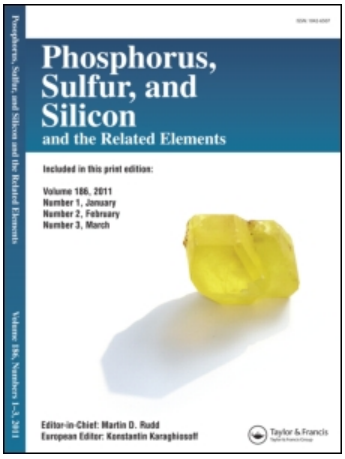

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SYNTHESIS OF NOVEL α-(N-PENTAFLUORO-PHENYLAMINO)BENZYLPHOSPHONATES AND PHOSPHONIC ACIDS

Shizheng Zhu[a]; Bin Xu[a]; Jie Zhang[a]; Chaoyue Qin[a]; Qicheng Huang[b]; Chunxu Qu[b]
[a] Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai, P.R. China [b] Institute of Physical Chemistry, Peking University, Beijing, P.R. China

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SYNTHESIS OF NOVEL α-(N-PENTAFLUORO-PHENYLAMINO)BENZYLPHOSPHONATES AND PHOSPHONIC ACIDS

SHIZHENG ZHU,* BIN XU, JIE ZHANG and CHAOYUE QIN
Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, P.R. China

and

QICHENG HUANG and CHUNXU QU
Institute of Physical Chemistry, Peking University, Beijing 100871, P.R. China

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A series of novel α-(N-pentafluorophenylamino)benzyl phosphonic acids are prepared by hydrolysis of corresponding phosphonates, $C_6F_5NHCH(Ar)P(O)(OR)_2$, which are synthesized from the addition of N-pentafluorophenyl aromatic aldimines with dialkyl phosphite. The X-ray diffraction of $C_6F_5NHCH(4\text{-}CH_3C_6H_4)P(O)(OCH_3)_2$ is presented.

Key words: N-pentafluorophenylamino aromatic aldimine, dialkylphosphite, addition, α-(N-pentafluorophenylamino)benzylphosphonate, X-ray diffraction.

1. INTRODUCTION

The present interest in α-aminophosphonates and their derivatives center around the biological activities and the search for convenient synthesis of these compounds.[1–4] For example, some of α-aminoalkylphosphonic acids have been found to be useful inhibitors of enzymes[5,6] and some of them are used as effective plant growth regulators.[7,8] Skizela has first reported the antitumor activity of N-arylaminomethyl phosphonic acid.[9] Recently two novel α-substituted aminomethyl phosphonates have been synthesized and the bioassay showed that, some of these compounds inhibited the growth of leukemia L_{1210} cell in vitro.[4] The fluorine containing analogues, however, to our best knowledge, has not been reported as yet. During the study on the N-sulfinyl pentafluoroaniline C_6F_5NSO, we have reported its condensation with aromatic aldehydes to give N-pentafluorophenylaromatic aldimines $C_6F_5N{=}CHAr$ (1).[10]

In this paper, we report the synthesis of α-(N-pentafluorophenylamino)benzyl phosphonates (3) and the corresponding phosphonic acids (4) obtained by hydrolysis of compounds (3).

2. RESULTS AND DISCUSSION

Comparing with the moisture sensitive compound N-perfluoroalkanesulfonyl aromatic aldimine $R_fSO_2N{=}CHAr$[11,12] compound (1) is quite stable. For example, stir-

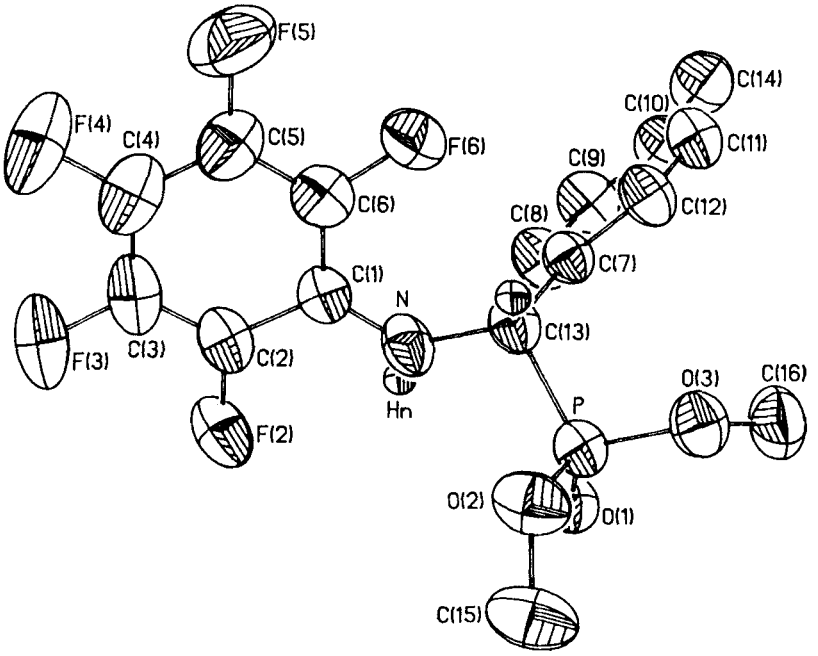
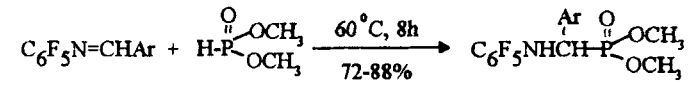


FIGURE 1

ring with water or alcohol at 60°C for 4 h, (1) is unchanged and recovered quantitatively. The addition reaction of dialkylphosphite (2) to the N=C double bond of compound (1), however, occurred smoothly at 60°C and without solvent, thus:



1 2 3

Ar: C_6H_5 a; 4-$CH_3C_6H_4$ b; 4-$CH_3OC_6H_4$ c; 4-ClC_6H_4 d.

Scheme 1

The addition products 3 are colorless solids, recrystallization from CH_3CN—CH_3OH (1:1) gave fine crystal for X-ray structure analysis. The molecular structure of 3b is shown in Fig. 1. The selected bond lengths and bond angles are listed in Table I, while the positioned and thermal parameters are listed in Table II. We have reported the structure of compound 1b[10]; its packing map shows that the pentafluorophenyl plane in one molecule is paralleled and just overlaps with the phenyl planes in the other two molecules; the phenyl plane also lying between the two pentafluorophenyl plane. These alternate overlapped molecules suggest some interaction between the π-electron systems. In the compound 1b there is no extended conjugated system, the phenyl and the pentafluorophenyl planes are not coplanar, the C=N bond length is 1.27 Å. In compound 3b, the phenyl and pentafluorophenyl planes

TABLE I

Selected bond lengths (Å) and angles (°) for compound 3b

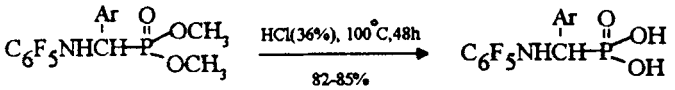
O(1)—P	1.456(3)	O(2)—P	1.571(2)	O(3)—P	1.580(3)
C(13)—P	1.815(3)	C(15)—O(2)	1.421(6)	C(16)—O(3)	1.432(5)
C(8)—C(7)	1.380(5)	C(12)—O(7)	1.381(6)	C(13)—C(7)	1.517(4)
O(9)—C(8)	1.393(6)	C(10)—C(9)	1.371(7)	C(11)—C(10)	1.387(6)
O(14)—C(10)	1.517(6)	C(12)—C(11)	1.397(5)	N—C(13)	1.454(5)
O(1)—N	1.354(4)	C(2)—F(2)	1.342(5)	C(3)—F(3)	1.351(5)
O(4)—F(4)	1.318(5)	C(5)—F(5)	1.343(6)	C(6)—F(6)	1.354(5)
O(2)—C(1)	1.410(5)	C(6)—C(1)	1.379(5)	C(3)—C(2)	1.353(4)
O(4)—C(3)	1.396(7)	C(5)—C(4)	1.373(7)	C(6)—C(5)	1.374(5)
O(2)—P—O(1)	116.2(2)	O(3)—P—O(1)	114.6(1)
O(3)—P—O(2)	102.8(2)	C(13)—P—O(1)	114.5(2)
C(13)—P—O(2)	101.7(1)	C(13)—P—O(3)	105.5(2)
C(15)—O(2)—P	122.2(3)	C(16)—O(3)—P	121.6(4)
C(12)—C(7)—C(8)	119.1(3)	C(13)—C(7)—C(8)	120.8(4)
C(13)—C(7)—C(12)	120.1(3)	C(9)—C(8)—C(7)	119.5(5)
C(10)—C(9)—C(8)	122.5(4)	C(11)—C(10)—C(9)	117.5(3)
C(14)—C(10)—C(9)	120.8(4)	C(14)—C(10)—C(11)	121.7(5)
C(12)—C(11)—C(10)	120.9(4)	C(11)—C(12)—C(7)	120.4(4)
C(7)—C(13)—P	111.0(2)	N—C(13)—P	107.4(3)
N—C(13)—C(7)	115.3(3)	C(1)—N—C(13)	124.5(3)
C(2)—C(1)—N	119.7(3)	C(6)—C(1)—N	126.2(3)
C(6)—C(1)—C(2)	114.1(3)	C(1)—C(2)—F(2)	118.0(3)
C(3)—C(2)—F(2)	118.7(4)	C(3)—C(2)—C(1)	123.3(4)
C(2)—C(3)—F(3)	120.9(4)	C(4)—C(3)—F(3)	118.2(3)
C(4)—C(3)—C(2)	120.9(4)	C(3)—C(4)—F(4)	121.4(5)
C(5)—C(4)—F(4)	121.5(5)	C(5)—C(4)—C(3)	117.0(3)
C(4)—C(5)—F(5)	118.9(3)	C(6)—C(5)—F(5)	119.8(4)
C(6)—C(5)—C(4)	121.2(4)	C(1)—C(6)—F(6)	120.5(3)
C(5)—C(6)—F(6)	116.2(4)	C(5)—C(6)—C(1)	123.3(4)

are not parallel and do not overlap each other. The C—N single bond length is 1.45 Å.

It was noticed that the proton chemical shifts of the two methoxyl groups —$P(OMe)_2$ are different. For example, in compound 3b the signals are at 3.75 and 3.30 ppm respectively and both being doublets ($^3J_{HP}$ = 11 Hz). It is reasonable to consider that the two methoxyl are diastereotopic with respect to the asymmetric carbon atom attached to the phosphorus atom.

Compounds 3 have an unsymmetric carbon atom. It was found that they are a racemic mixture by determining the optical activity ($[\alpha]^{25} = 0$).

Acidic hydrolysis of 3 with concentrated hydrochloric acid (36%) gave the corresponding phosphonic acids 4. The reaction results were summarized in Table III.



3 4

Scheme 2

The biological activities of 3 and 4 are currently being determined.

TABLE II

Positional and thermal parameters with estimated standard deviations for compound 3b

Atom	X/a	Y/b	Z/c	Ueq*
P	0.7213(1)	0.9207(1)	0.0723(1)	0.051(1)
O(1)	0.5660(2)	0.8907(2)	0.1012(2)	0.061(1)
O(2)	0.8502(2)	1.0167(2)	0.1790(2)	0.069(1)
O(3)	0.7626(2)	0.7917(2)	0.0793(2)	0.068(1)
O(7)	0.6906(3)	0.9165(3)	−0.2270(3)	0.051(1)
O(8)	0.5522(4)	0.9120(4)	−0.2932(4)	0.071(2)
O(9)	0.4796(4)	0.8261(4)	−0.4061(4)	0.074(2)
O(10)	0.5400(4)	0.7441(3)	−0.4545(3)	0.059(1)
O(11)	0.6774(4)	0.7472(3)	−0.3850(4)	0.066(2)
O(12)	0.7534(4)	0.3343(3)	−0.2732(4)	0.062(1)
O(13)	0.7726(3)	1.0089(3)	−0.1038(3)	0.051(1)
O(14)	0.4604(7)	0.6567(5)	−0.5821(5)	0.081(3)
O(15)	0.8334(6)	1.0157(6)	0.3295(5)	0.089(3)
O(16)	0.6482(7)	0.6587(4)	0.0565(8)	0.090(3)
N	0.7467(3)	1.1339(2)	−0.1108(3)	0.063(1)
F(2)	0.7380(2)	1.3660(2)	−0.0314(2)	0.082(1)
F(3)	0.9138(3)	1.6146(2)	−0.1395(3)	0.102(1)
F(4)	1.1175(3)	1.6405(2)	−0.3306(3)	0.118(2)
F(5)	1.1368(3)	1.4143(3)	−0.4145(3)	0.113(2)
F(6)	0.9528(2)	1.1687(2)	−0.3236(2)	0.081(1)
O(1)	0.8399(3)	1.2557(2)	−0.1685(3)	0.050(1)
O(2)	0.8352(3)	1.3766(3)	−0.1280(3)	0.061(1)
O(3)	0.9245(4)	1.5021(3)	−0.1805(4)	0.074(2)
O(4)	1.0312(4)	1.5188(4)	−0.2774(5)	0.081(2)
O(5)	1.0382(4)	1.4028(4)	−0.3188(4)	0.074(2)
O(6)	0.9428(3)	1.2760(3)	−0.2682(3)	0.064(1)

*Ueq = $1/3(U_{11}h^2a^{*2} + U_{22}k^2b^{*2} + U_{33}l^2c^{*2} + 2U_{33}klb^*c^* + 2U_{13}lhc^*a^* + 2U_{12}hka^*b^*)$.

TABLE III

Compounds 3 and 4 prepared

Products	Ar	Mp. (°C)	Yields (%)*
3a	C_6H_5	96–98	81
3b	4-$CH_3C_6H_4$	103–104	83
3c	4-$CH_3OC_6H_4$	98–100	88
3d	4-ClC_6H_4	97–99	72
4a	C_6H_5	114–117	85
4b	4-$CH_3C_6H_4$	110–112	82

*Isolated yields based on 1 or 3.

EXPERIMENTAL

Mp. were measured on a Thiele apparatus and reported uncorrected. Solvents were purified and dried highly before use. ^1H NMR (60 MHz) and ^{19}F NMR (54.6 MHz) spectra were recorded on a Varian-360L instrument with TMS and TFA ($\delta_{CFCl3} = \delta_{TFA} + 77.8$, and with the downfield as positive) as an internal and external standard, respectively. ^{31}P NMR (300 MHz) spectra were recorded on a Bruker AM-300 instrument using H_3PO_4 (85%) as external standard. Elemental analyses were performed by this Institute. IR spectra were obtained with an IR-440 Shimadzu spectrophotometer. Lower resolution mass spectra were obtained on a Finnigan GC-MS 4021 instrument.

Preparation of C_6F_5 NHCH(Ar)P(O)$(OCH_3)_2$ 3a–d

A solution of 1a (1.36 g, 5.0 mmol), dimethyl phosphite (0.55 g, 5.0 mmol) and 5 mL of dry benzene in a 10 mL flask was stirred for 8 h at 80°C. The reaction mixture was checked by IR. The C=N double bond (1630 cm^{-1}) disappeared. After removal of the solvent, the residue was poured into 6 mL

of CH_3CN. The crude product 3a crystallized out after two days in the refrigerator. Recrystallization from CH_2Cl_2—CH_3CN gave pure products. 3c–d were prepared similarly. The melting points and the yields of 3 are given in Table III.

Compound 3a: IR (KBr, ν, cm^{-1}): 3385, 3290 (m, NH), 3075 (w, C_6H_5), 2982, 2885 (m, OCH_3), 1523 (s, C_6H_5, C_6F_5), 1250 (s, P=O), 1070 (m, P—O—C), 1023 (s, C—F). ^1H NMR (δ, ppm): 7.35 (m, C_6H_5), 4.53 (d, CH, $^2J_{HP}$ = 24 Hz), 3.93 (s, NH), 3.83 (d, $POCH_3$, $^3J_{HP}$ = 10.5 Hz), 3.40 (d, $POCH_3$, $^3J_{HP}$ = 10.5 Hz). ^{19}F NMR (δ, ppm): 79.3 (m, 2F), 85.8 (m, 2F), 89.8 (m, 1F). MS (EI, m/z, %): 382 (M^+H. 0.7), 381 (M^+, 1.5), 272 (M^+-P(O)$(OCH_3)_2$, 42.1), 182 ($C_6F_5NH^+$, 1.7), 77 ($C_6H_5^+$, 100.0).

Analysis: calcd. for $C_{15}H_{13}F_5NO_3P$: C 47.24, H 3.41, N 3.67%; Found: C 46.89, H 3.67, N 3.45%.

Compound 3b: IR (KBr, ν, cm^{-1}): 3390, 3286 (m, NH), 3066 (w, C_6H_5), 2980, 2880 (m, CH_3), 1522 (s, C_6H_5, C_6F_5), 1240 (s, P=O), 1070 (m, P—O—C), 1020 (s, C—F). ^1H NMR (δ, ppm): 7.06 (m, C_6H_4), 4.80 (d, CH, $^2J_{HP}$ = 24 Hz), 4.03 (s, NH), 3.76 (d, $POCH_3$, $^3J_{HP}$ = 10.5 Hz), 3.26 (d, $POCH_3$, $^3J_{HP}$ = 10.5 Hz), 2.20 (s, CH_3). ^{19}F NMR (δ, ppm): 79.0 (m, 2F), 86.3 (m, 2F), 90.5 (m, 1F). ^{31}P NMR (δ, ppm): 25.0 (s). MS (EI, m/z, %): 395 (M^+, 1.0), 286 (M^+-P(O)$(OCH_3)_2$, 100.0), 167 ($C_6F_5^+$, 3.8).

Analysis: calcd. for $C_{16}H_{15}F_5NO_3P$: C 48.61, H 3.80, N 3.54%; Found: C 48.28, H 4.10, N 3.44%.

Compound 3c: IR (KBr, ν, cm^{-1}): 3385, 3290 (m, NH), 3066 (m, C_6H_5), 1605, 1520 (s, C_6H_4, C_6F_5), 1250 (s, P=O), 1050 (m, P—O—C), 1022 (s, C—F). ^1H NMR (δ, ppm): 7.10–8.03 (AA'BB', C_6H_4), 4.33 (d, CH, $^2J_{HP}$ = 24 Hz), 3.90 (s, OCH_3), 3.76 (s, NH), 3.80 (d, $POCH_3$, $^3J_{HP}$ = 10.5 Hz), 3.30 (d, $POCH_3$, $^3J_{HP}$ = 10.5 Hz),). ^{19}F NMR (δ, ppm): 78.6 (m, 2F), 85.3 (m, 2F), 89.3 (m, 1F). MS (EI, m/z, %): 411 (M^+, 1.3), 302 (M^+-P(O)$(OCH_3)_2$, 100.0), 167 ($C_6F_5^+$, 3.4).

Analysis: calcd. for $C_{16}H_{15}F_5NO_4P$: C 46.72, H 3.65, N 3.41%; Found: C 46.31, H 3.92, N 3.24%.

Compound 3d: IR (KBr, ν, cm^{-1}): 3385, 3290 (m, NH), 3070 (w, C_6H_4Cl), 2985, 2870 (m, CH_3), 1520 (s, C_6H_4Cl, C_6F_5), 1235 (s, P=O), 1070 (m, P—O—C), 1025 (s, C—F). ^1H NMR (δ, ppm): 7.30–7.86 (AA'BB', C_6H_4Cl), 4.50 (d, CH, $^2J_{HP}$ = 24 Hz), 3.86 (s, NH), 3.80 (d, $POCH_3$, $^3J_{HP}$ = 11 Hz), 3.36 (d, $POCH_3$, $^3J_{HP}$ = 11 Hz). ^{19}F NMR (δ, ppm): 79.0 (m, 2F), 86.0 (m, 2F), 89.6 (m, 1F). MS (EI, m/z, %): 417/415 (M^+, 0.4/1.1), 308/306 (M^+-P(O)$(OCH_3)_2$, 14.2/48.0), 194 ($C_6F_5NCH^+$, 13.2), 167 ($C_6F_5^+$, 3.4).

Analysis: calcd. for $C_{15}H_{12}ClF_5NO_3P$: C 43.32, H 2.89, N 3.37%; Found: C 43.02, H 3.10, N 3.43%.

Hydrolysis of Compounds 3

A solution of 3a (1.0 g, 2.6 mmol) and concentrated hydrochloric acid (36%, 2 mL) in a 10 mL flask was refluxed for 48 h. The reaction mixture was extracted by ether (5 mL × 3). The organic layers combined and the crude product 4a were solidified after two days in the atmosphere. The phosphonic acid 4b was similarly prepared.

Compound 4a: IR (KBr, ν, cm^{-1}): 3500–3020 (vs, NH, OH), 1520 (s, C_6H_5, C_6F_5), 1195 (s, P=O), 1027 (s, C—F). ^1H NMR (δ, D_2O, $(CD_3)_2CO$, ppm): 7.33 (m, C_6H_5), 5.00 (d, CH, $^2J_{HP}$ = 14 Hz). ^{19}F NMR (δ, ppm): 79.5 (m, 2F), 85.6 (m, 2F), 89.6 (m, 1F). MS (EI, m/z, %): 354 (M^+H, 23.1), 353 (M^+, 1.4), 272 (M^+-PO_3H_2, 42.1), 77 ($C_6H_5^+$, 100.0).

Compound 4b: IR (KBr, ν, cm^{-1}): 3500–3020 (vs, NH, OH), 1520 (s, C_6H_5, C_6H_5), 1200 (s, P=O), 1025 (s, C—F). ^1H NMR (δ, ppm): 7.63–6.93 (AA'BB', C_6H_4), 5.03 (d, CH, $^2J_{HP}$ = 14 Hz), 2.30 (s, CH_3). ^{19}F NMR (δ, ppm): 79.0 (m, 2F), 86.0 (m, 2F), 90.0 (m, 1F). ^{31}P NMR (δ, ppm): 21.0. MS (EI, m/z, %): 368 (M^+H, 3.6), 367 (M^+, 0.9), 286 (M^+-PO_3H_2, 100.0), 167 ($C_6F_5^+$, 14.1), 91 ($MeC_6H_4^+$, 12.0).

Crystal Structure Analysis

$C_{16}H_{15}F_5O_3NP$: M = 395.3, triclinic, space group P1, a = 9.65(5), b = 10.74(6), c = 9.25(7) Å, b = 91.90(3)°, α = 83.67(6)°, β = 97.40(6)°, γ = 113.57(4)°, V = 870.0(9) $Å^3$, Z = 2, D_c = 1.50 g/cm^3. F(000) = 404.0. λ = 1.5418 A, μ(CuKα) = 2.04 mm^{-1}, Crystal dimension 0.3 × 0.3 × 0.6 mm. Intensity data were collected at 22°C with a Rigaku AFC-5R diffractometer using CuKα radiation and employing $\omega/2\theta$ scanning technique. Cell parameters determined from 25 reflections with $2\theta_{max}$ = 122°, $0 < h < 10$, $-12 < k < 12$, $-10 < l < 10$. Two standard reflections were monitored after every 100 reflections, but no significant variation in their intensities was found. The structure was determined by a direct method. All non-H atoms were positioned and anisotropic thermal parameters refined from 2240 observed reflections with $F > 3.92\ \sigma(F)$ by a block-matrix least squares technique to R = 0.067 and R_w = 0.072 ($w = [\sigma^2(F^2)$

+ 0.001 $(F^2)]^{-1}$. The calculations were performed on a SGI IRIS 4D/70 and a Micro-VAX II computer with SHELXS-76 and SHELXS-86 programs. Atomic scattering factors were taken from International Tables for X-ray Crystallography (1974, Vol. IV).

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REFERENCES

1. C.-Y. Yuan and G.-H. Wang, *Synthesis*, 256 (1990).
2. S.-Z. Zhu and X.-L. Jin, *J. Fluorine Chem.*, **72,** 19 (1995).
3. W. F. Gilmore and H. A. McBride, *J. Am. Chem. Soc.*, **94,** 4361 (1972).
4. R.-Y. Chen and L.-J. Mao, *Phosphorus, Sulfur, and Silicon*, **89,** 97 (1994).
5. E. Neuzil and A. Cassaigne, *Exp. Ann. Biochem. Med.*, **34,** 165 (1980).
6. B. Dhawan and D. Redmore, *Phosphorus and Sulfur*, **32,** 119 (1987).
7. A. L. Paul, *et al.*, *J. Am. Chem. Soc.*, **106,** 4282 (1984).
8. A. N. Pudovik, *Dokl. Akad, Nauk SSSR*, **92,** 773 (1953).
9. B. Wysocka-Skizela, *Polish. J. Chem.*, **56,** 1573 (1982).
10. A.-W. Li, S.-Z. Zhu, Q.-C. Huang and J.-S. Liu, *J. Fluorine Chem.*, **68,** 145 (1994).
11. S.-Z. Zhu, Q.-Y. Chen, *J. Chem. Soc. Chem. Commu.*, 732 (1991).
12. S.-Z. Zhu, A.-W. Li and Y.-H. Zhu, *J. Fluorine Chem.*, **60,** 283 (1993).