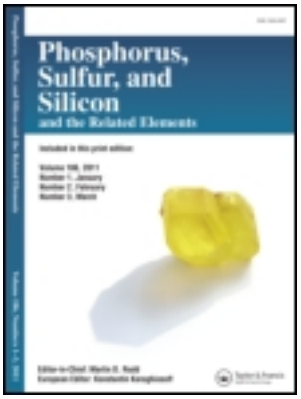

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Synthesis and Dynamic NMR Study of a Functionalized Sulfonamide Phosphonate Diester

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SYNTHESIS AND DYNAMIC NMR STUDY OF A FUNCTIONALIZED SULFONAMIDE PHOSPHONATE DIESTER

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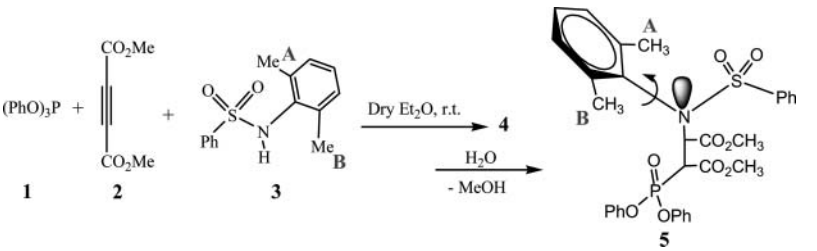
GRAPHICAL ABSTRACT



Abstract *Protonation of the highly reactive 1:1 intermediate produced in the reaction between triphenylphosphite and activated acetylene by sulfonamide leads to a phosphonate ylide, which undergoes methanol elimination in the presence of moisture to produce a highly functionalized sulfonamide phosphonate diester. A dynamic nuclear magnetic resonance (NMR) effect is observed in the ^1H NMR spectra of this compound as a result of restricted rotation around the single C−N bond. The coalescence temperature was observed at $T_C = 352.5$ K, and the free energy of activation ($\Delta G^{\#}$) for this process is 75.6 ± 2 kJ.mol^{-1}.*

Keywords Activated acetylenes; dynamic NMR effect; sulfonamide; triphenylphosphite

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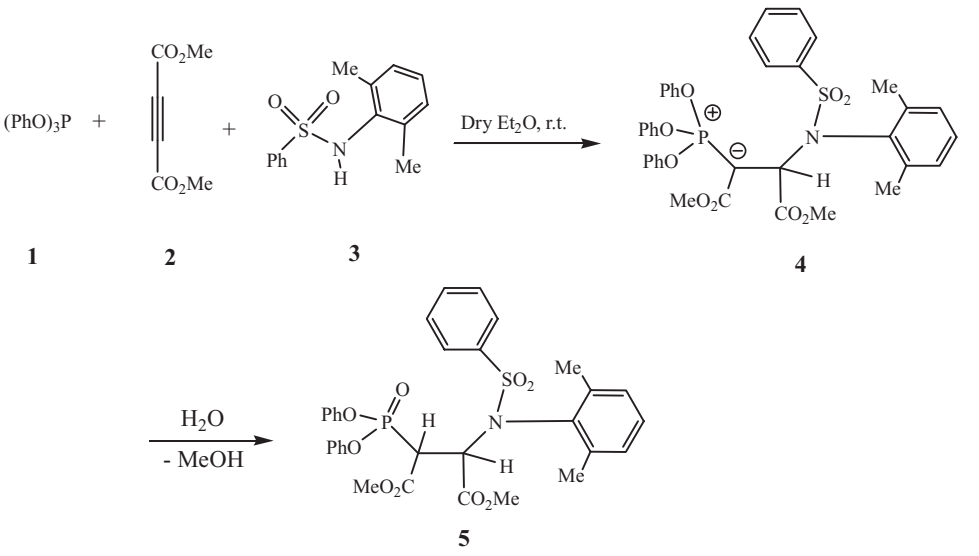
INTRODUCTION

Organophosphorus compounds are synthesis targets of interest, because of their value in a variety of industrial, biological, and chemical synthetic systems.[1–5] The physical properties and chemical reactivity of phosphate esters interlink many areas in chemistry and biology. Introduction of a phosphate monoester into a molecule such as a drug candidate enhances the water solubility, hence altering its bioavailability.[6–8] As a result, many methods have appeared describing novel syntheses of organophosphorus compounds.[3] There have been many reports of studies on the reactions between trivalent phosphorus nucleophiles and α,β-unsaturated carbonyl compounds in the presence of a proton source such as an alcohol or a phenol.[9–11] We report here the reaction of dimethyl acetylenedicarboxylate (DMAD) with a trivalent phosphorus nucleophile, namely, triphenylphosphite, in the presence of sulfonamide.

RESULTS AND DISCUSSION

As part of our research on the development of new synthetic methods in organic synthesis, we describe the reaction of triphenylphosphite **1** and dimethyl acetylenedicarboxylate **2** in the presence of sulfonamide **3**, which proceeds smoothly in dry diethyl ether at ambient temperature, in the absence of a catalyst, to produce the sulfonamide phosphonate diester **5** in good yields (Scheme 1).

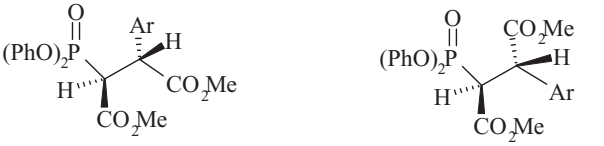


Scheme 1 Synthesis of sulfonamide phosphonate diester **5** from the reaction of triphenylphosphite, dimethyl acetylenedicarboxylate, and sulfonamide.

The structure of compound **5** as a 1:1:1 adduct was apparent from its mass spectra, which displayed a molecular ion peak at appropriate m/z values. The ^{1}H and ^{13}C NMR spectroscopic data, as well as infrared (IR) spectra, are in agreement with the proposed structure. The structure of compound **5** was also confirmed by X-ray diffraction (Figure 1).

The ^{1}H NMR spectrum of **5** exhibited two singlets readily recognized as arising from the two diastereotopic methyl groups in the phenyl ring (1.78 and 1.79). The two singlets at 3.52 and 3.63 belong to the ester methoxy protons. The proton-decoupled ^{13}C NMR spectrum of **5** showed 32 distinct resonances in agreement with the proposed structure.

The observation of $^3J_{HH} = 12$ Hz for the vicinal methane protons in **5** indicates the dominance of the *anti* arrangement. Because compound **5** possesses two stereogenic centers, two diastereomers with the *anti* HCCH arrangement are possible (Scheme 2).



(2S, 3R)-**5** or (2R, 3S)-**5** (2S, 3S)-**5** or (2R, 3R)-**5**

Scheme 2 Two diastereomers with *anti* HCCH arrangement for **5**.

The observation of $^3J_{CP} = 0$ for the carbonyl carbon atom of CO_2Me group is in agreement with the (2S, 3S) or (2R, 3R) diastereomer. However, as long as the coupling constant of at least one other diastereomer is not known, the assignment remains uncertain. In pursuing our research for synthesis of phosphonate esters by use of triphenyl phosphite as the reagent in nonpolar solvent media (mixture of *n*-hexane and diethyl ether), some classes of phosphonate esters were synthesized.[12–14] Herein a new class of sulfonamide phosphonate ester resulted (compound **5**) that has two changeable methyl groups A and B. Due to the restricted rotation around the C—N bond in this molecule, two methyl groups in the phenyl ring are diastereotopic (Figure 2).

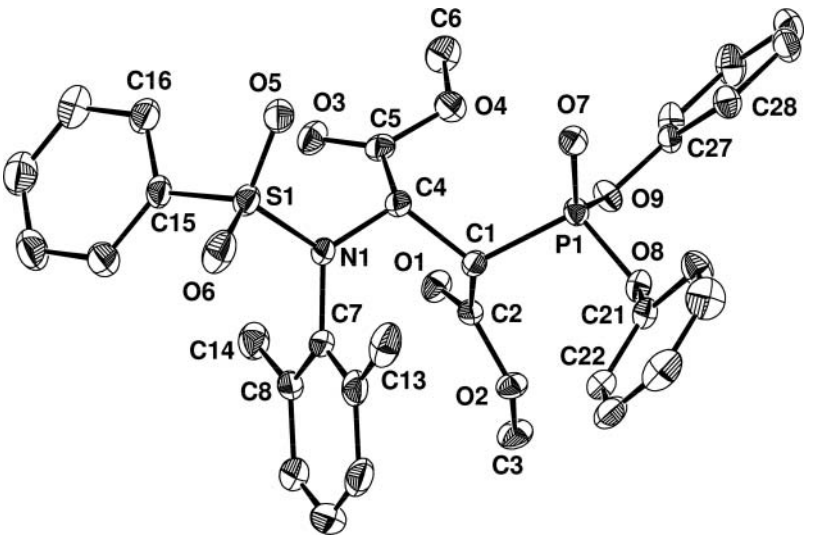


Figure 1 Molecular structure of molecule A of **5**. The hydrogen atoms have been omitted for clarity and the ellipsoids are drawn at the 50% probability level.

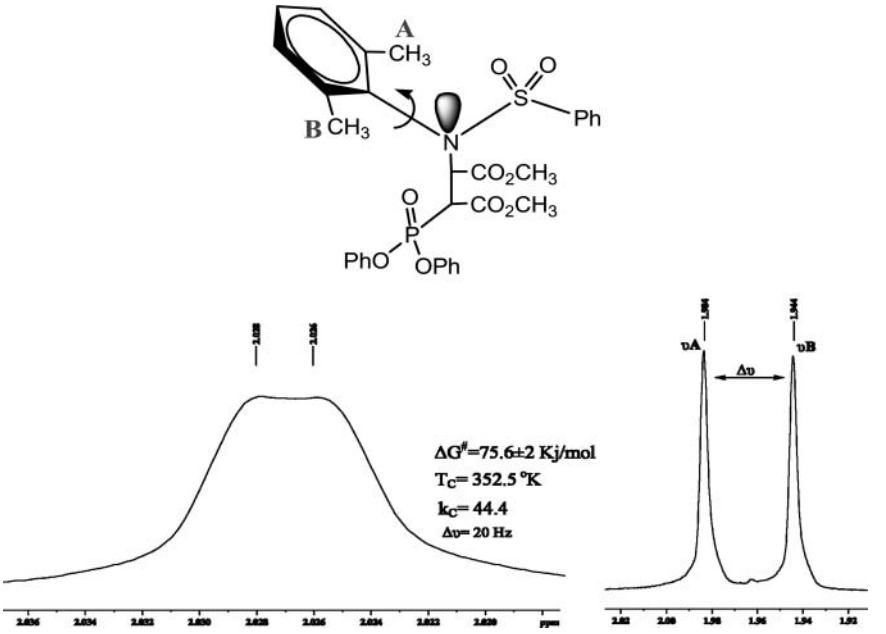


Figure 2 Dynamic NMR effect of restricted rotation around the C—N bond in a molecule of **5**.

The dynamic nuclear magnetic resonance (NMR) effect of the following compound is attributed to a rotational barrier around the C—N single bond.[15–20] For this phenomenon, the behavior of the molecule was monitored by ^{1}H NMR techniques at variable temperatures. From the data, the relevant thermodynamic parameters were calculated. To examine their behavior, the NMR tube containing compound **5** was placed in the NMR probe and heated slowly from 298 to 360 K. The coalescence temperature was eventually observed at T_C = 352.5 K, and the activation energy ($\Delta G^{\#}$) of the rotation around C—N single bond was calculated as 75.6 ± 2 kJ.mol^{-1}. In the ^{1}H NMR, the collected spectra relevant to the dynamic effect are shown in the following variable-temperature (VT) NMR (Figure 3).

In conclusion, the observed dynamic NMR effect of compound **5** arises from the rotational barrier around the C—N single bond. The reaction of dialkyl acetylenedicarboxylate with triphenyl phosphite in the presence of an NH acid such as sulfonamide leads to a facile synthesis of some functionalized phosphonate ylide and phosphonate esters. The ability to perform this reaction under neutral conditions using these reagents is an advantage in the synthesis of a new class of sulfonamide phosphonate esters.

EXPERIMENTAL

Chemicals were purchased from Fluka and used without further purification. Melting points were measured on an Electrothermal 9100 apparatus (Markham, Ontario, Canada). Elemental analyses for the C, H, and N were performed using a Heraeus CHN-O rapid analyzer (Texas City, TX, USA). Mass spectra were recorded on a Finnigan-MAT 8430 spectrometer operating at an ionization potential of 70 eV. IR spectra were measured on a Shimadzu IR-460 spectrometer. ^{1}H-, ^{13}C, and ^{31}P-NMR spectra were measured with a Bruker DRX-500 Avance spectrometer at 500.1, 125.8, and 202.4 MHz, respectively.

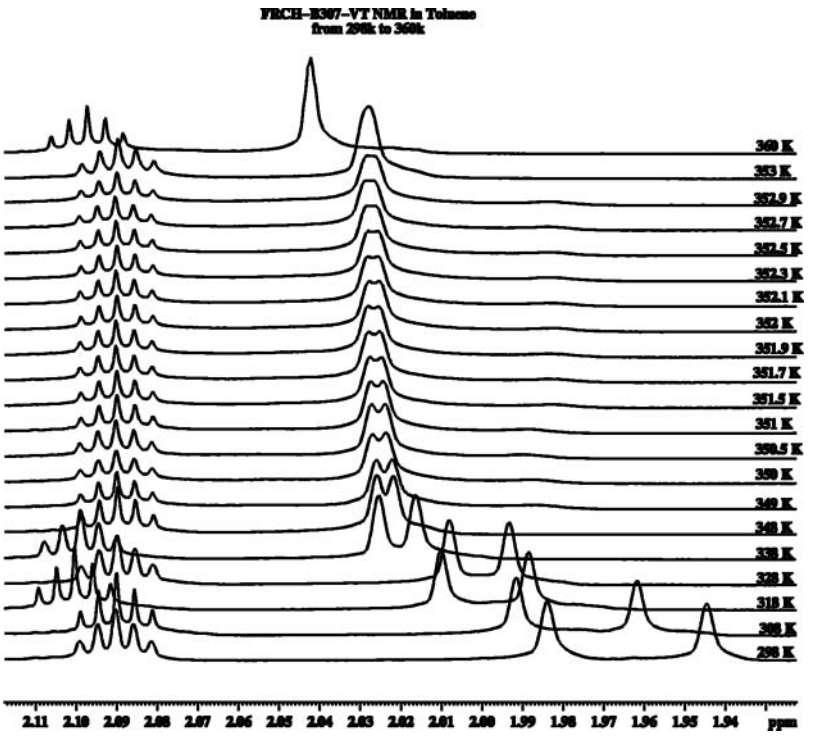


Figure 3 VT NMR of compound **5**.

General Procedure for Preparation of Compound 5

Triphenylphosphite (0.62, 2 mmol) was added slowly to a magnetically stirred solution of dimethyl acetylendicarboxylate **2** (0.284, 2 mmol) and sulfonamide **3** (0.522, 2 mmol) in dry diethyl ether at room temperature. The reaction mixture was then stirred for 2 h at room temperature. The resultant precipitate was collected and washed with cold *n*-hexane and diethyl ether (3 × 5 mL) to yield the phosphonate ylide **4**. If a few drops of distilled water were added to the reaction mixture and then left in an exposed vessel to air for a week, the phosphonate ester **5** resulted. The workup followed removal of the solvent under reduced pressure and the resultant yellow residue was collected and crystallized from ether/*n*-hexane (4:1).

Dimethyl-*N*-(1,6-dimethylphenylsulfonamino-*N*-yl)-3-(diphenoxyphosphoryl) Butenedioate (5)

Colorless crystals, 0.53 g, yield 70%, m.p. 168–170 °C. IR (KBr) (ν_{max}/cm^{-1}): 2951 (SO_2), 1781 and 1750 (2 C=O of esters), 1591 (C=C). ^{1}H NMR (500.1 MHz, $CDCl_3$): 1.78 (3 H, s, CH_3), 1.79 (3 H, s, CH_3), 3.52 (3 H, s, OCH_3), 3.63 (3 H, s, OCH_3), 3.75 (1 H, dd, $^2J_{PH}$ = 17 Hz, $^3J_{HH}$ = 12 Hz, CH), 5.75 (1 H, dd, $^3J_{PH}$ = 9.6 Hz, $^3J_{HH}$ = 12 Hz, CH), 6.9–7.7 (18 H, m, aromatic moiety). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 18.7 (CH_3), 19.7 (CH_3), 46.5 (d, $^1J_{CP}$ = 130.9 Hz, CH), 52.6 (OCH_3), 52.9 (OCH_3), 60.4 (d, $^2J_{CP}$ = 4 Hz, CH), 120.3 (d, $^3J_{CP}$ = 4.9 Hz, 2 CH_{ortho} of C_6H_5), 121.6 (d, $^3J_{CP}$ = 4.3 Hz, 2 CH_{ortho} of C_6H_5), 125.5 (CH_{para} of C_6H_5), 125.6 (CH_{para} of C_6H_5), 128.4 (2 CH), 129.0 (2 CH),

Table 1 Crystal data and structure refinement for compound **5**

Empirical formula	$C_{32}H_{32}NO_9PS$
Formula weight	637.62
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	$P\bar{1}$
Unit cell dimensions	a = 8.2746(1) Å
	b = 16.2970(2) Å
	c = 23.2316(4) Å
	A = 80.451(1)°
	B = 89.518(1)°
	γ = 87.915(1)°
Volume	3087.35(8) Å^3
Z	4
Density (calculated)	1.372 mg/m^3
Absorption coefficient	0.213 mm^{-1}
Crystal size	0.33 × 0.23 × 0.11 mm^3
θ range for data collection	2.73 to 30.00°
Reflections collected	91,069
Independent reflections	17,954 [R(int) = 0.0516]
Max./min. transmission	1.00/0.92
Data/restraints/parameters	17,954/0/801
Goodness of fit on F2 (GOOF) on F^2	1.002
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0690$, $wR_2 = 0.1781$
R indices (all data)	$R_1 = 0.1066$, $wR_2 = 0.1914$
Largest diff. peak and hole	0.888 and −0.502 e.Å^{-3}

129.2 (CH), 129.4 (C), 129.5 (2 CH$_{metha}$ of C_6H_5), 129.8 (2 CH$_{metha}$ of C_6H_5), 130.1 (2 CH), 132.9 (CH), 134.2 (2 C), 137.9 (C), 149.9 (d, $^2J_{CP} = 7.7$ Hz, C$_{ipso}$ of C_6H_5), 150.5 (d, $^3J_{CP} = 9.5$ Hz, C$_{ipso}$ of C_6H_5), 165.3 (d, $^2J_{CP} = 5.5$ Hz, C=O), 169.3 (C=O). MS, (*m/z*,%): 637 (M^+, 80), 544 (M^+-OPh, 95), 451 (M^+-2 Oph, 55). Anal. Calcd. for $C_{32}H_{32}NO_9PS$ C, 60.28; H, 5.06; N, 2.20; Found: C, 60.65; H, 5.40; N, 2.18.

X-Ray Crystallography of (5): Crystal/Refinement Details

The X-ray diffracted intensities were measured from a single crystal of **5** on an Oxford Diffraction Xcalibur or Gemini-R Ultra charge-coupled device (CCD) diffractometer using monochromatized Mo-$K\alpha$ radiation ($\lambda = 0.71073$ Å). Data were corrected for Lorentz and polarization effects and absorption correction applied using multiple symmetry equivalent reflections. The structure was solved by direct method and refined on F^2 using the SHELX-97 crystallographic package. A full-matrix least-squares refinement procedure was used, minimizing $\Sigma w(F_o^2 - F_c^2)$, with $w = [\sigma^2(F_o^2) + (AP)^2 + BP]^{-1}$, where $P = (F_o^2 + 2F_c^2)/3$. Agreement factors ($R_1 = \Sigma \| F_o| - |F_c \| / \Sigma |F_o|$, $wR_2 = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$ and GOF $= \{\Sigma[w(F_o^2 - F_c^2)^2]/(n-p)\}^{1/2}$ are cited, where n is the number of reflections and p is the total number of parameters refined. $A = 0.04$, $B = 4.7$). All nonhydrogen atoms were refined with anisotropic displacement parameters using all reflections. Positions of hydrogen atoms were localized from difference Fourier synthesis and their atomic parameters were constrained to the bonded atoms during refinement. Crystallographic details are listed in Table 1. Selected bond lengths and angles are provided in Table 2. Crystallographic

Table 2 Selected bond lengths (Å) and angles (°) for **5**

	Molecule A	Molecule B
P(1)−O(7)	1.461 (2)	1.459 (2)
P(1)−O(9)	1.567 (2)	1.569 (2)
P(1)−O(8)	1.587 (2)	1.592 (2)
P(1)−C(1)	1.821 (3)	1.817 (3)
S(1)−O(6)	1.426 (2)	1.433 (2)
S(1)−O(5)	1.439 (2)	1.434 (2)
S(1)−N(1)	1.650 (2)	1.656 (2)
S(1)−C(15)	1.767 (3)	1.763 (3)
O(7)−P(1)−O(9)	119.53 (12)	119.29 (12)
O(7)−P(1)−O(8)	114.23 (11)	114.13 (11)
O(9)−P(1)−O(8)	99.61 (11)	100.30 (11)
O(7)−P(1)−C(1)	112.93 (12)	112.79 (12)
O(9)−P(1)−C(1)	103.96 (12)	104.11 (11)
O(8)−P(1)−C(1)	104.72 (12)	104.43 (12)
O(6)−S(1)−O(5)	120.69 (15)	119.02 (14)
O(6)−S(1)−N(1)	107.89 (14)	109.44 (13)
O(5)−S(1)−N(1)	105.39 (13)	105.58 (12)
O(6)−S(1)−C(15)	105.64 (15)	105.91 (14)
O(5)−S(1)−C(15)	108.04 (14)	110.12 (15)
N(1)−S(1)−C(15)	108.82 (13)	106.14 (13)

data of compound **5** have been deposited at the Cambridge Crystallographic Data Centre (CCDC number 715537). Copies of the information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge CB21EZ, UK (Fax: + 44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk).

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