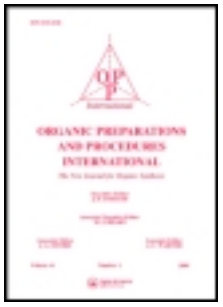

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MICROWAWASSISTED SYNTHESIS OF HEXASUBSTITUTED CYCLOTRIPHOSPHAZENES

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MICROWAVE-ASSISTED SYNTHESIS OF HEXASUBSTITUTED CYCLOTRIPHOSPHAZENES

Submitted by (01/23/01)

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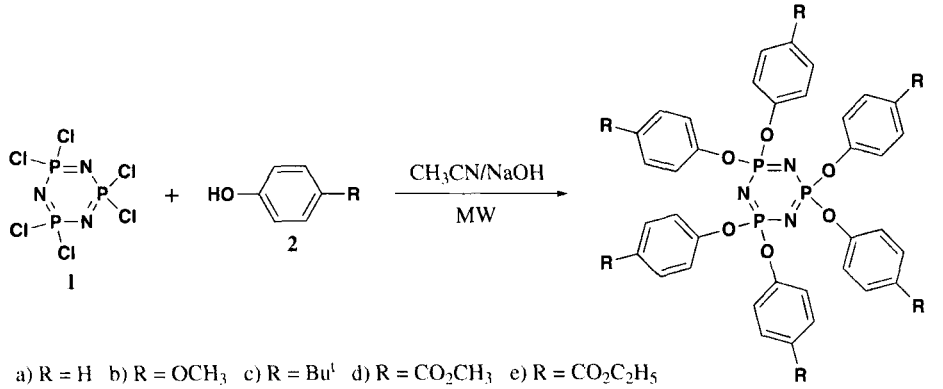
In recent years, many efforts have been focused on the preparation and characterization of phosphazenes which contain a framework of alternating phosphorus and nitrogen atoms and with two substituent groups attached to each phosphorus atom.[1] It is noticeable that cyclophosphazenes, especially hexaaryloxyphosphazenes exhibits excellent thermal and chemical stability, and they can be used as fire-proof materials, high temperature lubricants, vacuum pump oils and hard disk surface lubricants.[2~3] To meet the needs of both the scientific and technological communities, a wide variety of hexaaryloxyphosphazenes have been prepared. The most common synthetic method involves the reaction of hexachlorocyclotriphosphazene [$N_3P_3Cl_6$] with phenols in the presence of NaH in an appropriate organic solvent.[4] However, this method requires a long reaction period, usually 48 h and also a tedious workup. Carriedo *et al.*[5] described a very convenient preparation for some known cyclic aryloxyphosphazenes directly from [$N_3P_3Cl_6$], phenols and K_2CO_3 in acetone. However, in the case of phenols HOC_6H_4-R (R = H, Bu^t, OCH_3), the reactions were very slow, requiring 20 h even in the presence of a phase-transfer catalyst.

It is known that many organic reactions may be conducted safely in microwave ovens with remarkable rate enhancements, compared with conventional heating.[6~8] To our knowledge, there is no report on the microwave-assisted displacement reactions of hexachlorocyclotriphosphazene. Herein we describe a practical and simple one-pot synthesis of hexaaryloxyphosphazene (shown in the **Scheme**).



a) R = H b) R = OCH_3 c) R = Bu^t d) R = CO_2CH_3 e) R = $CO_2C_2H_5$
f) R = C_6H_5 g) R = F h) R = 4-F-3-CF_3

3

Our initial intention was to carry out the process in dry media using silica or activated carbon as solid supports. However, various attempts were all unsuccessful because hexachlorocyclotriphosphazene was prone to sublimation and phenols tended to become oxidized. When acetonitrile was used as the solvent, irradiation for 20~50 min afforded the target products with *ca.* 75% yields. However, when these mixtures were refluxed for 2 hours by conventional heating, only small amounts of products could be detected in reactions monitored by TLC. Moreover, it should be noted that reactions of 4-nitrophenol, 4-hydroxybenzaldehyde and 4-hydroxyacetophenone with hexachlorocyclotriphosphazene using this procedure did not produce the hexaaryloxyphosphazene because of oxidation of the phenols under irradiation.

EXPERIMENTAL SECTION

The FT-IR spectra were recorded with a Bio-Rad Win-IR spectrometer. NMR spectra were measured on a Varian FT-80A NMR spectrometer, using $CDCl_3$ as the solvent for ^{1}H-NMR spectroscopy as well as $CDCl_3/C_6D_6$ for ^{31}P-NMR spectroscopy. The chemical shifts for ^{31}P-NMR spectra are relative to that of the external standard, 85% phosphoric acid. C, H, N analyses were performed with a CE-1106 microanalyzer. Microwave irradiation was carried out with a modified Galanz WP800BS microwave oven.

Typical Procedure.- Hexachlorocyclotriphosphazene (0.2 g, 0.57 mmol), a substituted phenol (3.50 mmol), NaOH (6.0 mmol), and 15 mL of dry acetonitrile were placed in 100 mL flask. The mixture was irradiated in a microwave oven connected with a condenser for 20~50 min and then cooled to room temperature. The solid was filtered off and washed with 10 mL of acetonitrile. The filtrate and the washings were combined, and the solvent was distilled under reduced pressure. The residue was dissolved in ethyl acetate (15 mL) and washed twice with 5 mL aqueous sodium hydroxide solution (10%), then with water, and finally dried over anhydrous sodium sulfate. After filtration and evaporation, the product was purified by recrystallization from the appropriate solvent (**Table 1**).

Table 1. Yields, mps, Time and Spectral Data of Phosphazenes

Cmpd	Yield (%)	mp (°C)	*lit* mp (°C)	Time[a] (min)	Solvent[b]	IR (cm^{-1})	^{1}H NMR (δ)	^{31}P NMR (δ)
3a	70	111-112	110-111[c]	30	EtOAc	1486 1197 952	7.18-6.85	8.45 (s)
3b	67	100-102	100-102[d]	40	EtOH	1504 1198 971	6.76 (d, 12H) 6.86 (d, 12H) 3.73 (s, 18H)	9.80 (s)
3c	70	130-131	132-133[d]	48	EtOH	1509 1203 956	7.14 (d, 12H) 6.88 (d, 12H) 1.27 (s, 54H)	8.75(s)
3d	80	152	---[e]	20	Me_2CO	1725 1208 958	7.80 (d, 12H) 7.04 (d, 12H) 3.92 (s, 18H)	6.90 (s)

Table 1. Continued...

Cmpd	Yield (%)	mp (°C)	*lit* mp (°C)	Time[a] (min)	Solvent[b]	IR (cm^{-1})	^1H NMR (δ)	^{31}P NMR (δ)
3e	72	87-88	78-80[f]	30	MeOH	1717 1217 958	7.83 (d, 12H) 7.05 (d, 12H) 4.42 (q, 12H) 1.40 (t, 18H)	7.46 (s)
3f	75	199-201	202-203[g]	30	EtOH	1504 1208 954	7.33-6.95	9.33 (s)
3g	78	126-127	127-129[h]	35	MeOH	1504 1215 957	6.89 (d, 12H) 6.81 (d, 12H)	8.95 (s)
3h	74	73	- - -[i]	35	MeOH	1321 1263 1221	7.26-7.06	8.19 (s)

a) Irradiation time b) Recrystallization solvent; all products are white solids c) Ref. 9 d) Ref. 10 e) *Anal.* Calcd for $C_{48}H_{42}N_3O_{18}P_3$: C, 55.34; H, 4.06; N, 4.03. Found: C, 55.23; H, 4.01; N, 3 .91 f) Ref. 11 *Anal.* Calcd for $C_{54}H_{54}N_3O_{18}P_3$: C, 57.60; H, 4.83; N, 3.73. Found: C, 57.48; H, 4.79; N, 3.60. g) Ref. 12 h) Ref.2 i) *Anal.* Calcd for $C_{42}H_{18}F_{24}N_3O_6P_3$: C, 41.71; H, 1.50; N, 3.47 Found: C, 41.67; H, 1.37; N, 3.23.

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A FACILE SYNTHESIS OF N^2-BENZYLOXYCARBONYL-(S)-2-AMINO-3-(DIMETHYLAMINO)PROPANOIC ACID

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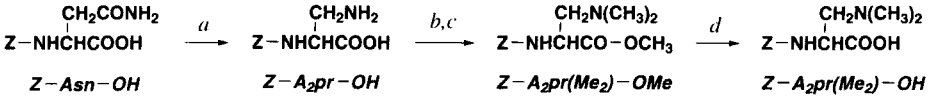
In our research program aimed at the design and synthesis of selective inhibitors of glucosamine-6-phosphate synthase[1,2] and edeine antibiotics,[3] we required a wide range of functionalized (S)-2,3-diaminopropanoic acids that could be converted into N,N-dimethylated residues. Several methods for the preparation of (S)-2-amino-3-(dimethylamino)propanoic acid have been published recently. Application of chiral Co(III) complexes with (S)-aspartic acid or (S)-2,3-diaminopropanoic acid[4] has been shown to be a multi-step and tedious preparative method. The ring opening of protected serine β-lactones with N,N-dimethylamine seems to be a convenient and attractive route to optically pure $A_2pr(Me_2)$ derivatives.[5,6,7] However, despite its simplicity, nucleophilic ring opening of Boc- or Z-serine-β-lactone with N,N-dimethylamine under various reaction conditions (THF, acetonitrile and methylene chloride as solvents and temperatures 0° and 20°) resulted in the formation of the corresponding amides in high yield arising from acyl-oxygen cleavage, and traces of products arising from alkyl-oxygen cleavage. Moreover, reaction of N,N-dimethyl-N-(trimethylsilyl)amine with the same β-lactones, in our hands, gave a mixture of both amino acids and amides, the latter only in 37-45% yield respectively. Reductive methylation[8] of protected A_2pr with formaldehyde and sodium cyanoborohydride thus appeared to be the method of choice. Herein, we report a complete description of the preparation of Z-$A_2pr(Me_2)$-OH[9] in high yield and purity.



a) PIDA b) CH_2O,$NaBH_3CN$ c) MeOH/$SOCl_2$ d) NaOH