

Vilsmeier-Haack Reaction of Phosphonic Dihydrazide: Synthesis of 4- {[(Dimethyl)azanylidene] methyl} Amino-2,3-Dihydro-3-Oxo-4*H*-1,2,4,3-Triazaphosphole

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Abstract A simple method for the synthesis of 4- {[(dimethyl)azanylidene] methyl} amino-2,3-dihydro-3-oxo-4*H*-1,2,4,3-triazaphosphole (2) is described. Treatment of phosphonic dihydrazide (1) with Vilsmeier-Haack reagent led directly to the title compound in high yield.

Keywords Phosphonic Dihydrazide, Vilsmeier Reagent, 1,2,4,3-Triazaphosphole

1. Introduction

A Literature search of the last decade revealed sustained interest in the application of the Vilsmeier Haack reagent in organic synthesis. The versatility of the reagent had been extended to activating agents as oxygen and nitrogen nucleophiles to yield the corresponding iminium salts[1-5]. On the other hand, phosphorus heterocycles containing nitrogen heteroatoms adjacent to phosphorus atom exhibited interesting biological properties[6, 7]. As a part of our search for new expected biologically active phosphorus heterocycles[8-11], we are interested in introducing such N-P-N pattern into heterocyclic structure by applying the Vilsmeier Haack reaction on phosphonic dihydrazide. To the best of our knowledge, the synthesis of phosphorus heterocycles by the Vilsmeier reagent has not been reported in literature.

2. Experimental

2.1. General

The melting point was determined in an open capillary tube on a digital Stuart SMP-3 apparatus. Infrared spectrum was measured on Perkin-Elmer 293 spectrophotometer (cm^{-1}), using KBr disks. ^1H NMR spectrum was measured on Gemini-200 spectrometer (200 MHz), using $\text{DMSO}-d_6$ as a solvent and TMS (δ) as the internal standard. ^{13}C and

^{31}P NMR spectra were registered on a Varian Inova 500 MHz spectrometer at room temperature using $\text{DMSO}-d_6$ as a solvent and TMS as internal standard and 85% H_3PO_4 as external reference. Elemental microanalysis was performed at microanalysis center in National Research Center, Giza. The purity of the synthesized compound was checked by thin layer chromatography (TLC). Phosphonic dihydrazide was prepared according to the reported method[12].

2.2. Synthesis of {[(dimethyl)azanylidene] methyl} amino-2,3-dihydro-3-oxo-4*H*-1,2,4,3-triazaphosphole (2)

The Vilsmeier reagent was prepared by adding dimethylformamide (3.86 mL, 50 mmol) in an ice-cold condition ($0-5^\circ\text{C}$) under constant stirring. To this, phosphorus oxychloride (1.304 mL, 14 mmol) was added dropwise over a period of 30 minutes and the resulting mixture was stirred for a further 30 minutes. Phosphonic dihydrazide (1) (550 mg, 5 mmol) was added to the Vilsmeier reagent and stirred for 4 hours at $50-60^\circ\text{C}$. The reaction mixture was cooled and poured crushed ice (30 g) under constant manual stirring. The reaction mixture was kept aside overnight. After adding acetone, the precipitate obtained was washed well with acetone. The product was filtered off and crystallized from acetone/water affording white crystals in 86% yield, m.p. $230-232^\circ\text{C}$. IR (ν_{max} , cm^{-1}): 3474–3150 (H-bonded, OH and NH), 2778 (P–H), 1713 ($\text{C}=\text{N}^+$), 1661 ($\text{C}=\text{N}$), 1291 ($\text{P}=\text{O}$). ^1H NMR (DMSO): δ 3.01 (s, 6H, 2 CH_3), 6.00 (br, 1H, NH exchangeable with D_2O), 8.35 (d, 1H, $J_{\text{PH}}=328$ Hz, P–H), 8.05, 8.17 (dd, 1H, $J=14$ Hz, $\text{CH}=\text{N}_{\text{exocyclic}}$), 8.40 (s, 1H, $\text{CH}=\text{N}_{\text{endocyclic}}$), 11.32 (br, 1H, NH exchangeable with D_2O). ^{13}C NMR (DMSO): 45.2 (CH_3), 47.3 (CH_3), 158.1 ($\text{C}=\text{N}_{\text{exocyclic}}$), 166.3

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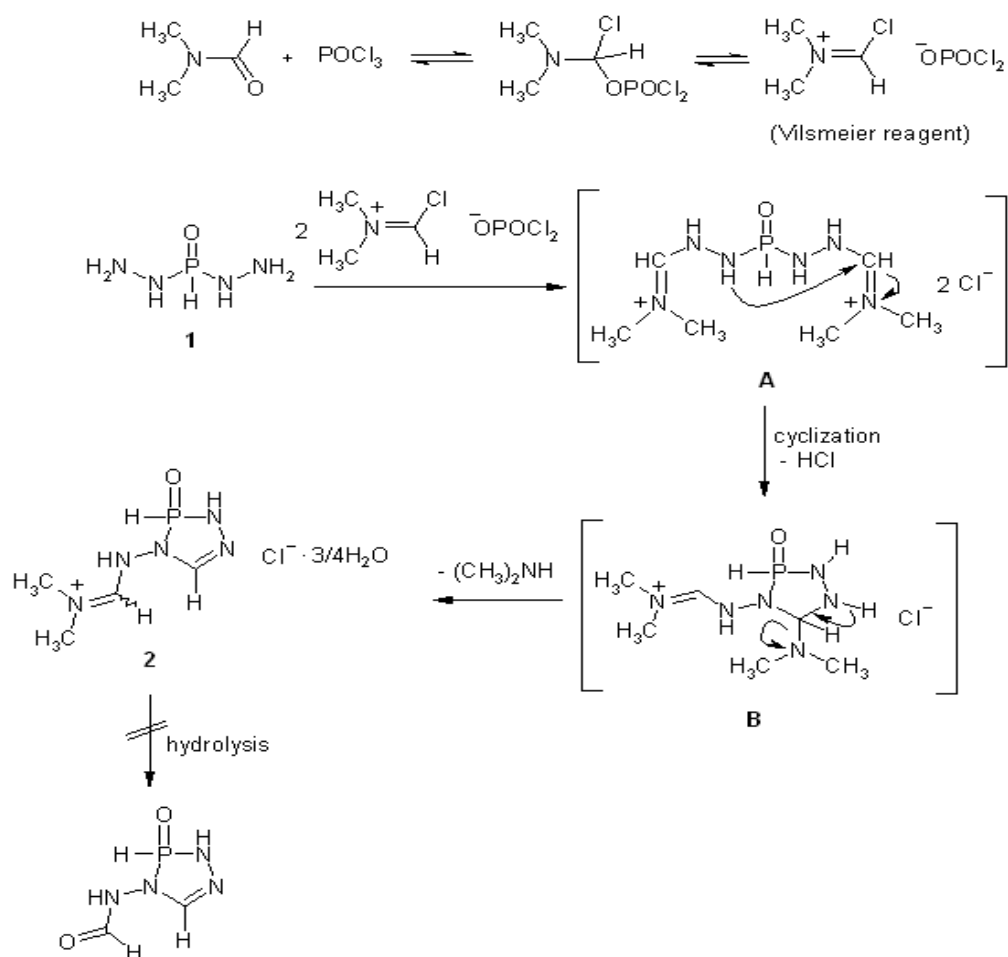
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(C=N_{endocyclic}). ³¹P NMR (DMSO): δ 7.58 ppm. MS (I %): 226 (M+1, 7%), 225 (M⁺, 8%), 99 (3), 98 (17), 71 (42), 70 (24), 57 (100). Anal. Calcd for C₄H₁₁ClN₅OP. 3/4H₂O (225.10): C, 21.32; H, 5.55; N, 31.09. Found: C, 21.43; H, 5.62; N, 30.74%.

3. Results and Discussion

The Vilsmeier-Haack reaction[13] was applied to phosphonic dihydrazide (**1**) to give 4-[(dimethyl)azanylideneamino-2,3-dihydro-3-oxo-4*H*-1,2,4,3-triazaphosphole]methyl}amino-2,3-dihydro-3-oxo-4*H*-1,2,4,3-triazaphosphole (**2**). A possible mechanism for this reaction could involve attack of the chloromethyleniminium species obtained *in situ* from phosphorus oxychloride and dimethylformamide to react with the terminal amino groups of **1** leading to the iminium intermediate **A**. The intramolecular cyclization of **A** through addition of NH group adjacent to phosphorus atom to C=N⁺ group afforded the cyclic intermediate **B**, which underwent removal of one molecule of dimethylamine to give the isolated product **2**. Unfortunately, our attempts to hydrolyze of **2** were unsuccessful under different basic condition which resulted in the formation of a tarry material instead of the

expected aldehyde **3**, and we failed to isolate individual compound[14]. Elemental analysis and mass spectrometry indicated a formula with composition C₄H₁₁ClN₅OP. 3/4H₂O (225.10). This is explained by the presence of a water in the crystallized form, *i.e.* the molecular formula of the proposed structure is the hydrated form of C₄H₁₁ClN₅OP. Its IR spectrum displayed OH, NH, C=N⁺ and C=N functions at 3474–3150, 1713 and 1661 cm⁻¹, respectively[15] (Figure 1). Also, its ¹H NMR spectrum exhibited two characteristic signals at δ 8.35 and δ 8.40 ppm corresponding to P–H and CH=N_{endocyclic}, respectively. Moreover, the proton of CH=N_{exocyclic} appeared as doublet doublet at δ 8.05 and 8.17 ppm with coupling constant around 14 Hz[16], along with the signals of NH protons which appeared at δ 6.00 and 11.32 ppm which are replaceable with deuterium on addition of D₂O (Figure 2). Furthermore, its ¹³C NMR spectrum supported the suggested structure which showed the methyl carbon atoms at δ 45.2 and 47.3 ppm, while the exocyclic and endocyclic C=N atoms appeared at δ 158.1 and 166.3 ppm, respectively (Figure 3). Finally, ³¹P NMR spectrum displayed a signal at δ 7.58 ppm.



Scheme 1. The synthetic pathway and its mechanism for formation **2** via applying Vilsmeier-Haack reaction on phosphonic dihydrazide **1**

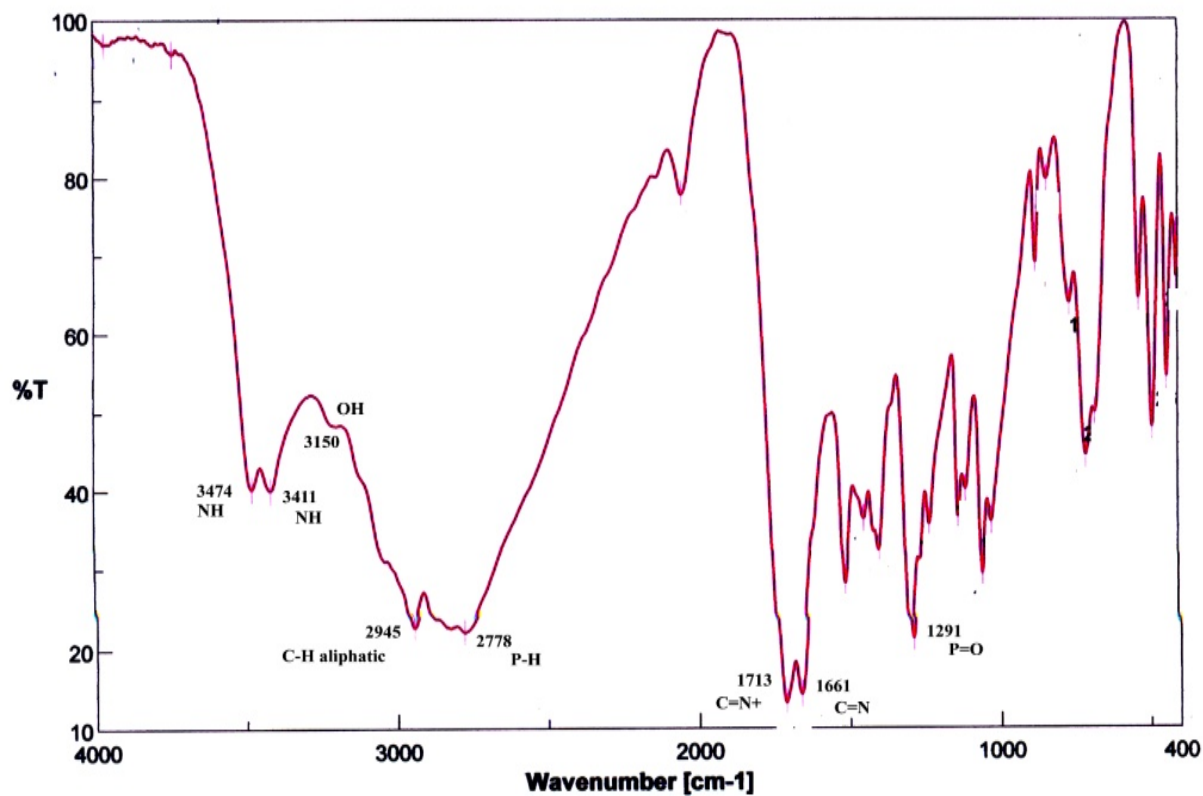


Figure 1. The IR spectrum of compound 2

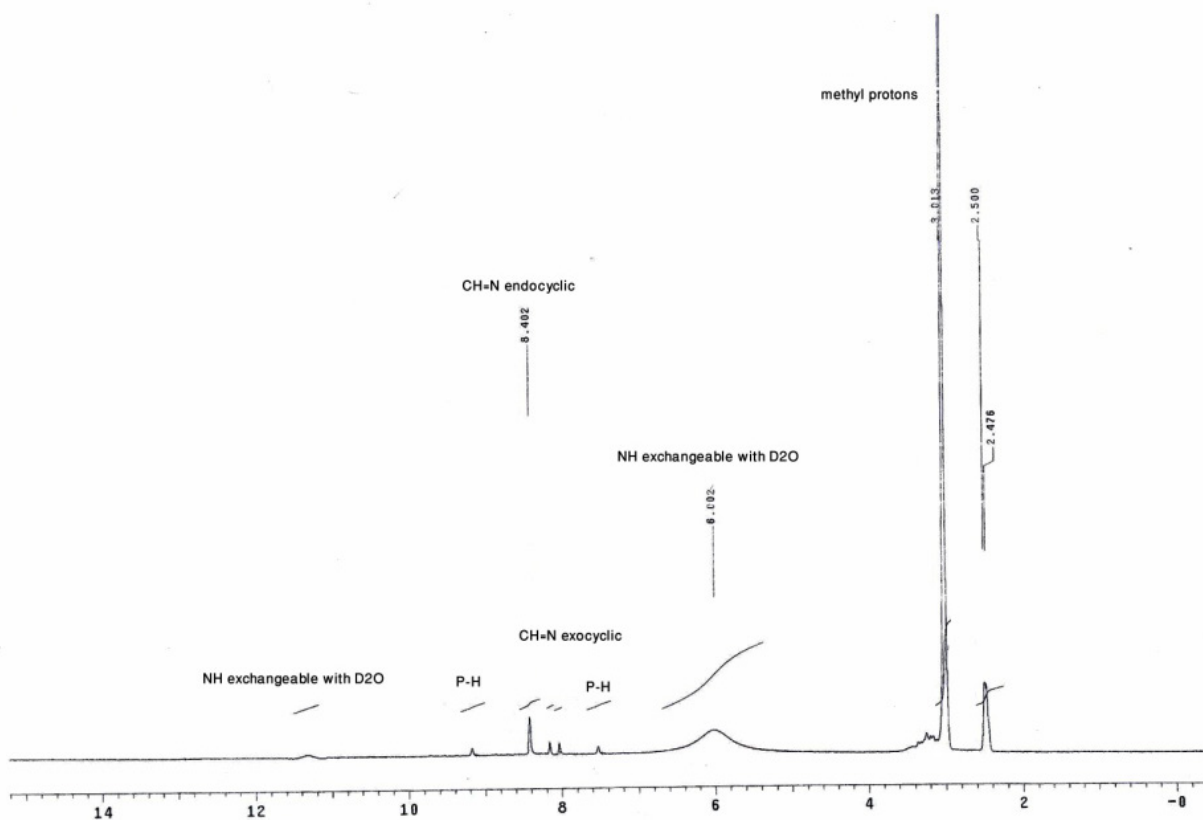


Figure 2. The ¹H-NMR spectrum of compound 2

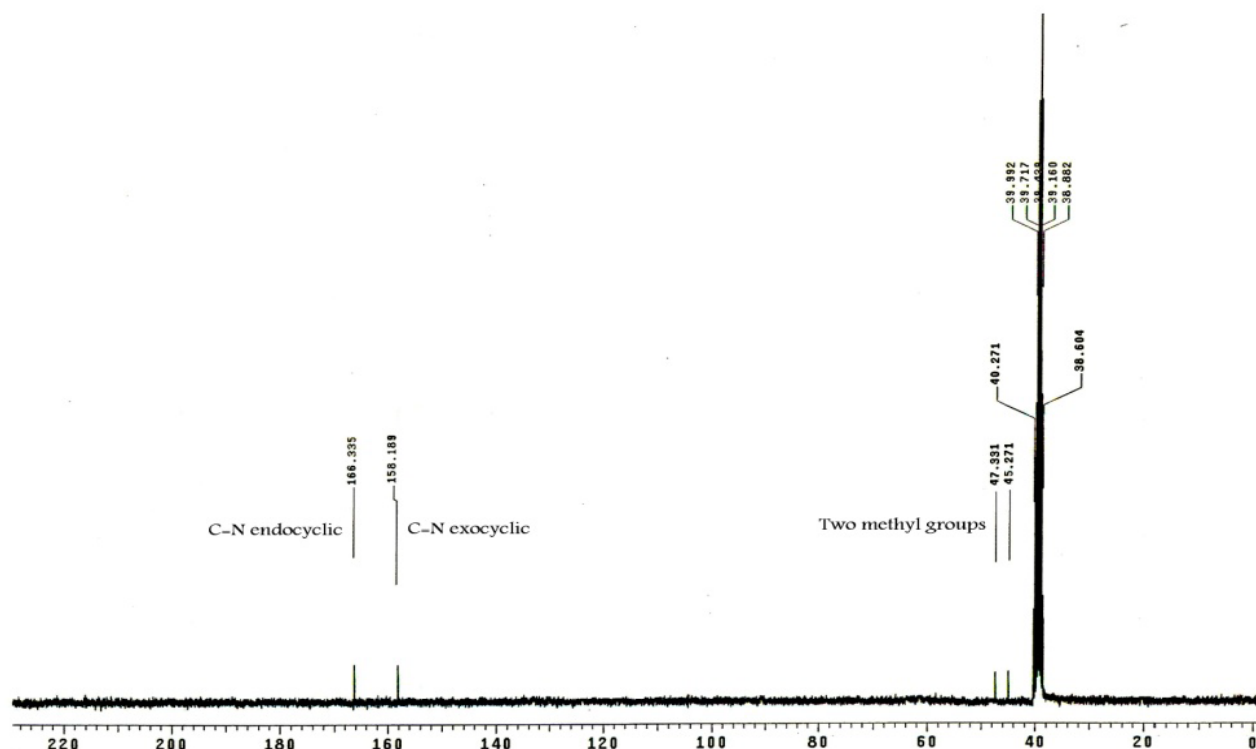


Figure 3. The ^{13}C -NMR spectrum of compound 2

4. Conclusions

4-[(Dimethyl)azanylidene]methyl} amino-2,3-dihydro-3-oxo-4H-1,2,4,3-triazaphosphole (2) is achieved in high yield *via* treatment of phosphonic dihydrazide (1) with Vilsmeier-Haack reagent.

REFERENCES

- [1] Katritzky AR, C. M. Marson. Synthesis of a dodecahydro-18,21-dioxoniacekulene. *J Am Chem Soc* 1983; 105; 3279-3284.
- [2] Horvath A, Hermecz I, Podanyi B, Meszaros Z. Nitrogen bridgehead compounds. Vilsmeier Haack acylation of 6,7,8,9-tetrahydro-4*h*-pyrido[1,2-*a*] pyrimidin-4-ones. *J Heterocycl Chem* 1985; 22; 593-598.
- [3] Balasundaram B, Venugopal M, Perumal PT. Synthetic studies on N-acetyl derivatives of amino acids and thiolactone using Vilsmeier-haack reagent. *Tetrahedron Lett* 1993; 34; 4249-4254.
- [4] Becker C, Roshchupkina G, Rybalova T, Gatilov Y, Reznikov V. Transformations of 2,2-dimethyl-2,4-dihydro-3*H*-pyrrol-3-on-1-oxide derivatives in the Vilsmeier-Haack reaction conditions. *Tetrahedron* 2008; 64; 9191-9199.
- [5] Ali Tasneem M M, Rajanna KC, Prakash PK. An efficient and facile synthesis of 2-chloro- 3-formyl-quinolines from acetanilides in micellar media by vilsmeier-haack cyclisation. *Synlett* 2001; 2; 251-257.
- [6] He LN, Zhuo RX, Chen RY, Li K, Zhang YJ. Synthesis of biologically active phosphorus heterocycles via cyclization reactions of Lawesson's reagent. *Heteroatom Chem* 1999; 10; 105-111.
- [7] Wan L, Alkorta I, Elguero J, Sun J, Zheng W. The structural and theoretical study of 1*H*-3,5-diphenyl- 1,2,4-diazaphosphole in the solid state. *Tetrahedron* 2007; 63; 9129-9135.
- [8] Ali TE, Halacheva SS. Synthetic approach of novel bis (α -aminophosphonic acid) derivatives of chromone containing 1,2,4,3-triazaphosphole moieties. *Heteroatom Chem* 2009; 20; 117-122.
- [9] Ali TE. Synthesis and antibacterial activity of some new thiadiazatriazaphospholes, thiadiazatriaza-tetra- phosphinine and thiadiazatriazaphosphepines containing 1,2,4-triazinone moiety. *Eur J Med Chem* 2009; 44; 4539-4546.
- [10] Ali TE. Synthesis of some new 1,3,2-oxazaphosphinine, 1,3,2-diazaphosphinine, acyclic and/or cyclic α -aminophosphonate derivatives containing chromone moiety. *Phosphorus Sulfur Silicon and Relat Elem* 2010; 185; 88-96.
- [11] Abdel-Aziz SA, Ali TE, El-Mahdy KM, Abdel-Karim SM. Synthesis and antimicrobial activities of some novel bis-pyrazole derivatives containing a hydrophosphoryl unit. *Eur J Chem* 2011; 2; 25-35.
- [12] Shukla JS, Zaidi MGH. Synthesis of some newer polyhydrazides containing hydrazinophosphite linkage. *Asian J Chem* 1993; 5; 253-258.
- [13] Nohara A, Umetani T, Sanno A. Studies on antianaphylactic agents-I : A facile synthesis of 4-oxo-4*H*-1-benzopyran-3-carboxaldehydes by Vilsmeier reagents. *Tetrahedron* 1974; 30; 3553-3559.
- [14] Golyanskaya OM, Voloshin NA, Chernyshev AV, Dubonosov

AD, Metelitsa AV, Mezheritskii VV, Bern VA. Synthesis and reactions of 2-(dimethyl-aminomethylidene)-6-methoxynaphtho[1,8-*bc*]pyran-3-one. Russ J Org Chem 2008; 44; 602-607.

infrarouge des groupes immonium. Spectrochim Acta, 1967; 23A; 383-385.

[15] Elguero J, Gil R, Jacquier R. Sur l'identification par

[16] Kira MA, Aboul-Enien MN, Korkor MI. The Vilsmeier-Haack reaction. IV. Reaction of phosphorus oxychloride-dimethylformamide with semicarbazones. J Heterocycl Chem 1970; 7; 25-28.