

Notes

Synthesis and crystal structure of ethyl benzimidazole-2-yl phosphonate

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When *N*-cyanoimido-(*O*, *O*-diethyl)phosphonyl/*S*-methyl thiocarbonate (**1**) was treated with *o*-phenylenediamine in the presence of Et₃N in ethanol, diethyl benzimidazole-2-yl phosphonate (**2**) was obtained and hydrolyzed during the recrystallization in MeOH/H₂O, generating ethyl benzimidazole-2-yl phosphonate (**3**). The crystal structure of compound **3** was determined by X-ray diffraction method. The crystals belong to monoclinic, space group *C2/c*, *a* = 1.78408(18), *b* = 0.83725(9), *c* = 1.67401(18) nm, β = 118.997(2)°, *V* = 2.1870(4) nm³, *Z* = 8, *D_c* = 1.374 g/cm³, *F*(000) = 944. The final *R* and *wR* are 0.0499 and 0.1436, respectively. The mechanism of the above reaction is also discussed.

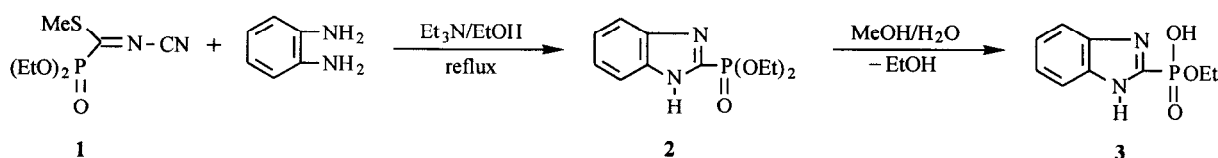
Keywords Ethyl benzimidazole-2-yl phosphonate, crystal structure, synthesis, mechanism

Introduction

The increasing and sustained interest has been paid to organophosphorus chemistry in the past decades owing to the discovery of more and more naturally occurring C-P compounds, which show antibacterial, antiviral, antibiotic, pesticidal, and anti-cancer activity.^{1,2} On the other hand, heterocyclic compounds attracted the attention of chemists because of their pharmaceutical impor-

tance and various application in organic synthesis. Iso-cyano-methylphosphonate,^{3,4} and 1-cyano-1-phosphonyl thioenolethers⁵ were utilized as useful synthetic building block for preparing heterocyclic compounds containing phosphono group. We also demonstrated that α, α-dicyano (α-cyano-α-ethoxycarbonyl) phosphonyl/*S*-methyl ketene acetals could be utilized as synthons for the synthesis of pyrazole-, isoxazole-, and pyrimidine-phosphonates through cyclization reaction with various binucleophilic reagents.⁶ In addition, a new and useful building block, *N*-cyanoimido phosphonyl/*S*-methyl thiocarbonate (**1**) was derived from *N*-cyanoimido-*S*, *S*-dimethyl dithiocarbonate. Triazine-,⁷ triazole-, oxadiazole-phosphonates were prepared by the reaction of **1** with various binucleophilic reagents.⁸ Meanwhile, we discovered that when **1** was treated with *o*-phenylenediamine under reflux in ethanol, diethyl benzimidazole-2-yl phosphonate (**2**) was obtained, confirmed by ¹H NMR, and hydrolyzed during the recrystallization in MeOH/H₂O (*V/V* = 100:1), generating the title compound ethyl benzimidazole-2-yl phosphonate (**3**) (Scheme 1). The crystal structure of **3** was determined by X-ray diffraction method. The mechanism of the above reaction is also discussed.

Scheme 1 Procedure of preparing the title compound



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Experimental

General

Solvent EtOH and catalyst Et₃N were dried over molecular sieves and distilled before use. *o*-Phenylenediamine was recrystallized with ethanol. ¹H NMR and ³¹P NMR spectra were recorded on a BRUKER AC-P200 spectrometer using TMS and H₃PO₄ (85%) as the internal standards respectively. IR spectra were recorded on a Shimadzu IR-435 instrument. Elemental analysis was performed on a Yanaco CHN CORDER MT-3 instrument. The X-ray data were measured by BRUKER SMART 1000.

Preparation of ethyl benzimidazole-2-yl phosphonate (3)

To a mixture of *o*-phenylenediamine (1.08 g, 10 mmol) and *N*-cyanoimido-(*O*, *O*-diethyl) phosphonyl-*S*-methyl thiocarbonate (1) (3.93 g, 60%, 10 mmol) was added triethylamine (1 mL) in anhydrous ethanol (20 mL) and the resulting mixture was refluxed for 16 h as monitored by TLC. Removal of the solvent under reduced pressure gave a residue which was purified by column chromatography on silica gel (eluent petroleum ether:ethyl acetate = 2:1) to afford 1.33 g of 2, yield: 52.1%, mp: 282–284 °C. δ_H(DMSO-*d*₆): 1.08 (t, *J* = 7.06 Hz, 6H, P-OCH₂CH₃), 3.51–3.70 (m, 4H, P-OCH₂CH₃), 7.56 (m, 2H, Aromatic-hydrogen), 7.68 (m, 2H, aromatic-hydrogen). Compound 2 was hydrolyzed in MeOH/H₂O during the recrystallization to generate the title compound 3 in excellent yield (93%), mp: 291–293 °C. ν_{max}: 1244 (P=O), 1109 (P-O), 1041 (P-O) cm⁻¹. δ_H(DMSO-*d*₆): 1.08 (t, *J* = 7.05 Hz, 3H, P-OCH₂CH₃), 3.71–3.90 (m, 2H, P-OCH₂CH₃), 7.55 (m, 2H, aromatic-hydrogen), 7.67 (m, 2H, aromatic-hydrogen). δ₃₁P(DMSO-*d*₆): -5.668. Anal. C₉H₁₁N₂O₃P. Calcd: C, 47.79; H, 4.87; N, 12.39. Found: C, 47.73; H, 4.84; N, 12.28.

X-ray structural determination

A colorless crystal of the title compound 3 having approximate dimensions of 0.3 mm × 0.15 mm × 0.1 mm was mounted on a glass fiber in a random orientation. The determination of the unit cell parameters and the data collection were performed with Mo K_α radiation

(λ = 0.071073 nm) on a SMART 1000 CCD diffractometer equipped with a graphite crystal monochromator situated in the incident beam at 298(2) K. The SADABS absorption correction was applied. The structure was solved by direct method with SHELXS-97 program and successive Fourier syntheses, and it was refined by full-matrix least-squares procedure of SHELXL-97 program with anisotropic thermal parameters for all the non-hydrogen atoms. Hydrogen atoms were generated geometrically.

Results and discussion

A proposed mechanism of the generation of the title compound 3 is shown in Scheme 2. The first step of the above reaction probably involves the formation of the intermediate 4 and the removal of MeSH. Compound 2 further results from an intramolecular addition of the nitrogen atom, followed by the elimination of NH₂CN, favored by an extension of the aromaticity. However, cyclic product 5, resulting from another intramolecular addition of the nitrogen atom, is not observed. Diethyl benzimidazole-2-yl phosphonate (2) was hydrolyzed in MeOH/H₂O to generate ethyl benzimidazole-2-yl phosphonate (3)

Fig. 1 shows the molecular structure of ethyl ben-

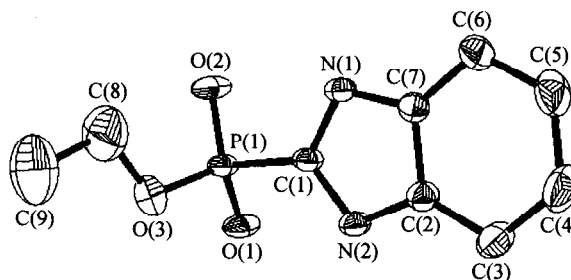


Fig. 1 Molecular structure of compound 3.

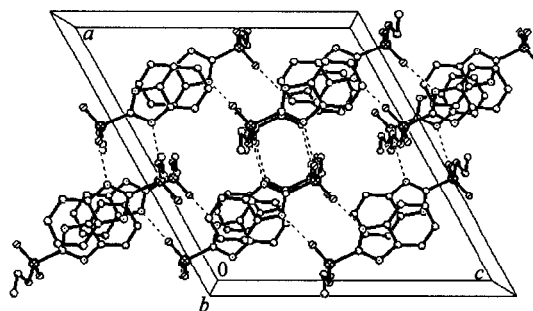


Fig. 2 Crystal packing diagram of compound 3.

imidazole-2-yl phosphonate (**3**). Fig. 2 shows the crystal packing diagram of compound **3**. A summary of data collection and refinement is given in Table 1. The final atomic parameters, selected bond lengths and bond angles are given in Tables 2 and 3, respectively. The ethyl group shows high thermal parameters because the ethoxy C(9)-C(8)-O(3) is located in a large space so that the ethyl group can vibrate in a large area. The

bond length of P(1)—O(1) (0.1476 nm) is similar to that of P(1)—O(2) (0.1469 nm), and both of them are longer than that of P=O double bond and shorter than that of P—O single bond,⁹ which indicates that H(1) is not fixed in O(1) or O(2). Similarly, H(2) is not fixed in N(1) or N(2), either. From the above results, we assume that the title compound may be described as structure 1.

Scheme 2 Proposed mechanism of generation of the title compound

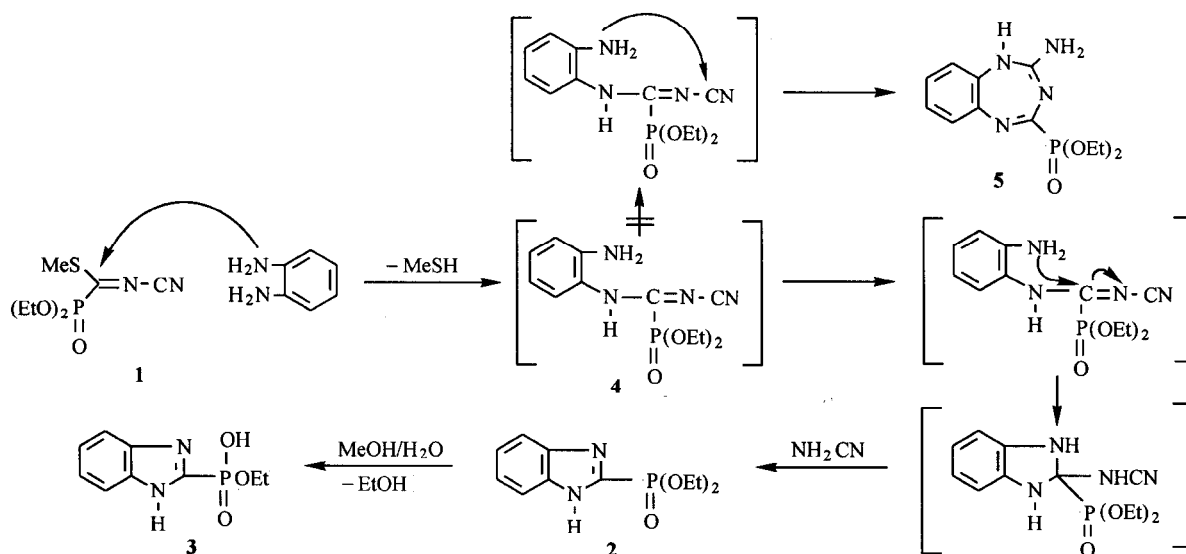


Table 1 Crystal data and structure refinement

Compound	C ₉ H ₁₁ N ₂ O ₃ P
Color/shape	White/diamond
Formula weight	226.17
Crystal system	Monoclinic
Space group	C ₂ /c
Z	8
a (nm)	1.78404(18)
b (nm)	0.83725(9)
c (nm)	1.67401(18)
β (°)	118.997(2)
V (nm ³)	2.1870(4)
D _c (g/cm ³)	1.374
Absorption coefficient	0.240 mm ⁻¹
F(000)	944
θ range for data collection	2.61 to 26.39
Reflections collected	4982
Completeness up to θ = 26.39°	99.4%
Independent reflection [I > 2σ(I)]	2240 (R _{int} = 0.0259)
Max. and min. transmission coefficient	0.9764, 0.9314
Data/restraints/parameters	2240/0/144
Goodness-of-fit on F ²	1.028
Final R indices	R = 0.0499, wR = 0.1436
(Δρ) _{max} /(Δρ) _{min} , e/nm ³	377/-395

$$w = 1/[\sigma^2(F_o^2) + (0.0937P)^2 + 1.7803P] \text{ where } P = (F_o^2 + F_c^2)/3.$$

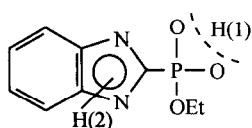
Table 2 Atomic coordinates and equivalent isotropic thermal parameters (10^{-2} nm^2)^a

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{eq}
P(1)	0.4044(1)	0.1384(1)	1.0548(1)	0.0393(2)
O(1)	0.4573(1)	-0.0073(3)	1.0773(1)	0.0555(6)
O(2)	0.3339(1)	0.1498(3)	1.0763(1)	0.0576(6)
C(1)	0.3543(2)	0.1629(3)	0.9314(2)	0.0371(5)
N(1)	0.2748(1)	0.2179(3)	0.8777(2)	0.0421(5)
C(2)	0.3322(2)	0.1614(3)	0.7888(2)	0.0430(6)
C(3)	0.3371(2)	0.1441(4)	0.7091(2)	0.0587(8)
C(4)	0.2657(3)	0.1871(5)	0.6293(2)	0.0721(10)
C(5)	0.1917(2)	0.2439(4)	0.6282(2)	0.0723(10)
C(6)	0.1859(2)	0.2602(4)	0.7068(2)	0.0590(8)
C(7)	0.2584(2)	0.2184(3)	0.7876(2)	0.0435(6)
N(2)	0.3902(1)	0.1280(3)	0.8793(1)	0.0399(5)
O(3)	0.4660(1)	0.2872(3)	1.0905(2)	0.0662(6)
C(8)	0.4244(3)	0.4408(5)	1.0900(5)	0.1249(2)
C(9)	0.4918(4)	0.5714(7)	1.1233(5)	0.1470(1)

^a U_{eq} defined as one third of the trace of the orthogonalized U_{ij} tensor.

Table 3 Selected bond lengths (10^{-1} nm) and bond angles ($^{\circ}$)

Bond distance					
P(1)—O(2)	1.469(2)	N(1)—C(7)	1.389(3)	C(5)—C(6)	1.376(5)
P(1)—O(1)	1.476(2)	C(2)—N(2)	1.388(4)	C(6)—C(7)	1.389(4)
P(1)—O(3)	1.575(2)	C(2)—C(3)	1.388(3)	O(3)—C(8)	1.483(5)
P(1)—C(1)	1.821(3)	C(2)—C(7)	1.391(4)	C(8)—C(9)	1.517(1)
C(1)—N(1)	1.339(3)	C(3)—C(4)	1.373(5)		
C(1)—N(2)	1.345(3)	C(4)—C(5)	1.395(5)		
Bond angle					
O(2)-P(1)-O(1)	120.6(1)	N(2)-C(1)-P(1)	125.8(2)	C(5)-C(6)-C(7)	116.1(3)
O(2)-P(1)-O(3)	112.2(1)	C(1)-N(1)-C(7)	109.2(2)	N(1)-C(7)-C(2)	106.4(2)
O(1)-P(1)-O(3)	108.3(1)	N(2)-C(2)-C(3)	131.7(3)	N(1)-C(7)-C(6)	131.7(3)
O(2)-P(1)-C(1)	105.2(1)	N(2)-C(2)-C(7)	106.7(2)	C(2)-C(7)-C(6)	121.9(3)
O(1)-P(1)-C(1)	106.5(1)	C(3)-C(2)-C(7)	121.5(3)	C(1)-N(2)-C(2)	108.8(2)
O(3)-P(1)-C(1)	102.1(1)	C(4)-C(3)-C(2)	116.3(3)	C(8)-O(3)-P(1)	115.4(2)
N(1)-C(1)-N(2)	108.9(2)	C(3)-C(4)-C(5)	121.8(3)	C(9)-C(8)-O(3)	108.5(4)
N(1)-C(1)-P(1)	125.3(2)	C(6)-C(5)-C(4)	122.1(3)		



Structure 1

The hydrogen bond lengths of N(2)—H(1)—O(1) and N(1)—H(2)—O(2) are 0.2650 nm and 0.2652 nm, respectively (Table 4). The P atom exhibits a distorted tetrahedral configuration because the bond angles of O(2)-P(1)-O(1) (120.6°) and O(2)-P(1)-C(1) (105.2°) are both larger than that of O(3)-P(1)-

C(1) (102.1°).⁹ The bond length of P(1)—C(1) (0.1823 nm) is a little shorter than normal P—C single bond length (0.1850 nm). The bioassay of the title compound is underway.

Table 4 Bond lengths (10^{-1} nm) and bond angles ($^{\circ}$) of hydrogen bonds N-H-O and N-H-O

N—H—O	d(N—H)	d(H—O)	d(N—O)	\angle NHO
N(2)—H(1)—O(1)	0.936	1.725	2.650	168.92
N(1)—H(2)—O(2)	0.788	1.866	2.652	175.41

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