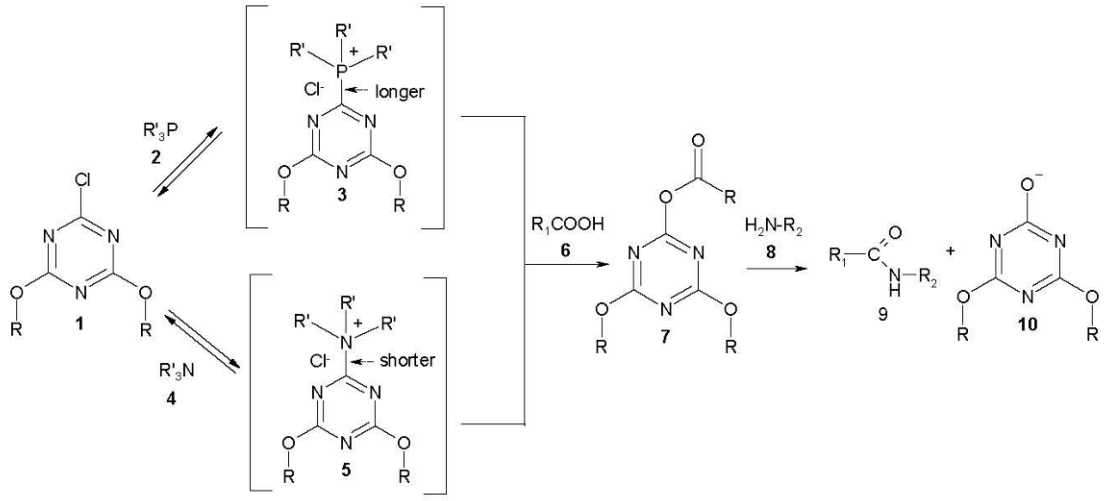


Scheme 1. Condensation involving "superactive" triazine ester 7 *via* N-triazinylammonium 5 or P-triazinylphosphonium 3 salts.

efficiency of the coupling procedure has been inspiring for the further improvement of triazine-based coupling reagents.

The crucial transformations in the process of activation of the carboxylic component with classic triazine-based reagents are the formation of a *N*-triazinylammonium salt followed by the substitution of the ammonium leaving group with a carboxylic acid moiety yielding a "superactive" triazine ester [2]. The process of developing a new *N*-triazinylammonium salt is, however, severely restricted by the sensitivity of the precursors to the steric hindrance effect of the tertiary amine. This in practice reduces the scope of the preparative procedure to aliphatic *N*,*N*-dimethylamines and/or *N*-methylated cyclic aliphatic amines. One can expect that the exchange of the ammonium fragment with a phosphonium analogue [3] will provide an advantageous modification to the reagent structure because the lengths of the C-P^+ bonds directly engaged in the activation process are substantially longer than the C-N^+ bonds (see Scheme 1).

The longer (weaker) C-P^+ bond should facilitate the activation of the less reactive carboxylic components, leaving intact the benefits of the accelerated acylation of the amino-component with "superactive" triazine esters. Thus, herein we initiated research on the reaction of phosphines with 2-chloro-4,6-disubstituted-1,3,5-triazines.

2. Experimental procedure

Thin layer chromatographies (TLC) were carried out on SiO_2 (Merck; 60 Å F254) and spots were located with: UV light (254 and 366 nm) and 1% ethanolic 4-(4-nitrobenzyl)pyridine (NBP). Melting points were determined on a Buchi apparatus, model 510. IR spectra were recorded as KBr pellets or film on a Bruker ALPHA spectrometer or a PerkinElmer Spectrum 100. ^{1}H-NMR, ^{13}C-NMR and ^{31}P-NMR spectra were recorded on a Bruker Avance DPX 250 (250 MHz) spectrometer. Chemical shifts (ppm) are relative to TMS used as an internal standard. The multiplicity were marked: s-singlet, d-doublet, t-triplet, q-quartet, qu-quintet, m-multiplet. Electrospray ionization mass spectra (ESI-MS) were acquired on a LCQ-Advantage ESI ion trap spectrometer (ThermoFinnigan) for positive and negative ions detection. HPLC-ESI-MS (ESI Ion Trap LCQ Advantage ThermoFinnigan; equipped with a diode array detector) using a Phenomenex Aqua C18 column (5 µ m, 150×2.0 mm) (flow rate: 200 µL min^{-1}) with a gradient of 5-95% CH_3CN/H_2O. Analytical HPLC were performed by a Waters 600S instrument using a Phenomenex Jupiter column 5µ C18 300 Å (250×4.6 mm). The solvent systems used were: A (0.1% TFA in H_2O) and B (0.1% TFA in CH_3CN). In all experiments, in order to protect oxygen-sensitive phosphines, reactions were carried out under an inert atmosphere (argon). In all cases the used solvents were dried by standard procedures and then by 3 Å molecular sieves [4].

2.1. Synthesis of tributyl-(4-oxy-6-methoxy-1,3,5-triazin-2-yl)-phosphonium salt (11a). Typical procedure A

The vigorously stirred and cooled to 0ºC solution of CDMT (**1a**) (0.175 g, 1 mmol) in chloroform (5 mL) was treated with Bu_3P (**2a**) (0.202 g, 1 mmol). Solution was stirred at room temperature for 5 days until all CDMT was consumed (according to TLC disappearing of spot

colored with 0.5% solution of NBP in ethanol). Solvent was evaporated under reduced pressure. To the solid residue was added hexane (5 mL) and the mixture was stirred using a magnetic bar for 30 min, after which the hexane layer was removed. The procedure was repeated three times yielding tributyl-(4-oxy-6-methoxy-1,3,5-triazin-2-yl)-phosphonium salt (**11a**) (0.108 g, 33%), mp = 127-131ºC, lit. mp = 166-168ºC [5]. ^{31}P-NMR ($CDCl_3$): δ = 32.27 [ppm]. ^{1}H-NMR ($CDCl_3$): δ = 0.79 (t, 3 x 3H, J = 7 Hz, -CH_2-CH_3); 1.32-1.54 (m, 3 x 4H, -CH_2-CH_2-CH_3); 2.00-2.76 (t, 3 x 2H, J = 6.5 Hz, -P-CH_2-); 3.83 (s, 3H, -OCH_3) [ppm]. ^{13}C-NMR ($CDCl_3$): δ =12.9, 23.2, 26.4. 27.4. 55.7, 149.3, 170.4, 171.4 [ppm]. IR (film): v = 3206.0, 2957.5, 2933.0, 2872.3, 2801.5, 1752.4, 1710.0, 1562.0. 1464.5, 1414.7, 1360.8, 1230.3, 1139.4, 1043.8, 969.5, 902, 808.9, 768.6 [cm^{-1}]. ESI-MS m/z: 329.4 $[M+H]^+$. Analysis: for $C_{16}H_{30}N_3O_2P$ (327.41): calcd.: C 58.70%, H 9.24%, N 12.83%, P 9.46%; found: C 56.33%, H 9.30%, N 12.82%, P 9.42%.

2.2. Synthesis of tributyl-(4-oxy-6-methoxy-1,3,5-triazin-2-yl)-phosphonium salt (11a) in $CHCl_3$. Typical procedure B

To the vigorously stirred solution of CDMT (**1a**) (0.175 g, 1 mmol) in chloroform (5 mL) Bu_3P (**2a**) (0.202 g, 1 mmol) was added and the solution was refluxed until all CDMT was consumed (according to TLC disappearing of spot colored with 0.5% solution of NBP in ethanol). Solvent was evaporated under reduced pressure. To the solid residue was added hexane (5 mL) and the mixture was stirred using a magnetic bar for 30 min after which the hexane layer was removed. The procedure was repeated three times, yielding tributyl-(4-oxy-6-methoxy-1,3,5- triazin-2-yl)-phosphonium salt (**11a**) (0.209 g, 64%) spectroscopically identical with product described above.

2.3. Synthesis of triphenyl-(4-oxy-6-methoxy-1,3,5-triazin-2-yl)-phosphonium salt (11b) in THF according to procedure A

Starting materials: CDMT (0.175 g, 1 mmol), PPh_3 (**2b**) (0.262 g, 1 mmol), THF (5 mL). After 5 days triphenyl-(4-oxy-6-methoxy-1,3,5-triazin-2-yl)-phosphonium salt (**11b**) was obtained (0.159 g, 41%), mp = 83-87ºC, lit. mp. 247-260ºC [5]. ^{31}P-NMR (CD_3CN): δ = 13.7 [ppm]. ^{1}H-NMR (CD_3CN): δ = 3.91 (s, 3H, -OCH_3); 7.45-7.96 (m, 15H, -P-(C_6H_5)$_3$) [ppm]. ^{13}C-NMR (CD_3CN): δ = 55.1, 116.5, 117.9, 120.1, 129.8, 156.9, 157.9, 159.2 [ppm]. IR (film): v = 3057.2, 2922.4, 2853.3, 1682.4, 1617.5, 1470.3, 1435.7, 1393.3, 1361.3, 1187.8, 1114.9, 996.4, 899.7, 791.0, 747.2, 719.0, 690.7 [cm^{-1}]. ESI-MS m/z: 389.4 $[M+H]^+$. Analysis: for $C_{22}H_{18}N_3O_2P$ (387.38): calcd.: C 68.21%, H 4.68%, N 10.85%, P 8.00%: found: C 68.42%, H 4.55%, N 10.80%, P 7.95%.

2.4. Synthesis of triphenyl-(4-oxy-6-methoxy-1,3,5-triazin-2-yl)-phosphonium salt (11b) in $CHCl_3$ according to procedure B

Starting materials: CDMT (0.175 g, 1 mmol), PPh_3 (**2b**) (0.262 g, 1 mmol), $CHCl_3$ (5 mL). After 4 hours triphenyl-(4-oxy-6-methoxy-1,3,5-triazin-2-yl)-phosphonium salt (**11b**) was obtained (0.306 g, 79%). Spectroscopically product was identical with described above.

2.5. Synthesis of tributyl-(4-oxy-6-benzyloxy-1,3,5-triazin-2-yl)-phosphonium salt (11c) in $CHCl_3$ according to procedure A

Starting materials: 2-chloro-4,6-dibenzyloxy-1,3,5-triazine (**1b**) (6.560 g, 20 mmol), Bu_3P (**2a**) (4.040 g, 20 mmol), $CHCl_3$ (50 mL). After 7 days tributyl-(4-oxy-6-benzyloxy-1,3,5-triazin-2-yl)-phosphonium salt (**11c**) (2.100 g, 26%) was obtained, mp = 136-138ºC, lit. mp = 166-169ºC [5]. ^{31}P-NMR ($CDCl_3$): δ = 26.91 [ppm]. ^{1}H-NMR ($CDCl_3$): δ = 0.91 (t, 3 x 3H, J = 7.8 Hz, -CH_2-CH_3); 1.34-1.57 (m, 3 x 4H, -CH_2-CH_2-CH_2-); 3.00 (t, 3 x 2H, J = 6.6 Hz, -CH_2-CH_2-); 5.53 (s, 2H, -O-CH_2-); 7.23-7.50 (m, 5H, -CH_2-C_6H_5) [ppm]. ^{13}C-NMR ($CDCl_3$): δ = 13.6, 23.4, 26.4, 27.1, 68.8, 127.3, 130.3, 131.2, 135.2, 169.7, 170.8, 173.0 [ppm]. IR (film): v = 2957.8, 2932.9, 2871.8, 2802.2, 1752.3, 1711.4, 1557.9, 1455.6, 1410.0, 1339.3, 1229.7, 1132.4, 1046.9, 1027.7, 969.1, 902.9, 820.8, 767.0, 733.7, 697.4 [cm^{-1}]. ESI-MS m/z: 405.0 $[M+H]^+$. Analysis: for $C_{22}H_{34}N_3O_2P$ (403.51): calcd.: C 65.49%, H 8.49%, N 10.41%, P 7.68%; found: C 65.32%, H 8.41%, N 10.38%, P 7.72%.

Isolation of benzyl chloride

The hexane extract were collected and washed with water, 1M aqueous $KHSO_4$, and water, dried with $CaCl_2$, filtered and solvent was evaporated under reduced pressure. The remaining liquid was distilled yielding benzyl chloride (1.723 g, 68%); b.p = 176°C [6] b.p. = 174°C; n_D^{20} = 1.5390 [7] n_D^{20} = 1.3910. ^{1}H-NMR ($CDCl_3$): δ = 4.55 (2H, s, H_2C); 7.33 (5H, br s, C_6H_5) [ppm]. ESI-MS m/z: 127.8 $[M+H]^+$.

2.6. Synthesis of tributyl-(4-oxy-6-benzyloxy-1,3,5-triazin-2-yl)-phosphonium salt (11c) in $CHCl_3$ according to procedure B

Starting materials: 2-chloro-4,6-dibenzyloxy-1,3,5-triazine (**1b**) (0.328 g, 1 mmol), Bu_3P (**2a**) (0.202 g, 1 mmol), $CHCl_3$ (5 mL). After 20 hours tributyl-(4-oxy-6-benzyloxy-1,3,5-triazin-2-yl)-phosphonium salt (**11c**) (0.294 g, 73%) was obtained. Product was spectroscopically identical with the sample described above.

2.7. Synthesis of triphenyl-(4-oxy-6-benzyloxy-1,3,5-triazin-2-yl)-phosphonium salt (11d) in $CHCl_3$ according to procedure A

Starting materials: 2-chloro-4,6-dibenzyloxy-1,3,5-triazine (**1b**) (0.328 g, 1 mmol), PPh_3 (**2b**) (0.262 g, 1 mmol), $CHCl_3$ (5 mL). After 7 days triphenyl-(4-oxy-6-benzyloxy-1,3,5-triazin-2-yl)-phosphonium salt (**11d**) (0.283 g, 61%) was obtained, mp = 224-225ºC, lit. mp = 224-227ºC [5]. ^{31}P-NMR (CD_3CN): δ = 23.01 [ppm]. ^{1}H-NMR (CD_3CN): δ = 5.49 (s, 2H, -O-CH_2-Ph); 7.10-7.84 (m, 20H, -(CH_2-C_6H_5) + -P(C_6H_5)$_3$) [ppm]. ^{13}C-NMR (CD_3CN): δ = 71.1, 126.8, 127.8, 129.5, 131.2, 131.5, 131.8, 133.4, 134.8, 163.0, 170.0, 170.9 [ppm]. IR (film): v = 3059.6, 3032.1, 2785.8, 1694.2, 1568.7, 1541.4, 1434.9, 1339.8, 1309.1, 1177.3, 1115.9, 1089.7, 995.6, 821.4, 749.0, 719.1, 691.6 [cm^{-1}]. ESI-MS m/z: 464.5 [M+H]$^+$. Analysis: for $C_{28}H_{22}N_3O_2P$ (463.48): calcd.: C 72.56%, H 4.78%, N 9.07%, P 6.68%; found: C 72.48%, H 4.80%, N 9.09%, P 6.70%.

2.8. Synthesis of triphenyl-(4-oxy-6-benzyloxy-1,3,5-triazin-2-yl)-phosphonium salt (11d) in $CHCl_3$ according to procedure B

Starting materials: 2-chloro-4,6-dibenzyloxy-1,3,5-triazine (**1b**) (0.328 g, 1 mmol), PPh_3 (**2b**) (0.262 g, 1 mmol), $CHCl_3$ (5 mL). After 8 hours triphenyl-(4-oxy-6-benzyloxy-1,3,5-triazin-2-yl)-phosphonium salt (**11d**) (0.459 g, 99%) was obtained as a product spectroscopically identical with described above.

2.9. Synthesis of tributyl-(4-oxy-6-(2,2,2-trifluoro-ethoxy)-1,3,5-triazin-2-yl)-phosphonium salt (11e) in CH_2Cl_2 according to procedure A

Starting materials: 2-chloro-4,6-bis-(2,2,2-trifluoro-ethoxy)-1,3,5-triazine (**1c**) (0.312 g, 1 mmol), Bu_3P (**2a**) (0.202 g, 1 mmol), CH_2Cl_2 (5 mL). After 2 days tributyl-(4-oxy-6-(2,2,2-trifluoro-ethoxy)-1,3,5-triazin-2-yl)-phosphonium salt (**11e**) (0.301 g, 76%) was obtained as a colorless oil. ^{31}P-NMR ($CDCl_3$): δ = 32.27 [ppm]. ^{1}H-NMR ($CDCl_3$): δ = 0.91 (t, 3 x 3H, J = 7 Hz, -CH_3); 1.42-1.54 (m, 3×4, -CH_2-CH_2-); 2.97 (7, 3 x 2H, J = 7.2 Hz, -P-CH_2-) 4.46-4.51 (m, 2H, CH_2); 5.07 (q, J^3H-F =8.4 Hz, 4H, CF_3-CH_2) [ppm]. ^{13}C-NMR (CD_3CN) δ = 12.9, 23.2, 26.4. 27.4, 64.5, 122.3, 171.3, 173.7 [ppm]. IR (film): v = 3044.1, 3030.0, 2781.8, 1695.7, 1569.1, 1545.7, 1438.1, 1336.8, 1304.9, 1175.2, 1114.9, 1087.9, 992.1, 828.0, 749.0, 716.2, 691.8 [cm^{-1}]. ESI-MS m/z: 396.5 [M+H]$^+$. Analysis: for $C_{17}H_{29}F_3N_3O_2P$ (455.38): calcd.: C 51.64%, H 7.39%, F 14.41%, N 10.63%, P 7.83%; found: C 51.66%, H 7.41%, F 14.40%, N 10.65%, P 7.85%.

2.10. Synthesis of triphenyl-(4-oxy-6-(2,2,2-trifluoro-ethoxy)-1,3,5-triazin-2-yl)-phosphonium salt (11f) in CH_2Cl_2 according to procedure A

Starting materials: 2-chloro-4,6-bis-(2,2,2-trifluoro-ethoxy)-1,3,5-triazine (**1c**) (0.312 g, 1 mmol), PPh_3 (**2b**) (0.262 g, 1 mmol), CH_2Cl_2 (5 mL). After 2 days triphenyl-(4-oxy-6-(2,2,2-trifluoro-ethoxy)-1,3,5-triazin-2-yl)-phosphonium salt (**11f**) (0.320 g, 70%) was obtained as a colorless oil. ^{31}P-NMR (CD_3CN): δ = 13.7 [ppm]. ^{1}H-NMR (CD_3CN): δ = 5.06 (q, J^3H-F = 8.5 Hz, 4H, CF_3-CH_2) 7.45-8.26 (m, 15H, -P-(C_6H_5)$_3$) [ppm]. ^{13}C-NMR (CD_3CN) δ = 64.5, 122.3, 125.6, 127.8, 129.5, 131.2, 171.9, 173.5, 175.1 [ppm]. IR (film): v = 3057.1, 3030.6, 2788.9, 1697.1, 1569.5, 1542.8, 1433.8, 1337.1, 1312.7, 1179.1, 1116.0, 1088.2, 996.8, 823.6, 748.9, 717.8, 691.3 [cm^{-1}]. ESI-MS m/z: 456.4 [M+H]$^+$. Analysis: for $C_{23}H_{17}F_3N_3O_2P$ (455.38): calcd.: C 60.67%, H 3.76%, F 12.52%, N 9.23%, P 6.80%; found: C 60.63%, H 3.79%, F 12.50%, N 9.19%, P 6.82%.

2.11. Synthesis of tributyl-(4-oxy-6-(2-ethoxy-ethoxy)-1,3,5-triazin-2-yl)-phosphonium salt (11g) in CH_2Cl_2 according to procedure A

Starting materials: 2-chloro-4,6-bis-(2-ethoxy-ethoxy)-1,3,5-triazine (**1d**) (5.840 g, 20 mmol), Bu_3P (**2a**) (4.040 g, 20 mmol), CH_2Cl_2 (50 mL). After 2 days tributyl-(4-oxy-6-(2-ethoxy-ethoxy)-1,3,5-triazin-2-yl)-phosphonium salt (**11g**) (5.480 g, 71%) was obtained as a colorless oil. ^{31}P-NMR ($CDCl_3$): δ = 29.27 [ppm]. ^{1}H-NMR ($CDCl_3$): δ = 0.91 (t, 3 x 3H, J = 7 Hz, -CH_3); 1.05 (t, 3H, J = 7.5 Hz, CH_3-CH_2O); 1.36-1.54 (m, 3 x 4H, -CH_2-CH_2-); 2.98 (t, 3 x 2H, J = 6.5 Hz, -P-CH_2-); 3.45 (q, 2H, J = 7.5 Hz, –O-CH_2-); 3.61 (t, 2H, J = 5.8 Hz, –CH_2-O-); 4.21 (t, 2H, J = 5.8 Hz, -O-CH_2-) [ppm]. ^{13}C-NMR ($CDCl_3$): δ = 13.3, 14.9. 22.5, 23.4, 27.1, 65.5, 66.5, 67.9, 140.0, 171.0, 171.7 [ppm]. IR (film): v = 3203.7, 3054.0, 2960.1, 2873.9, 2831.2, 2779.7, 1777.3, 1753.7, 1688.8, 1455.9, 1414.0, 1060.0, 1049.9, 838.2, 776.3, 756.6, 737.5, 690.2 [cm^{-1}]. ESI-MS m/z: 388 [M+H]$^+$. Analysis: for $C_{19}H_{36}N_3O_3P$ (385.49): calcd.: C 59.20%, H 9.41%, N 10.90%, P 8.03%; found: C 59.15%, H 9.45%, N 10.88%, P 8.05%.

Isolation of 2-chloroethyl-ethyl ether

The hexane extract were collected and washed with water, 1 M aqueous $KHSO_4$, and water, dried with $CaCl_2$, filtrated and solvent was evaporated under reduced

pressure. The remaining liquid was distilled yielding 2-chloroethyl-ethyl ether

(1.194 g, 55%); b.p = 106°C, lit. [8] b.p. = 107°C; n_D^{20} = 1.392, lit. [8] n_D^{20} = 1.411. ^{1}H-NMR ($CDCl_3$): δ = 1.71 (3H, t, J = 6.5 Hz, CH_3-CH_2-O); 3.45 (2H, q, J = 6.5 Hz, CH_3-CH_2-O); 3.66 (2H, t, J = 7.0 Hz, Cl-CH_2-CH_2-O); 3.91 (2H, t, J = 7.0 Hz, Cl-CH_2-CH_2-O) [ppm]. ESI-MS m/z: 109.6 $[M+H]^+$.

2.12. Synthesis of triphenyl-(4-oxy-6-(2-ethoxy-ethoxy)-1,3,5-triazin-2-yl)-phosphonium salt (11h) in CH_2Cl_2 according to procedure A

Starting materials: 2-chloro-4,6-bis-(2-ethoxy-ethoxy)-1,3,5-triazine (**1d**) (0.292 g, 1 mmol), PPh_3 (**2b**) (0.262 g, 1 mmol), CH_2Cl_2 (5 mL). After 2 days triphenyl-(4-oxy-6-(2-ethoxy-ethoxy)-1,3,5-triazin-2-yl)-phosphonium salt (**11h**) (0.304 g, 68%) was obtained as a colorless oil. ^{31}P-NMR ($CDCl_3$): δ = 34.27 [ppm]. ^{1}H-NMR ($CDCl_3$): δ = 1.07 (t, 3H, J = 7.5 Hz, -CH_3); 3.48 (q, 2H, J = 7.5 Hz, –O-CH_2-); 3.62 (t, 2H, J = 5.8 Hz, –CH_2-O-); 4.25 (t, 2H, J = 5.8 Hz, -O-CH_2-); 7.45-8.26 (m, 15H, -P-(C_6H_5)$_3$) [ppm]. ^{13}C-NMR ($CDCl_3$): δ = 14.9, 63.5, 65.5, 70.7, 125.5, 127.8, 129.5, 131.2, 171.9, 173.5, 175.1 [ppm]. IR (film): v = 3214.8, 3057.2, 2975.7, 288.3, 1704.6, 1589.8, 1483.8, 1436.2, 1406.6, 1156.5, 1117.5, 1069.6, 996.6, 747.2, 720.1, 691.1 [cm^{-1}]. ESI-MS m/z: 447 $[M+H]^+$. Analysis: for $C_{25}H_{24}N_3O_3P$ (445.46): calcd.: C 67.41%, H 5.43%, N 9.43%, P 6.95%; found: C 67.43%, H 5.42%, N 9.44%, P 6.97%.

2.13. Synthesis of bis-tributyl-(2-oxo-1,3,5-triazin-4,6-di-yl) phosphonium salt (11k) in CH_2Cl_2 according to procedure A

Starting materials: 2,4-dichloro-6-methoxy-1,3,5-triazine (**1e**) (0.180 g, 1 mmol), Bu_3P (**2a**) (0.404 g, 2 mmol), CH_2Cl_2 (5 mL). After 1 day bis-tributyl-(2-oxo-1,3,5-triazin-4,6-di-yl) phosphonium salt (**11k**) (0.446 g, 89%) was obtained as a colorless oil. ^{31}P-NMR ($CDCl_3$): δ = 11.10 [ppm]. ^{1}H ($CDCl_3$): δ = 0.83 (t, 18 H, J = 5 Hz, -CH_2-CH_3); 1.03-1.20 (m, 24 H, -CH_2-CH_2-CH_3); 2.32 (broad t, 12H, -P-CH_2-) [ppm]. ^{13}C ($CDCl_3$): δ = 13.7, 23.7, 25.7, 27.4, 146.8, 149.7 [ppm]. IR (film): v = 3207.3, 3056.0, 2959.7, 2933.2, 2872.0, 2831.6, 1979.7, 1754.7, 1709.3, 1621.6, 1589.5, 1482.7, 1463.8, 1436.0, 1400.9, 1309.6, 1189.8, 1180.3, 1117.8, 1068.5, 996.2, 749.5, 718.6, 691.4 [cm^{-1}]. ESI-MS m/z: 501.2 $[M+H]^+$. Analysis: for $C_{27}H_{54}N_3OP_2$ (498.70): calcd.: C 65.03%, H 10.91%, N 8.43%, P 12.42%; found: C 65.04%, H 10.90%, N 8.44%, P 12.43%.

2.14. Synthesis of of bis-triphenyl-(2-oxo-1,3,5-triazin-4,6-di-yl) phosphonium salt (11l) in CH_2Cl_2 according to procedure A

Starting materials: 2,4-dichloro-6-methoxy-1,3,5-triazine (**1e**) (0.180 g, 1 mmol), PPh_3 (**2b**) (0.524 g, 2 mmol), CH_2Cl_2 (5 mL). After 1 day bis-triphenyl-(2-oxo-1,3,5-triazin-4,6-di-yl)-phosphonium salt (**11l**) was obtained, (0.230 g, 37%) mp = 210 - 215ºC. ^{31}P-NMR ($CDCl_3$): δ = 12.15 [ppm]. ^{1}H-NMR ($CDCl_3$): δ = 7.90-7.32 (m, 30H, (C_6H_5)$_3$P)$_2$-) [ppm]. ^{13}C-NMR ($CDCl_3$): δ = 118.1, 128.3, 130.6, 134.5, 149.4, 156.3 [ppm]. IR (film): v = 3213.3, 3056.6, 2831.7, 1777.7, 1698.8, 1617.0, 1589.7, 1483.7, 1436.6, 1400.8, 1359.6, 1310.8, 1181.6, 1117.5, 1070.5, 995.6, 899.1, 856.3, 846.7, 790.1, 747.1, 718.9, 691.1 [cm^{-1}]. ESI-MS m/z: 620.1 $[M+H]^+$. Analysis: for $C_{39}H_{30}N_3OP_2$ (618.64): calcd C 75.72%, H 4.89%, N 6.79%, P 10.01%; found: C 75.74%, H 4.90%, N 6.78%, P 10.03%.

2.15. Synthesis of tributyl-(4,6-diphenoxy-1,3,5-triazin-2-yl)-phosphonium chloride (3k)

To the vigorously stirred solution of 2-chloro-4,6-diphenoxy-1,3,5-triazine (**1f**) (0.300 g, 1 mmol) in DCM (5 mL) at room temperature was added Bu_3P (**2a**) (0.202 g, 1 mmol). The solution was stirred until 2-chloro-4,6-diphenoxy-1,3,5-triazine was consumed (according to TLC disappearing of spot developed with 0.5% solution of NBP in ethanol). Solvent was evaporated under reduced pressure. To the solid residue was added hexane (5 mL) and the mixture was stirred using a magnetic bar for 30 min, after which the hexane layer was removed. The procedure was repeated three times, yielding tributyl-(4,6-diphenoxy-1,3,5-triazin-2-yl)-phosphonium chloride (**3k**) (0.342 g, 68%) as a colorless oil. ^{31}P-NMR (CD_3CN): δ = 35.20 [ppm]. ^{1}H-NMR (CD_3CN): δ = 0.95 (t, 3 x 3H, J = 7.5 Hz, -CH_2-CH_3); 1.33-1.55 (m, 3 x 4H, -CH_2-CH_2-CH_2-); 2.31 (t, 3 x 2H, J = 6.8 Hz, -CH_2-CH_2-); 7.28-7.49 (m, 10H, -O-C_6H_5) [ppm]. ^{13}C-NMR (CD_3CN): δ = 13.6, 23.5, 25.6, 27.3, 122.2, 126.8; 129.7, 130.0, 165.6, 172.3 [ppm]. ESI-MS m/z: 468.5 $[M+H]^+$.

2.16. Synthesis of triphenyl-(4,6-diphenoxy-1,3,5-triazin-2-yl)-phosphonium chloride (3l)

To the vigorously stirred solution of 2-chloro-4,6-diphenoxy-1,3,5-triazine (**1f**) (0.300 g, 1 mmol) in CH_2Cl_2 (5 mL) at room temperature was added Ph_3P (2b) (0.262 g, 1 mmol). Solution was stirred until 2-chloro-

4,6-diphenoxy-1,3,5-triazine was consumed. Solvent was evaporated under reduced pressure. To the solid residue was added hexane (5 mL) and the mixture was stirred using a magnetic bar for 30 min, after which the hexane layer was removed. The procedure was repeated three times, yielding triphenyl-(4,6-diphenoxy-1,3,5-triazin-2-yl)-phosphonium chloride (**3l**) (0.275 g, 49%) as a colorless oil. ^{31}P-NMR ($CDCl_3$): δ = 22.45 [ppm]. ^{1}H-NMR ($CDCl_3$): δ = 6.40-7.79 (m, 25H, (C_6H_5-O-)$_2$ + (C_6H_5)$_3$-P) [ppm]. ^{13}C-NMR ($CDCl_3$): δ = 116.1, 120.9, 122.2, 126.8; 129.7, 130.0, 131.4, 133,0, 165.6, 172.3 [ppm]. ESI-MS m/z: 550.4 $[M+Na]^+$.

2.17. Synthesis of 2-(4-methoxybenzoyloxy)-4,6-dimethoxy-1,3,5-triazine (7a). Typical Procedure

Solution of 2-chloro-4,6-dimethoxy-1,3,5-triazine (**1a**) (0.175 g, 1 mmol) and Bu_3P (**2a**) (0.202 g, 1 mmol) in CH_2Cl_2 (5 mL) was stirred at room temperature. After 60 minutes 4-methoxybenzoic acid (**6a**) (0.152 g, 1 mmol) and DIPEA (0.16 mL, 1 mmol) were added and stirring was continued overnight. The solution was diluted with CH_2Cl_2 (5 mL), and then washed successively with water, 0.5 M aqueous $KHSO_4$, water, 0.5 M aqueous $NaHCO_3$, and water again. The organic layer was dried with $MgSO_4$, filtered and concentrated to dryness. The residue was dried under vacuum with P_2O_5 and KOH to constant weight yielding 2-(4-methoxybenzoyloxy)-4,6-dimethoxy-1,3,5-triazine (**7a**) (0.250 g, 86%), mp = 86-88ºC, lit. mp = 83-85ºC [2]. ^{1}H-NMR ($CDCl_3$): δ = 3.85 (s, 3H, OCH_3); 4.00 (s, 6H, OCH_3); 6.99 (d, 2H, J = 7.5 Hz, C_6H_4-); 8.09 (d, 2H, J = 7.5 Hz, C_6H_4-) [ppm]. ^{13}C-NMR ($CDCl_3$): δ = 55.6, 55.9, 113.9, 120.1, 132.8, 161.9, 164.4, 170.8, 173.1 [ppm]. IR (film/NaCl): v = 3009, 2955, 2871, 1788, 1750, 1678, 1556, 1541, 1516, 1466, 1449, 1353, 1307, 1225, 1202, 1189, 1171, 1130, 1107, 1082, 1036, 1010 [cm^{-1}]. ESI-MS m/z: 314.0 $[M+Na]^+$.

2.18. Synthesis of 4-methoxybenzoic acid 4,6-diphenoxy-1,3,5-triazin-2-yl ester (7f) using tributyl-(4,6-diphenoxy-1,3,5-triazin-2-yl)-phosphonium chloride (3k)

To stirred solution of tributyl-(4,6-diphenoxy-1,3,5-triazin-2-yl)-phosphonium chloride (**3k**) (0.502 g, 1 mmol), in CH_2Cl_2 (5 mL) 4-methoxybenzoic acid (**9**) (0.304 g, 2 mmol) and DIPEA (0.16 mL, 1 mmol) were added. Stirring was continued until all (4,6-diphenoxy-1,3,5-triazin-2-yl)-triphenyl-phosphonium chloride was consumed (disappearing of spot of 4,6-diphenoxy-1,3,5-triazin-2-yl)-triphenyl-phosphonium chloride). The solution was diluted with CH_2Cl_2 (5 mL) and washed successively with water, 0.5 M aqueous $NaHSO_4$, water, 0.5 M aqueous $NaHCO_3$, and water again. The organic layer was dried with $MgSO_4$, filtered, and concentrated to dryness. The residue was dried under vacuum with P_2O_5 and KOH to constant weight yielding 2-(4-methoxybenzoyloxy)-4,6-diphenoxy-1,3,5-triazine (**7f**) (0.291 g, 70%). ^{1}H-NMR ($CDCl_3$): δ = 3.91 (s, 3H, CH_3O-C_6H_4-); 6.98 (d, 2H, J = 8 Hz, CH-CCOO-); 7.17-7.68 (m, 10 H, C_6H_5-O-); 7.71 (d, 2H, J = 8 Hz, CH_3OC-CH-) [ppm]. ^{13}C-NMR ($CDCl_3$): δ = 55.3, 113.3, 120.2, 125.7; 128.7, 130.1, 132.9, 133.3, 134.7, 164.4, 170.6, 172.9 [ppm]. IR (film/NaCl): v = 3015, 2975, 2860, 1790, 1745, 1666, 1555, 1544, 1511, 1455, 1444, 1343, 1301, 1229, 1201, 1188, 1173, 1133, 1102, 1080, 1031, 1010 [cm^{-1}]. ESI-MS m/z: 438.4 $[M+Na]^+$.

2.19. Synthesis of 4-methoxybenzoic acid 4,6-diphenoxy-1,3,5-triazin-2-yl ester (7f) using (4,6-diphenoxy-1,3,5-triazin-2-yl)-triphenyl-phosphonium chloride (3l)

Strating materials: (4,6-diphenoxy-1,3,5-triazin-2-yl)-triphenylphosphonium chloride (**3l**) (0.562 g, 1 mmol), 4-methoxybenzoic acid (**9**) (0.152 g, 1 mmol), DIPEA (0.16 mL, 1 mmol), DCM (5 mL). Product: 2-(4-methoxybenzoyloxy)-4,6-diphenoxy-1,3,5-triazine (**7f**) (0.237 g, 57%). Product was spectroscopically identical with described above.

2.20. Synthesis of 4-methoxy-N-p-tolylbenzamide (9a) by using *in situ* prepared (4,6-dimethoxy-1,3,5-triazin-2-yl)-triphenyl-phosphonium chloride (3b). Typical procedure

Solution of 2-chloro-4,6-dimethoxy-1,3,5-triazine (**1a**) (0.175 g, 1 mmol) and PPh_3 (**2b**) (0.262 g, 1mmol) in CH_2Cl_2 (5 mL) was stirred at room temperature. After 60 minutes 4-methoxybenzoic acid (**6a**) (0.152 g, 1 mmol) and DIPEA (0.16 mL, 1 mmol) were added and stirring was continued 6 hours. According to TLC spot of (4,6-dimethoxy-1,3,5-triazin-2-yl)-triphenyl-phosphonium chloride disappeared and spot of 2-(4-methoxybenzoyloxy)-4,6-dimethoxy-1,3,5-triazine developed (R_f = 0.2). *p*-Toluidine (0.107 g, 1 mmol) (**8a**) was added, and the mixture was stirred overnight at room temperature. The solution was diluted with CH_2Cl_2 (5 mL) and then washed successively with water, 0.5 M aqueous $NaHSO_4$, water, 0.5 M aqueous $NaHCO_3$, and water again. The organic layer was dried with $MgSO_4$, filtered, and concentrated to dryness. The residue was dried under vacuum with P_2O_5 and KOH to constant

weight yielding 4-methoxy-N-*p*-tolyl-benzamide (**9a**) (0.174 g, 72%), mp 143-145ºC, lit. mp 145-148ºC [9]. HPLC: gradient 50-100%B, 20 min: R_t = 10.92 min, 79%. IR (NaCl/film):v = 3344, 2960, 1648, 1604, 1524,1248,1032, 760, 656 [cm^{-1}]. 1H-NMR ($CDCl_3$): δ = 2.34 (s, 3H, $CH_3C_6H_4$-); 3.87 (s, 3H, -COO-CH_3); 6.94-6.99 (d, 2H, J = 8 Hz, C_6H_4-); 7.17 (d, 2H, J = 7.5 Hz, C_6H_4-); 7.51 (d, 2H, J = 7.5 Hz, C_6H_4-); 7,81-7.87 (t, 2H, J = 8 Hz, C_6H_4-) [ppm].

2.21. Synthesis of 4-methoxy-N-p-tolylbenzamide (9a) by using *in situ* prepared tributyl-(4,6-dimethoxy-1,3,5-triazin-2-yl)-phosphonium chloride (3a). Typical procedure

Solution of 2-chloro-4,6-dimethoxy-1,3,5-triazine (**1a**) (0.175 g, 1 mmol) and Bu_3P (**2a**) (0.202 g, 1 mmol) in CH_2Cl_2 (5 mL) was stirred at room temperature. After 60 minutes 4-methoxybenzoic acid (0.152 g, 1 mmol) (**6a**) and DIPEA (0.16 mL, 1 mmol) were added and stirring was continued for 6 hours. According to TLC spot of tributyl-(4,6-dimethoxy-1,3,5-triazin-2-yl)-phosphonium chloride disappeared and spot of 2-(4-methoxybenzoyloxy)-4,6-dimethoxy-1,3,5-triazine developed (R_f = 0.2). *p*-Toluidine (0.107 g, 1 mmol) (**8a**) was added, and the mixture was stirred overnight at room temperature. The solution was diluted with CH_2Cl_2 (5 mL) and then washed successively with water, 0.5 M aqueous $NaHSO_4$, water, 0.5 M aqueous $NaHCO_3$, and water again. The organic layer was dried with $MgSO_4$, filtered, and concentrated to dryness. The residue was dried under vacuum with P_2O_5 and KOH to constant weight yielding 4-methoxy-N-*p*-tolylbenzamide (**9a**) (0.183 g, 76%) which was spectroscopically identical with described above. HPLC: gradient 50-100%B, 20 min: R_t = 10.90 min, 88%.

2.22. Synthesis of 4-methoxy-N-p-tolylbenzamide (9a) by using (4,6-diphenoxy-1,3,5-triazin-2-yl)-triphenyl-phosphonium chloride (3l)

To a stirred solution of (4,6-diphenoxy-1,3,5-triazin-2-yl)-triphenylphosphonium chloride (**3l**) (0.562 g, 1 mmol) in CH_2Cl_2 (5 mL) 4-methoxybenzoic acid (**6a**) (0.152 g, 1 mmol) and DIPEA (0.16 mL, 1 mmol) were added. Stirring was continued until all (4,6-diphenoxy-1,3,5-triazin-2-yl)-triphenylphosphonium chloride was consumed (disappearing of spot of 4,6-diphenoxy-1,3,5-triazin-2-yl)-triphenylphosphonium chloride). *p*-Toluidine (**8a**) (0.107 g, 1 mmol) was added, and the mixture was stirred overnight at room temperature. The solution was diluted with CH_2Cl_2 (5 mL) and was washed successively with water, 0.5 M aqueous $NaHSO_4$, water, 0.5 M aqueous $NaHCO_3$, and water again. The organic layer was dried with $MgSO_4$, filtered, and concentrated to dryness. The residue was dried under vacuum with P_2O_5 and KOH to constant weight yielding 4-methoxy-*N*-*p*-tolylbenzamide (**9a**) (0.070 g, 29%) spectroscopically identical with described above. HPLC: gradient 50-100%B, 20 min: R_t = 10.93 min, 85%.

2.23. Synthesis of 4-methoxy-N-p-tolylbenzamide (9a) by using tributyl-(4,6-diphenoxy-1,3,5-triazin-2-yl)-phosphonium chloride (3k)

Starting materials: tributyl-(4,6-diphenoxy-1,3,5-triazin-2-yl)-phosphonium chloride (**3k**) (0.502 g, 1 mmol), 4-methoxybenzoic acid (**6a**) (0.152 g, 1 mmol), *p*-toluidine (**8a**) (0.214 g, 2 mmol), DIPEA (0.32 mL, 2 mmol). Product: 4-methoxy-*N*-*p*-tolyl-benzamide (**9a**) (0.099 g, 41%) spectroscopically identical with described above. HPLC: gradient 50-100%B, 20 min: R_t = 10.92 min, 84%.

3. Results and discussion

In order to compare the geometry of ammonium and phosphonium moieties, which play crucial role in the activation process, we have searched Cambridge Structural Database (CSD) [10] for fragments depicted in Fig. 1. We were especially interested in bond lengths marked as d1 (P^+-C_{ar}) and d2 (N^+-C_{ar}).

Review of CSD (CSD, ver. 5.32 of November, 2011) gave us 16 structures which contain phosphonium salt and 122 structures containing ammonium salt. During the search procedure structures without 3D coordinates and with the r factor exceeding 5% were eliminated.

The length of most of the N^+-C bonds (112 of 122) are between 1.490-1.519Å while for most of the P^+-C bonds (10 of 14) the lengths are between 1.780 and 1.799Å. Such significant elongation should facilitate the quaternization process due to increased polarizability of the phosphorus atom and reduce steric requirements of intermolecular reactions.

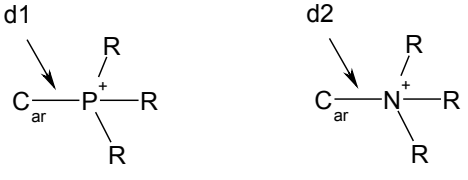
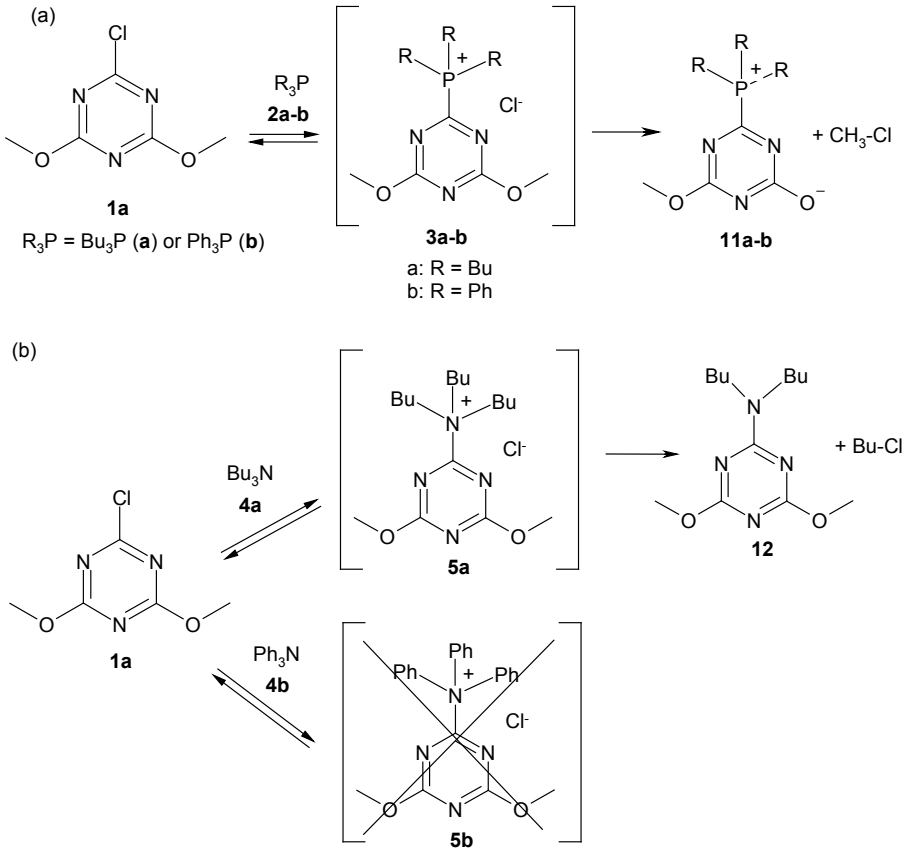


Figure 1. The structure's fragments for which the searching of CSD was made.



Scheme 2. **(a)** Synthesis of *P*-triazinylphosphonium chlorides **3a–b**, by using CDMT (**1a**) and teritiary phosphines (**2a-b**) with subsequent *O*-dealkylation leading to tributyl-(4-oxy-6-methoxy-1,3,5-triazin-2-yl)-phosphonium salt **11a** and triphenyl-(4-oxy-6-methoxy-1,3,5-triazin-2-yl)-phosphonium salt **11b**, (b) synthesis of *N*-triazinylammonium chloride **6a**, by using CDMT (**1a**) and tributhylamine (**4a**) with subsequent *N*-dealkylation leading to 2-(*N*,*N*-dibutylamino-)4,6-dimethoxy-1,3,5-triazine **12**. Reaction **1a** with triphenylamine (**4b**) was not observed.

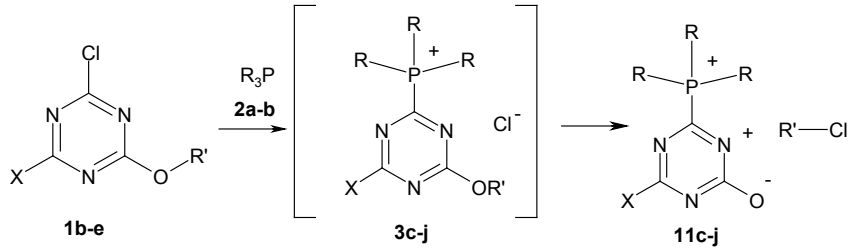
As expected, the treatment of 2-chloro-4,6-dimethoxy-1,3,5-triazine (**1a**) with tertiary phosphines **2a–b** gave *P*-triazinylphosphonium chlorides **3a–b**, which was confirmed by a positive test with 4-(4-nitrobenzyl) pyridine (NBP) [11]. The quaternization of Bu_3P and Ph_3P with **1a**, proceeding relatively slowly at 0ºC, was accelerated at elevated temperatures. The increased polarity of the solvent had a negligible effect on the reaction rate. Unfortunately, **3a–b** were found extremely unstable and easily decomposed yielding demethylated products **11a–b** (a negative test with NBP, see Scheme 2a). Products **11a–b** were isolated and their structures were unequivocally confirmed by the decreased intensity of the singlet methoxy group from 6H to 3H in ^{1}H-NMR strongly suggesting a degradation proceeding with the participation of a triazine substituent.

This pathway of decomposition of P-triazinylphosphonium chlorides **3a–b,** which was different from that of N-dealkylation of N-triazinylammonium chloride (see Scheme 2b) [12b,13,14] has been confirmed by ^{1}H-NMR and ^{31}P-NMR spectra of degradation products. Any attempts to prevent this degradation by modification of reaction conditions and to isolate the expected product **11a-b** were ineffective (see Table 1).

The most intensive degradation (74% and 72% yields, Table 1, entries 7 and 13) was observed in reaction of CDMT (**1a**) with Bu_3P in propan-2-ol and dichloromethane at 0ºC and under reflux in ethyl acetate used as a solvent (78% yield, Table 1, entry 5). In a more polar acetonitrile solution, only trace amounts of products **11a–b** were formed. In the case of Ph_3P, the highest yields were obtained in CH_2Cl_2 (68% yield, Table 1, entry 14) and at elevated temperature in toluene and/or acetonitrile (81% and 86% yields, Table 1, entries 10 and 12). Comparison of analytic data of crude **11a-c** showed in several cases divergences. This variation effect was dependent on tiny modifications of synthetic procedure, but was eliminated by recrystallisation of **11a-c**. The most notable divergences were found in the case of melting points and chemical shift of the phosphonium group in 31P-NMR. Therefore, analytical

Table 1. Tributyl-(4-oxy-6-methoxy-1,3,5-triazin-2-yl)-phosphonium salt **11a** and triphenyl-(4-oxy-6-methoxy-1,3,5-triazin-2-yl)-phosphonium salt **11b** prepared by the treatment of 2-chloro-4,6-dimethoxy-1,3,5-triazine (**1a**) with Bu_3P (**2a**) and PPh_3 (**2b**).

Entry	phosphine	solvent	room temp.		reflux	
			time	Yield [%]	time	Yield [%]
1	Bu_3P	$CHCl_3$	5 days	33	14 h	64
2	PPh_3	$CHCl_3$	7 days	0	4 h	79
3	Bu_3P	THF	5 days	49	14 h	52
4	PPh_3	THF	5 days	41	3 days	17
5	Bu_3P	AcOEt	3 days	55	7 h	78
6	PPh_3	AcOEt	3 days	14	12 h	37
7	Bu_3P	propan-2-ol	3 days	74	14 h	47
8	PPh_3	propan-2-ol	7 days	0	2 h	0
9	Bu_3P	toluene	4 days	67	4 h	59
10	PPh_3	toluene	7 days	0	3 h	81
11	Bu_3P	CH_3CN	7 days	0	20 h	0
12	PPh_3	CH_3CN	7 days	0	3 h	86
13	Bu_3P	CH_2Cl_2	3 days	72	-	-
14	PPh_3	CH_2Cl_2	3 days	68	-	-



1b-e **3c-j** **11c-j**

R_3P = Bu_3P or Ph_3P

3c: R' = $CH_2C_6H_5$, X = $OCH_2C_6H_5$, R = Bu; **3d:** R' = $CH_2C_6H_5$, X = $OCH_2C_6H_5$,R = Ph;
3e: R' = CH_2CF_3, X = OCH_2CF_3, R = Bu; **3f:** R' = CH_2CF_3, X = OCH_2CF_3, R = Bu;
3g: R' = $CH_2CH_2OCH_2CH_3$, X = $OCH_2CH_2OCH_2CH_3$, R = Bu; **3h:** R' = $CH_2CH_2OCH_2CH_3$, X = $OCH_2CH_2OCH_2CH_3$, R = Ph;
3i: X = Cl, R' = Me, R = Bu; **3j:** X = Cl, R' = Me, R = Ph

Scheme 3. Synthesis of (4-oxy-6-alkyloxy-1,3,5-triazin-2-yl) phosphonium salts **11c–j** by treatment of 2-chloro-4,6-dialkoxy-1,3,5-triazines **1b–e** with **2a-b**.

characterization of already known [5] **11a-d** was completed as required for the brand new products.

In order to verify whether the observed dealkylation is a general process or one specific for triazine substituted with a methoxy group, experiments were made involving other triazines with a broad range of substituents in the ring, e.g. 2-chloro-4,6-dibenzyloxy-1,3,5-triazine (**1b**), 2-chloro-4,6-bis-(2,2,2-trifluoroethoxy)-1,3,5-triazine (**1c**), 2-chloro-4,6-bis-(2-ethoxy-ethoxy)-1,3,5-triazine (**1d**), and 2,4-dichloro-6-methoxy-1,3,5-triazine (**1e**). Unfortunately, it was found again that in all of these cases, the treatment of **1b–e** with phosphines **2a–b** gave dealkylation products **11c–j** (see Scheme 3).

All attempts to use dealkylated products **11c–j** as coupling reagents were fruitless. None of **11c–j** activated 4-methoxybenzoic acid under a broad range of reaction conditions. In order to further elucidate this phenomenon, the structure of the dealkylation product was studied by the X-ray method, calculation of charge distribution in the zwitterionic product, and the comparison of results with experimental data collected in the Cambridge Structural Database.

It was found that crystallization from methanol-water mixture promoted further demethylation of **11a**, finally leading to tributyl-(4-hydroxy-6-oxy-1,3,5-triazin-2-yl)-phosphonium salt (**12**) (the deposition number CCDC 879925) (see Scheme 4). The structure of **8** was confirmed by X-ray analysis. It forms a dimer with hydrogen bonds between N1–H and O2 atoms (see Fig. 2).

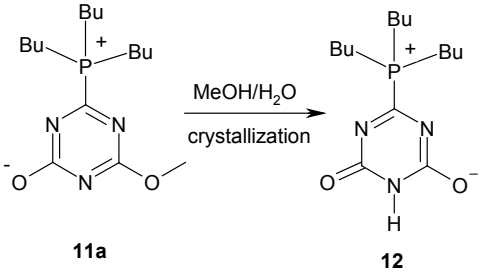
To arrive at a rational description of the structure of **12**, we divided the molecule into two parts:

the aromatic moiety of the triazine ring and the tributyl substituent around the phosphorus atom. The stability of the aromatic ring can be described using the HOMA index—a quantitative measure of aromaticity. The HOMA index is defined as follows [15]:

$$HOMA = 1 - \alpha(R_{opt} - R_{av})^2 - \alpha/n\sum(R_{av} - R_i)^2$$

where n is the number of bonds taken into summation; α is an empirical constant fixed to give HOMA = 0 for the hypothetical Kekule structures of aromatic systems and 1 for systems with all bonds equal to the optimal value R_{opt}, R_{av} is the average bond length; and Ri reflects the lengths of individual bonds.

To calculate the HOMA index based on geometrical parameters, we needed precise information concerning the molecular geometry of the 1,3,5-triazine ring. Therefore, we used crystallographic data for **12** as well



Scheme 4. Demethylation of **11a** to tributyl-(4-hydroxy-6-oxy-1,3,5-triazin-2-yl)-phosphonium salt (**12**) in aqueous methanol.

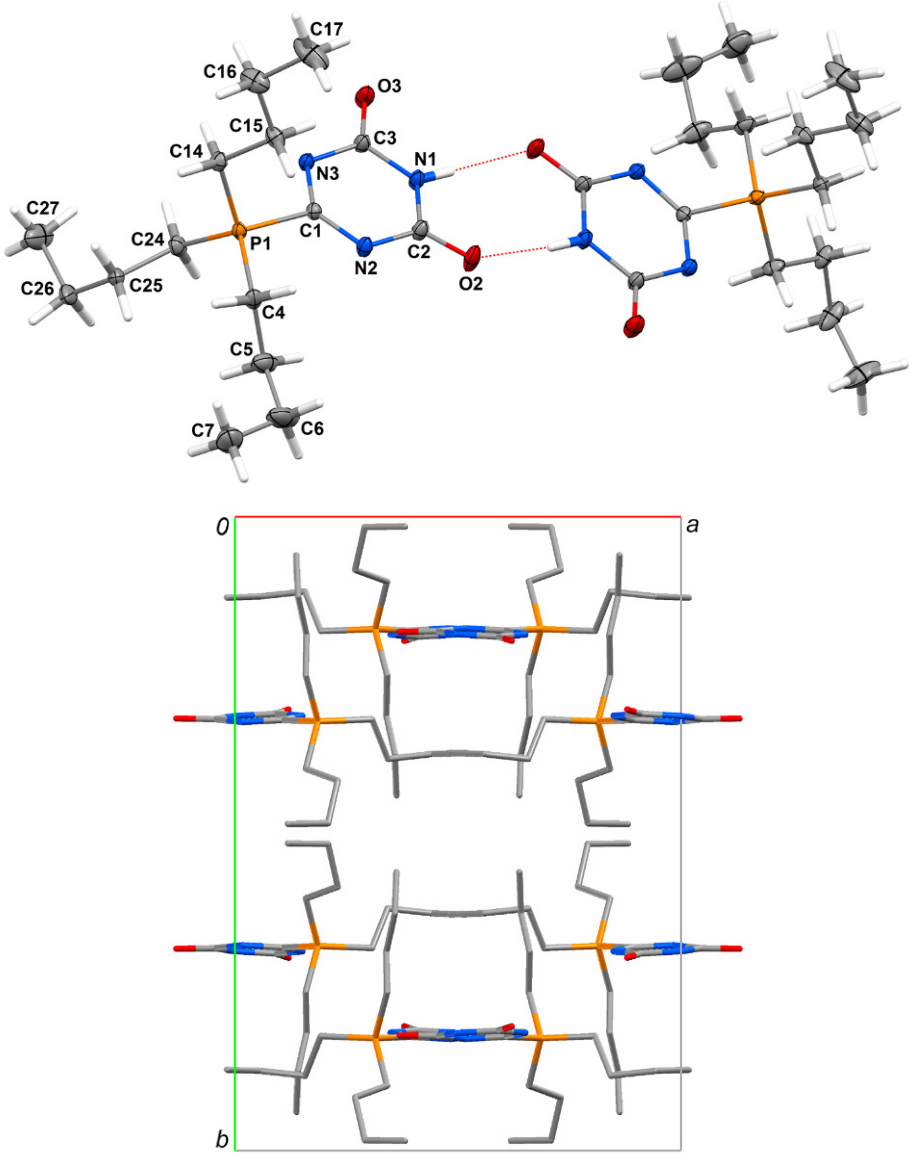


Figure 2. Structure of tributyl-(4-hydroxy-6-oxy-1,3,5-triazin-2-yl)-phosphonium salt (**12**).

as data collected in the Cambridge Structural Database for unsubstituted triazine rings [16]. We calculated the aromaticity of unsubstituted triazine and compared it to **12**. For triazine, this index equals 0.99, which is very close to the ideal aromatic ring (HOMA = 1) with all bonds conjugated. A significant lowering of the aromaticity of the triazine ring is observed following the transformation of the moiety into a phosphonium salt and substitution with two oxygens. The HOMA index is thus decreased from 0.99 to 0.88. The C–N bonds lengths in the aromatic ring of **12** vary from 1.322 to 1.335 Å and are much more alternated than in unsubstituted triazine. In the investigated compound, N1–C2, N1–C3, N3–C3, and N2–C2 are between 1.371 and 1.381 Å and close to formal single bonds, while C1–N3 and C1–N2 are 1.323 and 1.317 Å, respectively, and there are about 0.2 Å longer than formal double bonds.

The formal +1 charge located on the phosphorus atom is not balanced by the other −1 point charge. Quantum chemistry calculation for the investigated structure, based on crystallographic coordinates, showed that the negative partial charge is located mainly on carbon atoms, closest to P1 in the n-butane chains (C4, C14, C24) as well as on both oxygens O2 and O3. Calculation of partial charges was performed using Gaussian 09 by the following methods, classified by Cramer dipole derivative charges, also called atomic polar tensor derived charges (APT in Table 2), electrostatic potential (ESP), and natural population analysis (NPA).

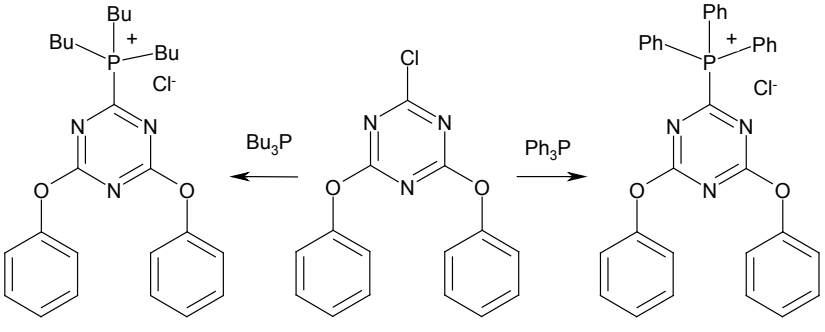
Table 2. Charge distribution, electrostatic potential (ESP), and natural population analysis (NPA) in **12**.

Atom	Charges		
	APT	ESP (MSK)	NPA
P1	1.220739	0.661411	1.56662
N1	-0.735926	-0.909375	-0.70463
N2	-0.966057	-0.959469	-0.62605
N3	-1.005213	-0.947613	-0.64464
O2	-0.915898	-0.661645	-0.62235
O3	-0.919325	-0.660679	-0.62579
C1	0.752618	0.811111	0.11434
C2	1.351001	1.130305	0.78658
C3	1.357554	1.110678	0.78801
C4	-0.282714	-0.516990	-1.04799
C14	-0.277681	-0.539896	-1.04553
C24	-0.277669	-0.539907	-1.04552

Crystallographic and computational data show that the positive charge is not located exclusively on the phosphorus and C1 atoms, but is diffused in the triazine ring and neutralized by the partial negative charge located on the C4, C14, and C24 carbons of the butyl groups surrounding the P1 phosphorus. Such a charge distribution does not favor S_{NAr} substitution involving an attack of the carboxylate anion and a departure of tertiary phosphine, which is the crucial stage in the process of "superactive" ester formation [12]. Therefore, in further research, an attempt was made to use 2-chloro-4,6-diphenoxy-1,3,5-triazine **1f** to verify whether the application of starting materials resistant to nucleophilic substitution facilitates the formation of P-quaternization products. As expected, it was found that in this case the treatment of **1f** with tertiary phosphine gave final P-triazinylphosphonium salts (see Scheme 5).

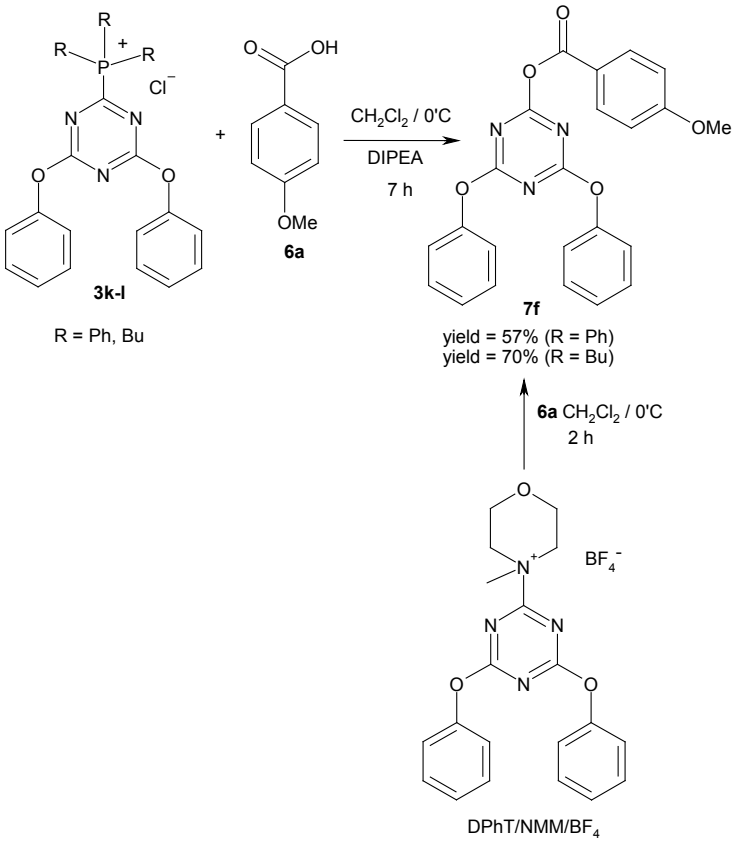
Salts **3k–l** were obtained with satisfactory yield, but the disadvantage of the procedure was the preactivation time prolonged to 10–14 days, necessary for the completion of the reaction. With access to stable salts **3k–l**, we were able to prove that that the activation of 4-methoxybenzoic acid (**6a**) yielded the same intermediate "superactive" ester **7f** (Scheme 6) as condensation mediated by means of a classic N-triazinylammonium salt DPhT/NMM/BF_4 [12a,17].

Anticipating that the primary products of the reaction of tertiary phosphines **2a–b** with triazines **1a–e** were unstable quaternary P-triazinylphosphonium salts **3a–j**, attempts were made to prepare them in

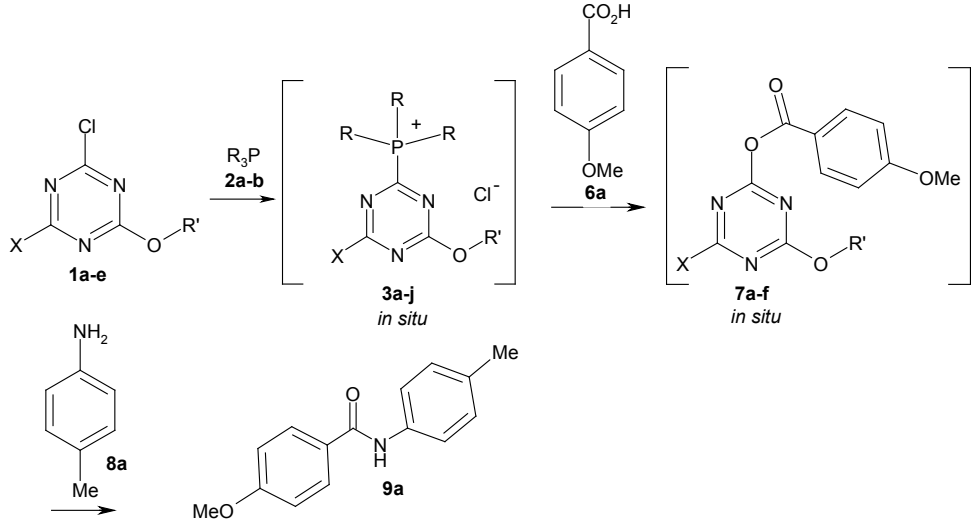


3k, 68% **1f** **3l**, 49%

Scheme 5. Stable *P*-triazinylphosphonium 2-chloro-4,6-diphenoxy-1,3,5-triazines **3k-l**.



Scheme 6. Synthesis of active triazine ester **7f** using phosphonium salts **3k-l** and classic coupling reagent DPhT/NMM/BF_4.

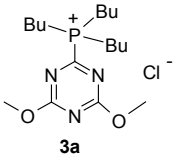
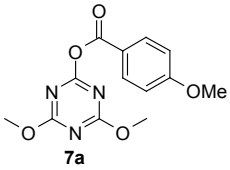
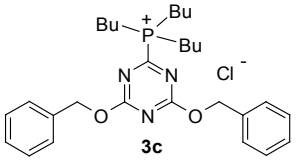
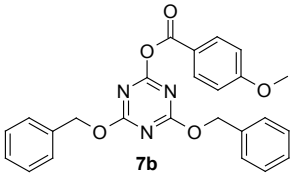
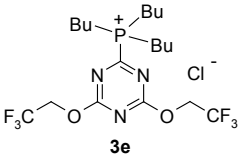
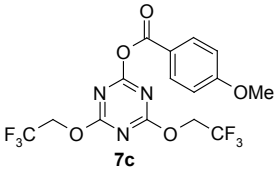
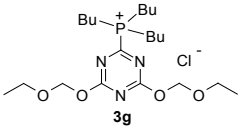
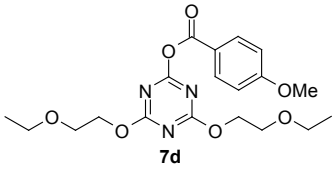
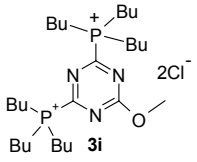
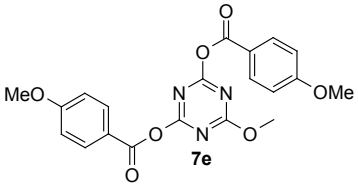


R_3P = Bu_3P or Ph_3P

3a: R' = CH_3, X = OCH_3, R = Bu; **3b:** R' = CH_3, X = OCH_3, R = Ph;
3c: R' = $CH_2C_6H_5$, X = $OCH_2C_6H_5$, R = Bu; **3d:** R' = $CH_2C_6H_5$, X = $OCH_2C_6H_5$,R = Ph;
3e: R' = CH_2CF_3, X = OCH_2CF_3, R = Bu; **3f:** R' = CH_2CF_3, X = OCH_2CF_3, R = Bu;
3g: R' = $CH_2CH_2OCH_2CH_3$, X = $OCH_2CH_2OCH_2CH_3$, R = Bu; **3h:** R' = $CH_2CH_2OCH_2CH_3$, X = $OCH_2CH_2OCH_2CH_3$, R = Ph;
3i: X = Cl, R' = Me, R = Bu; **3j:** X = Cl, R' = Me, R = Ph

Scheme 7. Synthesis of 4-methoxy-*N*-p-tolyl-benzamide **9a** with *in situ* prepared *P*-triazinylphosphonium chlorides **3**.

Table 3. Synthesis of 2-acyloxy-4,6-disubstituted-1,3,5-triazines **7a–e**.

P-triazinyl-phosphonium chloride (prepared *in situ*)	Product	Yield [%]	IR [2,18] [cm^{-1}]
 **3a**	 **7a**	86	1750
 **3c**	 **7b**	85	1750
 **3e**	 **7c**	77	1760
 **3g**	 **7d**	75	1755
 **3i**	 **7e**	71	1745

situ and consume immediately for the activation of 4-methoxybenzoic acid to appropriate "superactive" esters. As expected, this procedure was found very effective and the anticipated products of activation were isolated in 75%–86% yield. All of them were identical with the authentic samples obtained with classic N-triazinylammonium salts and identified as **7a–e** based on the characteristic carbonyl IR band at 1750–1760 cm^{-1} (see Table 3).

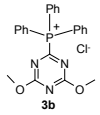
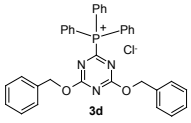
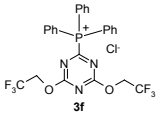
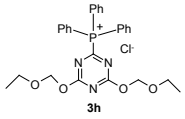
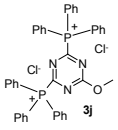
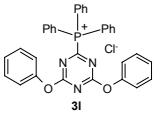
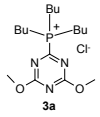
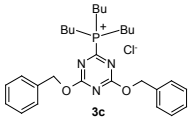
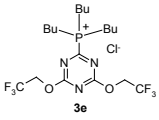
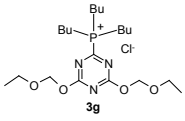
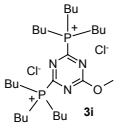
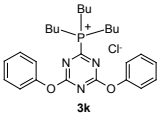
Moreover, it has been proven that P-triazinylphosphonium chlorides **3a–j** prepared *in situ* are very efficient coupling reagents, useful in the synthesis of amides (see Scheme 7 and Table 4).

In all cases, the application of P-triazinylphosphonium salts **3** prepared *in situ* gave 4-methoxy-N-p-tolylbenzamide isolated with acceptable yield and purity. Only **3k–l** derived from 2-chloro-4,6-diphenoxy-1,3,5-triazine were less efficient in the coupling procedure, and gave the product of condensation with moderate yield (see Table 4, entries 6 and 12).

4. Conclusions

Tertiary phosphines in reaction with 2-chloro-4,6-dialkoxy-1,3,5-triazines gave unstable quaternary *P*-triazinylphosphonium chlorides, which readily decomposed with a departure of the alkyl group of the triazine ring substituent. The dealkylation products are useless as reagents for the activation of carboxylic acids. Nevertheless, in accord with expectations, the activation of the carboxylic function, even in the presence of spatially expanded tributyl- or triphenylphosphine, was enhanced so significantly that the *in situ* procedure gave appropriate "superactive" esters and products of condensation with good yield. This means that the

Table 4. 4-Methoxy-*N*-p-tolyl-benzamide **9a** obtained by using *in situ* prepared *P*-triazinylphosphonium chlorides **3**.

Entry	Coupling reagent prepared *in situ*	Yield[a] [%] 4-Methoxy-N-p-tolyl-benzamide	Purity[a] [%]
1	 **3b**	72	79
2	 **3d**	91	81
3	 **3f**	80	83
4	 **3h**	89	80
5	 **3j**	91	78
6	 **3l**	29[b]	85
7	 **3a**	76	88
8	 **3c**	97	84
9	 **3e**	88	82
10	 **3g**	83	83
11	 **3i**	95	80
12	 **3k**	41[b]	84

a) isolated crude product, purity determined by HPLC, b) using stable, isolated chlorides 3l, 3k.

replacement of tertiary amines by tertiary phosphines paved the road to a new family of coupling reagents. The most interesting finding is the possible application of configurationally stable chiral phosphines bearing the stereogenic center on the phosphorus in enantioselective condensations.

Acknowledgements

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Supplementary Material

Supporting Information Available: Experimental procedures, characterization data.