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Synthesis and HPLC resolution of isomers of novel phosphorus fluorinated 2,4,6-trimethylphenylazo pyridines

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ABSTRACT

New compounds of phosphorus fluorinated 2,4,6-trimethylphenylazo pyridines (4a-c) have been synthesized in high yields via adding *n*-butyl lithium in hexane to a stirred solution of methyldiphenylphosphine oxide in dry THF at 0 °C, then cooled to around -78 °C, treated with azo-pyridines(2a-c) and then allowed to warm at room temperature over 2 h. The isomers of (*E*)-((5-chloro-3,6-difuoro-4-(mesityldiazenyl)pyridin-2-yl)methyl)diphenyl phosphine oxide (4b) and (*E*)-((3,6-difuoro-4-(mesityldiazenyl)5-methoxypyridin-2-yl)methyl)diphenyl phosphine oxide (4c) can be separated on analytical HPLC: Chiralcel OD-H column, hexane:2-PrOH, (9:1, *v*:*v*) mobile phase, flow-rate, 1.0 mL/min, 25 °C, λ = 254 nm and polarimetric detection, 20 µL injection volume. The resolution of this isomers were 2.12, 1.84, respectively.

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1. Introduction

The fluorinated organic phosphorus is a heterogeneous class of products widely used for the treatment of a number of cardiovascular diseases, including congestive heart failure and coronary heart disease. A combination of fluorinated and diphenylphosphinoyl groups in azo-compounds will hopefully make them very interesting biological active compounds. Since phosphorus substituents regulate important biological functions [1-3] and fluorine containing compounds play important role in organic synthesis and in medicinal chemistry [4-10].

Since the literature contains little or no information on phosphorus fluorinated azo type (Figure 1), in this article, we describe the synthesis, isolation of the novel isomers of the phosphorus fluorinated 2,4,6-trimethylphenylazo pyridines obtained by introducing a diphenylphosphinium ring on the terminal fluorine group of azo-pyridines (**2a-c**) (Scheme 1) [11]. The resulting of this reaction gave the structural isomers of phosphorus fluorinated azo, HPLC will be used to separate the structural isomers.

2. Experimental

2.1. Instrumentation

Melting points were determined with a capillary apparatus (Büchi 540) and are uncorrected. IR spectra were obtained with a Perkin-Elmer 983 G spectrometer on KBr disks. ^{1}H NMR spectra were run on a Bruker AC 300 spectrometer, ^{1}H NMR spectra was recorded using $CHCl_3$ as internal standard. ^{19}F spectra, chemical shifts were measured relative to trifluoro-acetic acid (TFA) as an external interchange reference unless otherwise stated. Fast atom bombardment (FAB) spectra were recorded on a Kratos MS 50, using a *meta*-nitrobenzyl alcohol matrix.

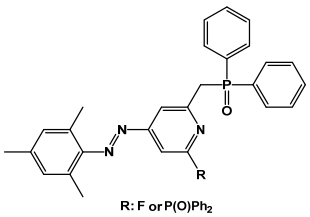

Figure 1. The structure chemical of phosphorus fluorinatedazo.

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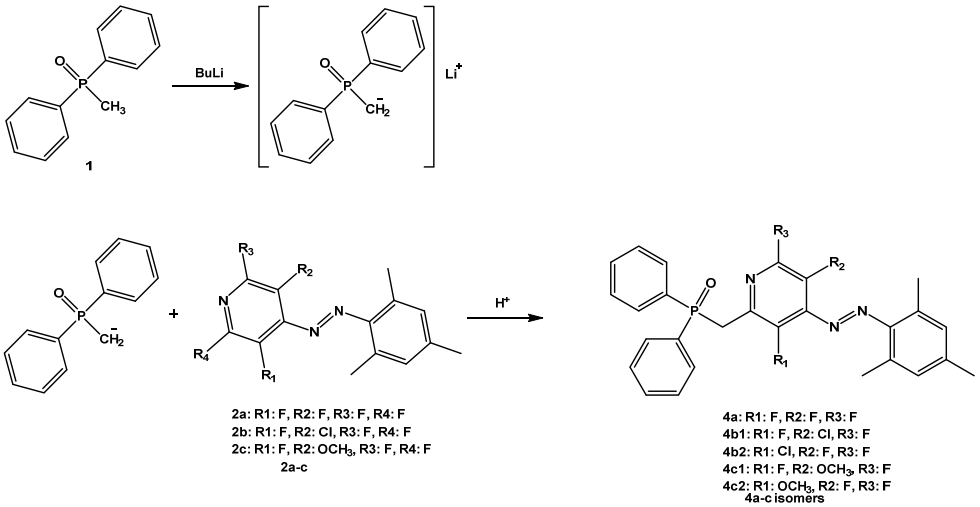

Scheme 1

Desorption chemical ionization (DCI) of the isomers (4a-c) were obtained with a Finnigan-Mat 8400 spectrometer using *iso*-butane as reacting gas. Flash column chromato-graphy was performed on silica gel (Merck Kieselgel 60, 230-400 mesh ASTM) using the indicated eluents. Petroleumether 40-60 °C (PE) was used as eluent. The progress of the reactions was followed by thin-layer chromatography (TLC) on 5×3×20 cm plates with a layer thickness of 0.25 mm. When necessary, they were developed with diphenylamine reagent. Anhydrous magnesium sulfate was used as a drying agent for the organic phases. Organic solvents were removed under vacuum at room temperature. Column chromatography was conducted using silica gel, pore size 60 Å, 230-400 mesh particle size (Merck & Co).Thin layer chromatography (TLC) was conducted on pre-coated aluminum sheets ($60F_{254}$) with a 0.2 mm thickness (Aldrich Chemical Co.). Elemental analysis of the target compounds was performed by REDOX (Monza) and the results are represented in full. Analytical isomers HPLC experiments on Chiralcel OD-H column (250×4.6 mm, 5 µm) (Daicel Co., Tokyo) were performed with LaChrom1 (Merck) screening unit equipped with an L-7100 pump, an L-7200 autosampler, an L-7360 oven which accommodates 12 columns alimented by a Valco positions valve, an L-7400 UV detector, and a Jasco OR-1590 polarimeter detector. Analyses were performed at 1 mL/min, at a controlled temperature (25 °C) with UV (254 nm) and polarimetric detection. Retention times (R_t) in minutes, retention factor $k_i = (R_{ti}-R_{t0})/R_{t0}$ and enantio selectivity factor $\alpha = k_2/k_1$ are given. Semi preparative separations were performed with a Merck-Hitachi LiChrograph Model L-6000 HPLC pump, and a Merck-Hitachi LiChrograph L-4000 UV detector (254 nm). For semi-preparative separations, a Chiralcel OD (250×10 mm, 10 µm) was used. The solvents were HPLC grade from SDS (Peypin, France) and were filtered on a Millipore membrane of 0.45µm and degassed before use. The optical rotations were measured on a 241 MC Perkin-Elmer polarimeter with a sodium lamp and a double-jacketed cell at 25 °C. All reagents were commercially available.

2.2. Synthesis of phosphorus fluorinated 2,4,6-trimethyl phenylazopyridine (4a-c)

2.2.1. Synthesis of (E)-diphenyl((3,5,6-trifuoro-4-(mesityl diazenyl)pyridin-2-yl)methyl)phosphine oxide (4a)

A dry 500 mL flask equipped with a magnetic stirring bar was charged with 6.0 g (27.6 mmol) of methyldiphenyl phosphine oxide, capped with a rubber septum, and flushed with nitrogen. Anhydrous tetrahydrofuran (175 mL) was then added to the flask via cannula, and the resulting solution cooled in an ice bath to 0 °C. A solution of *n*-butyllithium in hexane (11.04 mL, 27.6 mmol, 2.5 M) was added dropwise via a syringe over a 5 min period. The solution turned deep red. The resulting red solution was stirred for 30 min at 0 °C, then cooled to around -78 °C in an acetone-solid carbon dioxide cooling bath. Fresh solution compound **2a** (8.2 g, 27.6 mmol) was added in one portion by syringe. After the addition was complete, the red color of the anion had disappeared. The resulting pale yellow solution was stirred for 15 min at -78 °C, then allowed to warm to ambient temperature over 2 hrs. Water (40 mL) was added and the bulk of the tetrahydrofuran and hexane removed on a rotary evaporator (Bath temp.: 25-30 °C). Brine and dilute hydrochloric acid (200 mL) was added to the aqueous residue and extracted with dichloromethane (3 × 100 mL). The combined organic extracts were dried over magnesium sulfate and evaporated to dryness under reduced pressure on a rotavapor, and the residue, light yellow oil, was placed in a refrigerator overnight to crystallize. The resulting solid was recrystallized from ethylacetate to give compound **4a** (Scheme 1). Yield: 81%. Color: White. M.p.: 167-169 °C. FT-IR (KBr, ν, cm^{-1}): 1650-1565 (N=N), 1260-1454 (Ar-F), 1049 (P=O). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 2.52 (s, 3H, 4-CH_3), 2.32 (s, 6H, 2,6-CH_3), 3.33 (s, 2H, CH_2PO), 6.89 (s, 2H, Ar-H), 7.05 (m, 10H, Ar-H). MS (FAB, *m/z* (%)): 493 (M^++1, 100), 374 ($C_{18}H_{12}F_3PON_3^+$, 40), 292 (80.1), 278 (10.2), 215 (6.2), 201 (20), 119 (60). Anal. calcd. for $C_{27}H_{23}ON_3F_3P$: C, 65.72; H, 4.70; N, 8.52. Found: C, 65.80; H, 4.80; N, 8.50%.

2.2.2. Synthesis of (E)-((5-chloro-3,6-difuoro-4-(mesityl diazenyl)pyridin-2-yl)methyl)diphenyl phosphine oxide (4b) isomers

Compound **4b** was prepared from methyldiphenyl phosphine oxide (6.0 g, 27.6 mmol), and compound **2b** (8.65 g, 27.6 mmol) in a similar way to compound **4a**. Work-up of the reaction product gave a white crystalline solid of compound **4b** isomers (Scheme 1). Yield: 76%. Color: White. FT-IR (KBr, ν, cm^{-1}): 1600-1565 (N=N), 1436 (Ar-F), 1250-1070 (Ar-Cl), 1181 (P=O). ^{19}F NMR (54.6 MHz, $CDCl_3$, δ, ppm): -84.3 (1F, d, *J* = 25.6.6 Hz, F-5), -14.5 (1F, d, *J* = 25.6 Hz, F-2). MS (FAB, *m/z* (%)): 474 (M^++ 1-Cl, 100), 215 (6.0), 201 (20), 147 (17), 119

(60). Anal. calcd. for $C_{27}H_{23}ON_3F_2ClP$: C, 63.60; H, 4.55; N, 8.24. Found: C, 63.70; H, 4.50; N, 8.20 %.

Isomers purities (**4b$_1$**, **4b$_2$**) were assessed on analytical HPLC: Chiralcel OD-H column, hexane:2-PrOH, 9:1, *v*:*v* mobile phase, flow-rate 1.0 mL/min, 25 °C, λ = 254 nm and polarimetric detection, 20 µL injection volume (first eluted peak: k = 2.01; second peak: k = 2.36), α = 1.18, *R*s = 2.12.

2.2.3. Synthesis of (E)-((3,6-difluoro-4-(mesityldiazenyl)-5-methoxypyridin-2-yl)methyl)diphenyl phosphine oxide (4c) isomers

Compound **4c** was prepared from methyldiphenyl phosphine oxide (1.0 g, 4.6 mmol), and compound **2c** (0.5 g, 1.61 mmol) in a similar way to compound **4a**. The white solid resulted was recrystallized from ethyl acetate to give a solid of compound **4c** isomers (Scheme 1). Yield: 89%. Color: White. FT-IR (KBr, ν, cm^{-1}): 1600 (N=N), 1436 (Ar-F), 1173 (P=O), 1203-1277 (C-O asym. stretch), 1042 (C-O sym. stretch). ^{19}F NMR (54.6 MHz, $CDCl_3$, δ, ppm): -82.5 (1F, d, *J* = 25.3 Hz, F-5), -11.2 (1F, *d*, *J* = 25.3 Hz, F-2). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 2.30 (s, 6H, 2,6-CH_3), 2.45 (s, 3H, 4-CH_3), 3.32 (s, 2H, CH_2PO), 3.95 (s, 3H, O-CH_3), 6.85 (s, 2H, Ha), 7.02 (m, 10H, Ha). MS (FAB, *m/z* (%)): 490 (M^++1-Me, 100), 304 (78.5), 290 (18.5), 215 (6.0), 201 (22), 147 (18), 119 (63). Anal. calcd. for $C_{28}H_{26}O_2N_3F_2P$: C, 66.53; H, 5.18; N, 8.31. Found: C, 66.70; H, 5.10; N, 8.30 %.

The composition isomers **4c$_1$** and **4c$_2$** were assessed on analytical HPLC: Chiralcel OD-H column, hexane:2-PrOH, 9:1, *v*:*v* mobile phase, flow-rate 1.0 mL/min, 25 °C, λ = 254 nm and polarimetric detection, 20 µL injection volume (first eluted peak: k = 3.25; second peak: k = 3.65), α = 1.12, *R*s =1.84.

2.3. Single crystal structure determination

In order to establish the absolute configuration of the newly created isomers, the structure of the major product of compound **4b** and **4c** were elucidated by X-ray single crystal diffraction analysis (Figure 2-5).

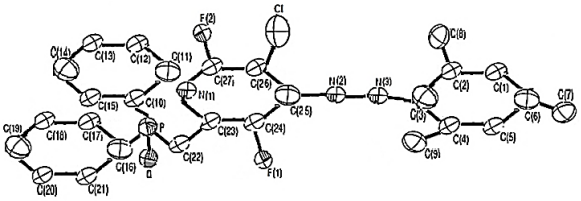

Figure 2. Molecular structure of compound **4b$_1$**.

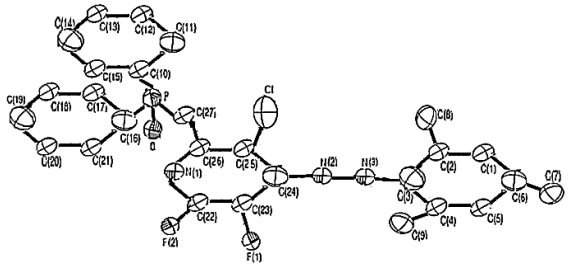

Figure 3. Molecular structure of compound **4b$_2$**.

The crystals used for the X-ray single crystal diffraction study were grown by routine recrystallization from acetonitrile and ethyl acetate for compound **4b** and **4c**, respectively. The crystal data are given in Table 1. The unit cell dimensions were determined by least-squares using 25 for compound **4b** and 15 for compound **4c** centered reflections using graphite monochromated Cu-Kα radiation. Data were corrected for Lorentz and polarization effects. A correction for secondary extinction was applied (coefficient = 0.53319×10^{-5} for **4b**, 0.878954×10^{-5} for compound **4c**). The structures for compound **4b** and **4c** were solved by direct methods. The non-hydrogen atoms (for compound **4b** and **4c**) were refined anisotropically. All other hydrogens were located on difference Fourier maps and were refined isotropically. The molecule of compound **4c** crystallizes with the solvent ethyl acetate in the proportion 2:1. The ethyl acetate molecule is disordered over two orientations about the two-fold axis. Each orientation corresponds to 50% occupancy. No atoms are on the axis but the methylene and carbonyl carbons are close. The carbonyl carbon was refined isotropically because of its proximity to the two-fold axis. Hydrogen atoms in the solvent molecule were not included in the model.

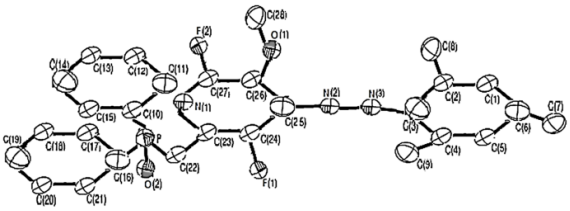

Figure 4. Molecular structure of compound **4c$_1$**.

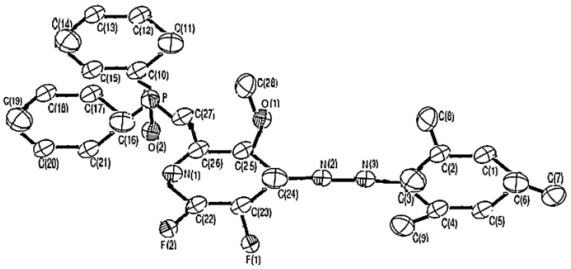

Figure 5. Molecular structure of compound **4c$_2$**.

Table 1. Crystal data of compound **4b** and **4c**.

Parameters	4b	4c
Chemical formula	$C_{27}H_{23}ON_3F_2ClP$	$C_{28}H_{26}O_2N_3F_2P$
Crystal system	Orthorhombic	Orthorhombic
Cell dimension, Å	*a* = 9.940(2)	*a* = 12.773(2)
	b = 25.077(7)	*b* = 6.694(3)
	c = 7.654(2)	*c* = 11.890(2)
Cell volume, Å^3	1907.7(3)	1006.1(5)
Space group	*P*2/*c* (no. 13)	*P*21/*c* (no. 14)
Z	4	4
ρ(calc.), g/cm^{-3}	1.13	1.11
µ, cm^{-1}	2.0	1.7

3. Results and discussion

Phosphorus fluorinated 2,4,6-trimethylphenylazo pyridines (**4a-c**) were synthesized according to the procedures reported in Scheme 1. The general procedure involves drop wise addition of an equimolar quantity of a solution of *n*-BuLi in hexane to a stirred solution of methyldiphenylphosphine oxide in dry THF at 0 °C, then cooled to around -78 °C. Fresh solution azo-pyridines (**2a-c**) [11] was added in one portion. After the addition was complete, the red color of the anion had disappeared. The resulting pale yellow solution was stirred for 15 min at -78 °C, then allowed to warm to ambient temperature over 2 h. Work-up of the reaction product gave the corresponding phosphorus fluorinated compound **4a-c** in high yields ranging from 76 to 89% after purification by column chromatography.

The obtained products were identified by elemental analysis and spectral data.

Table 2. Selected bond lengths (Å).

Compound 4b$_1$					
C(26)-C(27)	1.3401(6)	C(22)-C(23)	1.5090(16)	P-C(10)	1.8560(17)
C(24)-C(25)	1.3340(8)	C(23)-N(1)	1.2600(10)	P-C(16)	1.8560(17)
C(2)-C(8)	1.4970(24)	C(27)-N(1)	1. 2600(7)	P-C(22)	1.8560(15)
C(4)-C(9)	1.4970(23)	C(24)-F(1)	1.3920(2)	C(3)-N(3)	1.3430(4)
C(6)-C(7)	1.4970(23)	C(27)-F(2)	1.3920(9)	C(25)-N(2)	1.3430(3)
Compound 4b$_2$					
C(26)-C(27)	1.5090(28)	C(22)-C(23)	1.3340(30)	P-C(10)	1.8560(25)
C(24)-C(25)	1.3340(32)	C(22)-N(1)	1.2600(36)	P-C(16)	1.8560(17)
C(2)-C(8)	1.4970(21)	C(26)-N(1)	1.2600(36)	P-C(27)	1.8560(19)
C(4)-C(9)	1.4970(21)	C(22)-F(2)	1.3920(30)	C(3)-N(3)	1.2600(36)
C(6)-C(7)	1.4970(22)	C(23)-F(1)	1.3920(33)	C(24)-N(2)	1.2600(29)
Compound 4c$_1$					
C(26)-C(27)	1.4170(36)	C(22)-C(23)	1.5090(25)	P-C(10)	1.8560(24)
C(24)-C(25)	1.4170(36)	O(1)-C(28)	1.5090(36)	P-C(16)	1.8560(16)
C(2)-C(8)	1.4970(24)	C(26)-O(1)	1.4912(33)	P-C(22)	1.8560(15)
C(4)-C(9)	1.4970(23)	C(24)-F(1)	1.3920(17)	C(3)-N(3)	1.4170(33)
C(6)-C(7)	1.4970(23)	C(27)-F(2)	1.3920(19)	C(25)-N(2)	1.4170(28)
Compound 4c$_2$					
C(22)-C(23)	1.4200(15)	C(25)-C(26)	1.4200(13)	P-C(10)	1.8560(11)
C(26)-C(27)	1.4200(16)	O(1)-C(28)	1.3960(19)	P-C(16)	1.8560(16)
C(2)-C(8)	1.4970(14)	C(25)-O(1)	1.3550(21)	P-C(27)	1.8560(13)
C(4)-C(9)	1.4970(14)	C(22)-F(2)	1.3920(17)	C(3)-N(3)	1.4560(10)
C(6)-C(7)	1.4970(14)	C(23)-F(1)	1.3920(19)	C(24)-N(2)	1.4560(13)

Table 3. Selected bond angles (°).

Compound 4b$_1$			
C(10)-P-C(16)	109.5200(11)	C(8)-C(2)-C(3)	121.4000(12)
P-C(22)-C(23)	109.4618(11)	C(9)-C(4)-C(3)	121.4000(12)
F(1)-C(24)-(23)	120.0000(16)	C(24)-C(25)-C(26)	114.5118(14)
F(1)-C(24)-(25)	120.0000(16)	Cl-C(26)-C(27)	122.7441(18)
F(2)-C(27)-N(1)	117.2559(16)	Cl-C(26)-C(25)	122.7441(18)
Compound 4b$_2$			
C(10)-P-C(16)	109.5200(10)	C(8)-C(2)-C(3)	121.4000(12)
P-C(27)- C(26)	109.4618(10)	C(9)-C(4)-C(3)	121.4000(12)
F(1)-C(23)-C(22)	115.0000(10)	C(24)-C(25)-C(26)	117.2559(12)
F(1)-C(23)-C(24)	120.0000(16)	Cl-C(25)-C(26)	122.7441(18)
F(2)-C(22)-N(1)	116.5000(11)	Cl--C(25)-C(24)	122.7441(18)
Compound 4c$_1$			
C(10)-P-C(16)	109.4618(10)	C(8)-C(2)-C(3)	121.4000(12)
C(10)-P-C(22)	109.5200(17)	C(9)-C(4)-C(3)	121.4000(12)
F(1)-C(24)-C(23)	120.0000(16)	C(24)-C(25)-C(26)	120.0000(11)
F(1)-C(24)-C(25)	120.0000(14)	C(24)-C(25)-N(2)	117.2559(10)
F(2)-C(27)-N(1)	120.0000(14)	C(26)-C(27)-N(1)	125.4882(17)
Compound 4c$_2$			
C(10)-P-C(16)	109.5200(10)	C(8)-C(2)-C(3)	121.4000(12)
C(10)-P-C(27)	109.5000(10)	C(9)-C(4)-C(3)	121.4000(12)
F(1)-C(23)-C(24)	120.0000(16)	C(25)-C(26)-C(27)	121.4000(12)
F(1)-C(23)-C(22)	115.0000(10)	C(23)-C(22)-N(1)	120.0000(12)
F(2)-C(22)-N(1)	116.5000(11)	C(27)-C(26)-N(1)	125.4882(20)

The IR spectrum of the compounds showed characteristic P=O stretching at frequency in the region (1040-1180 cm^{-1}). The proton coupled ^{1}H NMR of compound **4b** and **4c** showed a singly centered at δ 3.33 and 3.32 ppm corresponding to the CH_2 group. The mass spectrum of compound **4a**, **4b** and **4c** showed the base peaks at *m/z* 493, 474 and 490, respectively, and clearly showed the presence of $(Ph)_2P=O$ and C_9H_{11} in the chemical structure.

Crystallization of compound **4a** from ethylacetate gave single crystals in 81% yield. Thus, attack by nucleophilic at the position 2 (or 6) has a faster rate than that at the 3- (or 5-) position. The preferential substitution at the 2- or 6-position because the result was by attained the essence compound. The substitution in these positions was preferred comparison with the 3- or 5-position because they offered a stable position (Scheme 1).

We have succeeded in achieving the nucleophilic aromatic substitution of the fluoro group in compound **2b** with $(Ph)_2$-$POCH_2$- anion at 2- and 6-position, thus obtaining compound **4b** isomers. The substitution at the 2- or 6-positionin exchange for the 5-position because they are crowd in this position.

Compound **4b** and **4c** were resolved into the corresponding isomers (Scheme 1) by chiral chromatography using a Chiralcel OD column in a high degree of optical purity. These separations were amenable to semi-preparative scale. Special care was taken during all the semi preparative experiments and the isolated isomers were kept covered by the solvent of elution during the concentration step to minimize the explosive hazard. However, as the alcohol, propan-2-ol, decreased, there solutions (R_s) was all steadily increased, suggesting that the polar interaction (mainly hydrogen-bonding interaction) between solute and stationary phase was not only the primary factor for solute retention but also playing some roles in isomeric recognition.

The phosphorus and fluorinated azo compounds **4b$_1$** (M.p.: 194-196 °C) was identified by elemental analysis and spectroscopic methods. The ^{1}H NMR spectrum showed four absorptions. The ^{19}F NMR spectrum showed two doublet absorption bands of equal intensity at δ -14.5(F2) and -84.3 (F5) ppm which suggests that the $(Ph)_2$-$POCH_2$- group lies in position 6 not 2, the X-ray single crystal diffraction analysis showed that the conformation of this bond (Figure 2). The bond distances and bond angles are given in Table 2 and 3. The mass spectrum of compound **4b$_1$** showed a molecular ion at *m/z* 119 and 201 clearly showed the presence of C_9H_{11} and $(Ph)_2$-P=O in the chemical structure and a base peak at *m/z* 474.

The other novel isomer compound **4b$_2$** (M.p.: 190-192 °C) was also identified by elemental analysis and spectroscopically. The IR, ^{1}H NMR and the mass spectrum were very

similar to that of compound **4b$_1$**. It's ^{19}F NMR spectrum showed two doublets absorptions of equal intensity at δ -9.4 and -79.0 ppm, which suggests that the $(Ph)_2$-$POCH_2$ group lies in position 2 not 6, the new structure of compound **4b$_2$** present in Figure 3 was elucidated by single crystal X-ray diffraction analysis. The bond distances and bond angles are listed in Table 2 and 3.

Isomers **4c** was separated by on analytical HPLC to give compound **4c$_1$** and **4c$_2$** (Scheme 1). The structure of compound **4c$_1$** and **4c$_2$** presented in Figure 4 and 5 was elucidated by single crystal X-ray diffraction analysis and reveals new carbon atom bonded together, C(25)-C(26) for compound **4c$_1$**, new carbon atom C(22)-C(23) for compound **4c$_2$** for compound and the distance between them (Table 2).

The novel phosphorus and fluorinated azo compounds **4c$_1$** (M.p.: 202-204 °C) possessed satisfactory elemental composition. It's ^{1}H NMR spectrum showed four absorption bands The ^{19}F NMR spectrum showed two doublets absorptions bands of intensity -11.2 and -82.5 ppm which clearly the position of $(Ph)_2$-$POCH_2$ group the mass spectrum showed a molecular ion at 260, 201, 119 and base peak at 490 *m/z*. The isomer **4c$_2$** (M.p.: 201-203 °C) was identified by comparison of its IR and ^{19}F-, ^{1}H NMR spectra. The ^{19}F NMR of compound **4c$_2$** exhibits showed two doublets absorptions bands of intensity -8.1 and -72.2 ppm, the mass spectrum were very similar to that of compound **4c$_1$**.

4. Conclusions

In conclusion the preparation of phosphorus fluorinated 2,4,6-trimethylphenylazo pyridines are easily achieved by the condensation of 2,4,6-trimethylphenylazopyridines with methyldiphenylphosphineoxide. The success and yields of the reaction are affected by the following factors: the stability and nucleophilicity of the fluorinated and the other is the electrophilicity of the group substitution, then we have developed a new method for the synthesis of phosphorus fluorinated 2,4,6-trimethylphenylazo pyridines. The identity of the isomers was then confirmed with the established HPLC method, the resolution of their structural isomers was superior. The methods have potential applications in the determination of this isomer. Furthermore, since ChiraSphe column is characterized by its high stability and high loading capacity, this column can be used for semi-preparative separation of phosphorus and fluorinated azo compounds isomers and therefore this method could be useful for further pharmacological investigation of the individual isomer of phosphorus and fluorinated azo compounds.

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