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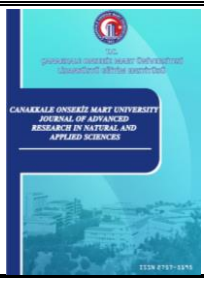

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Synthesis of *E*-Isomer of *α*-Hydrazone Phosphonates via Nucleophilic Addition of Trialkyl Phosphite to Nitrile Imines (NIs) and DFT Calculations

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Research Article

Abstract − Nitrile imines (NIs) belong to the nitrilium betaine family of 1,3-dipoles. Due to their high reactivity, NI compounds cannot be isolated and must be generated *in situ* before undergoing the desired transformation. NI derivatives were prepared by the utilization of *N*-phenyl hydrazine chloride precursors in the presence of a base. The title compounds *α*-hydrazone phosphonates have the potential to be biologically active and may serve as a precursor compound for other biologically active substances like amino phosphonic acids. Shortly, they are highly significant compounds in medicinal and synthetic chemistry. The derivatives of *α*-hydrazone phosphonate are synthesized by the nucleophilic addition of trialkyl phosphite to *in situ* generated NI derivatives and obtained in 44-95% isolated chemical yields. It is worth noting that only the *E*-isomer of the *α*-hydrazone phosphonates was obtained. Structural analyses of the *α*-hydrazone phosphonates were conducted by using proton and carbon NMR analysis along with FTIR. The researchers also performed DFT calculations including structural parameters (bond length, bond angle, and dihedral angle), HOMO and LUMO energy levels, and the zero-point vibrational energy (ZPE) for both *E* and *Z* geometric isomers of unsubstituted phenyl *α*-hydrazone phosphonate.

Keywords − *Nitrile imines, nucleophilic addition, trialkyl phosphite, 1,3-dipole, α-hydrazone phosphonates*

1. Introduction

The Nitrile imines (NI) are members of the nitrilium betaine family, one of the 1,3-dipole varieties [1]. NIs are very reactive unstable compounds and are generated *in situ* rather than isolated as pure compounds. Since NIs are highly reactive, they cannot be isolated, and they are prepared in the reaction medium, and the relevant reaction is carried out. Here are some common methods for the generation of NI derivatives: Decomposition of tetrazole compounds [2], catalytic oxidation of hydrazine compounds [3], and N-phenyl hydrazine chloride/bromide precursors [4]. Currently, the most common method to generate NI is the dehalogenation of the *N*-phenyl hydrazine chloride/bromide precursors in the presence of a base. This procedure includes deprotonation followed by the removal of the halide ion. The formation of NIs from hydrazonyl chlorides was described first by Huisgen et al. [2]. Huisgen contributed valuable insights to NI chemistry through numerous publications [5-7].

Although the most prevalent application of NIs involves their use as 1,3-dipoles in cycloaddition reactions to have access to *N*-based heterocyclic compounds, their utilization in nucleophilic addition reactions with substances such as alcohols, amines, thiols, carboxylic acids, and triphenylphosphine is seldom documented

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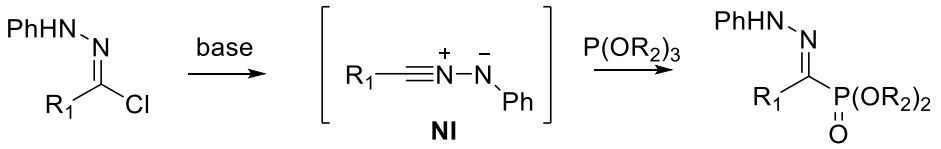
in existing literature [8-11]. Surprisingly, there is no detailed research concerning the nucleophilic addition reaction of trialkyl phosphite reagents (triethyl phosphite/trimethyl phosphite) to NI derivatives. (Scheme 1). *α*-Hydrazone phosphonates serve as precursors to *α*-amino phosphonates. The asymmetric synthesis of *α*-amino phosphonates is still a challenging process. *α*-Amino phosphonates are the close analogs of *α*-amino acids. Having phosphonate groups in its structure gives them unique properties and makes them valuable in various chemical and biological applications. *α*-Hydrazone phosphonate derivatives are of significant value in organic chemistry due to their role in accessing biologically active compounds containing phosphonate groups.

In the existing literature, one of the synthetic approaches for the synthesis of *α*-hydrazone phosphonates [12] is reacting phenylhydrazine with aroylphosphonate in pyridine as the solvent. Only the *Z* isomer of *α*-hydrazone phosphonate was isolated in 81% yield. The equilibrium between *Z* and *E* isomers was achieved by heating in acetic acid. Aroylphosphonates are not readily available and are prepared from benzoyl chloride. While the preparation of aroylphosphonate itself proceeds smoothly, the purification process demands high temperatures under vacuum conditions. The other work in the literature reported by Baccolini et al. [13] involves direct nucleophilic addition of triethyl phosphite/trimethyl phosphite to only diphenylnitrilimines. The reaction was carried out in benzene and the compound **2a** was isolated in 70% yields as a mixture of *E* and *Z* isomers with the 2:3 ratios. We have provided a detailed investigation of simple nucleophilic addition of trialkyl phosphite to NI derivatives to obtain *α*-hydrazone phosphonate derivatives to give solely *E* isomer. Although the *Z*-isomer is stable due to H-bonding, *E* configuration is less hindered.



Scheme 1. General method for the nucleophilic addition of trialkyl phosphite to NI

2. Materials and Methods

All solvents used in the reaction are commercially available and of sufficient purity. Reaction stages were monitored under UV light using TLC (Thin-Layer Chromatography). Both proton and carbon spectra were recorded in $CDCl_3$ solution; at 400 MHz and 100 MHz, respectively. In these spectra, the TMS (tetramethylsilane) peak was used as the reference solvent. All *J* values in the spectrum are in Hz; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet, indicating multiple peaks. Both trialkyl phosphites are commercially available and used without any purification. The information regarding the known compounds aligns with the values documented in the report by Kaushik et al. [12] and Baccolini et al. [13].

Commercially unavailable *N*-phenyl arylhydrazonoyl chloride compounds were prepared in two steps by following the literature procedure starting from the corresponding aldehydes [14]. Aldehyde (1 equivalent) and phenylhydrazine (1 equivalent) reagents were dissolved in 50 mL of ethanol. The mixture was stirred at room temperature for approximately 2 hours until the aldehyde reagent was completely consumed which was monitored by TLC. Afterward, the reaction mixture was concentrated under a vacuum, and the expected product aryl aryl-substituted *N*-phenyl hydrazone was obtained as a solid and used for the next step. In the chlorination step, NCS (3 equivalents) was dissolved in DCM (100 mL) by stirring at 0°C for 5 minutes. Subsequently, $S(CH_3)_2$ (6 equivalents) was introduced drop by drop, and the mixture was stirred for 15 minutes. After the formation of a white solid product, the *N*-phenyl arylhydrazone compound (1 equivalent, 20 mL DCM) was added dropwise to the reaction medium. The reaction was stirred for 2 hours at 0°C, and then cold distilled water was added to quench the reaction. Following the extraction, the organic phase was

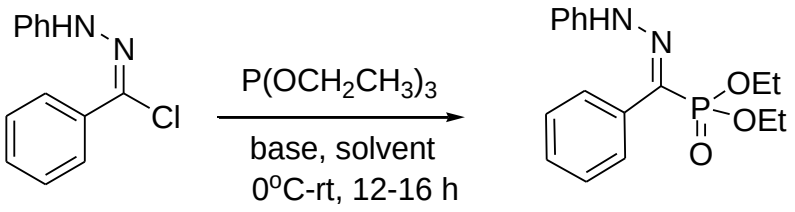
isolated, and the joined organic phase underwent washing with a saturated salt solution. The acquired organic phase was subsequently dried over sodium sulfate, filtered, and ultimately concentrated using a rotary evaporator. The resulting solid product, *N*-phenyl arylhydrazonoyl chloride, was used in the nucleophilic addition reaction without the need for any purification process.

3. Results and Discussion

3.1. Synthesis of Compounds 2a-j

There are no detailed studies in the literature that explore the addition reaction of trialkyl phosphites to NI derivatives. For this purpose, the optimization reaction has been carried out by using unsubstituted *N*-phenyl arylhydrazonoyl chloride **1a** and triethyl phosphite as shown in Table 1. *N*-Cl hydrazone compounds **1a-e** were easily prepared by following the literature procedure [14]. The generation of NI has been tested by using different bases such as triethyl amine, isopropyl amine, Ag_2CO_3, and Na_2CO_3. We have found that when the reaction was carried out in toluene and triethyl amine (entry 2) as the choice of base, the anticipated adduct **2a** was obtained in 72% yield. Isopropyl amine also gave the expected product **2a** (entry 6) albeit in low yield (55%). Inorganic bases such as Ag_2CO_3 and Na_2CO_3 were also tested in nucleophilic addition reaction of triethyl phosphite to NI **1a**. The former base did not give the product, but the later base gave the compound **2a** in acceptable chemical yield (entry 5, 63%). In all cases, we have isolated the ***E***-isomer of compound **2a**.

Table 1. Optimization reactions



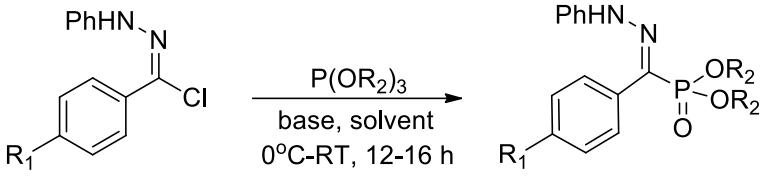
1a **2a**

Entry	Base[a]	Solvent	Yield (%)[b]
1	NEt_3	dichloromethane	67
2	NEt_3	toluene	72
3	NEt_3	asetonitrile	50
4	Ag_2CO_3	toluene[c]	-
5	Na_2CO_3	EtOAc	63
6	$NH(CHCH_3)_2$	toluene	55

[a]NI (1 equiv.), triethyl phosphite (1.2 equiv), and base (1.5 equiv.) [b]Isolated chemical yields. [c]No formation of product.

We have investigated the addition of triethyl phosphite/trimethyl phosphite to NI derivatives in the presence of triethyl amine as a choice of base. All NI derivatives were prepared *in situ* first and then trialkyl phosphite was introduced into the reaction mixture. In all cases, the expected compounds **2a-j** were obtained in good yields of 44%-95% as shown in Table 2. In the nucleophilic addition of trimethyl phosphite to NI both toluene and DCM were tested. Better chemical yields were obtained in the case of DCM (77%) and in the case of nucleophilic addition of trimethyl phosphite, DCM is the choice of solvent. It's worth noting that only the *E*-isomer of the *α*-hydrazone phosphonate compounds was obtained. We have tried to choose the different substituents at *para* position (CH_3, Br, and Cl and NO_2) in the aryl group. At *para* position, there is a direct effect on electrophilic properties of the *in situ* generated NI derivatives via resonance.

Table 2. Synthesis of α-hydrazone phosphonates **2a-j**

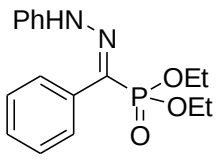


1

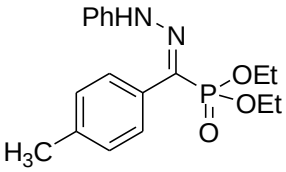
R_1= H (**1a**), CH_3 (**1b**), Br (**1c**), Cl (**1d**), NO_2(**1e**)

2

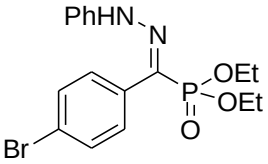
R_2= CH_2CH_3 (**2a-e**) and CH_3(**2f-j**)



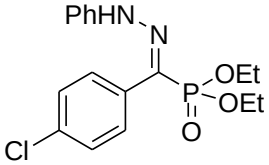
2a, 72%[a]



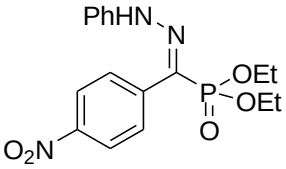
2b, 95%



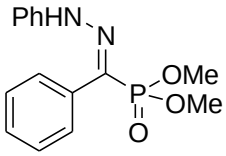
2c, 74%



2d, 82%

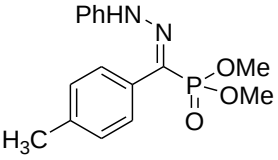


2e, 62%

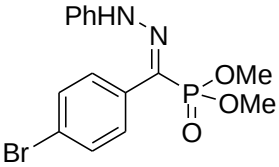


2f, 77% (DCM)[b]

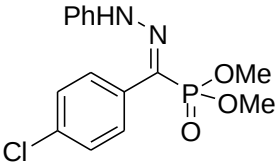
61% (toluene)



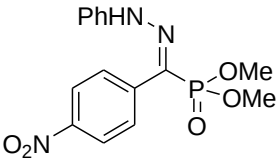
2g, 82%



2h, 44%



2i, 47%



2j, 78%

[a]The reaction was carried out in toluene in the case of triethyl phosphite addition. [b] The reaction carried out in DCM in the case of trimethyl phosphite addition

The synthesized compounds **2a-j** were analyzed by using spectroscopic methods. In the FT-IR spectrum compound **2a** the signal around 3200 cm^{-1} corresponds to the NH group, the signal around 1600 cm^{-1} is attributed to the C=N bond, the broad signal at 1200 cm^{-1} is related to the P=O bond, and finally, the signal at 970 cm^{-1} is due to the vibration of the P-O bond. In the proton NMR spectrum of compound **2a**, the signals corresponding to the -OCH_2 moiety attached to the phosphonate group, -$P(OCH_2CH_3)_2$, were observed in the range of 4.23-4.14 ppm, while the signal attributed to the -CH_3 group appeared at 1.31 ppm. The existence of a signal for the H atom attached to the -NHPh indicated the formation of the *E*-isomer of α-hydrazone phosphonate (Table 3). In the *Z*-isomer, this H-atom is involved in hydrogen bonding and does not give any signals in proton NMR [12,13]. When examining the carbon NMR spectra of this compound **2a** the quaternary C-atom of C=N attached to the phosphonate group exhibited a doublet due to the coupling with the P-atom, and a large coupling constant was observed and summarized in Table 3. In compound **2a**, the quaternary C-atom (C=N) attached to the phosphonate group showed a signal at 136 ppm as a doublet with splitting by the neighboring P-atom, with a coupling constant of 239.9 Hz.

Table 3. ^{1}H NMR data for signal -NHPh and ^{13}C NMR data for quaternary carbon C=N in compounds **2a-j**

Compound **2**	^{1}H NMR of -NHPh (in ppm)	^{13}C NMR chemical shifts (in ppm) and coupling constant values (*J* in Hz)
2a	8.15	136.0 (d, *J* = 239.9 Hz)
2b	8.22	136.3 (d, *J* = 237.9 Hz)
2c	8.15	134.8 (d, *J* = 242.3 Hz)
2d	8.15	134.6 (d, *J* = 242.1 Hz)
2e	12.4	124.8 (d, *J* = 236.7 Hz)
2f	8.23	135.2 (d, *J* = 240.1 Hz)
2g	8.15	135.6 (d, *J* = 240.0 Hz)
2h	8.15	133.9 (d, *J* = 242.2 Hz)
2i	8.20	133.9 (d, *J* = 242.2 Hz)
2j	12.3	124.9 (d, *J* = 234.0 Hz)

3.1.1. Experimental Part

General Procedure for the synthesis of compound **2**: To a solution of N-chloroaroylhydrazine (1 equiv.) in toluene or DCM (0.5 M) triethyl amine (1.5 equiv.) was added at 0 ºC. After five minutes at this temperature, trialkyl phosphite (1.2 equiv.) was added drop by drop. The reaction mixture was stirred at ambient temperature for about 12-16 hours and then subjected to purification. The raw product underwent purification on silica gel utilizing hexane:EtOAc mixture as the eluting solvent.

- *(E)-diethyl (2-phenylhydrazono) (phenyl) methylphosphonate* 2a: Yellow oil, R_f=0.25 (1:1, hexane:EtOAc. ^{1}H ($CDCl_3$, 400 MHz, ppm): δ 8.15 (s, 1H, NHPh), 7.51 (t, *J* = 7.3 Hz, 2H), 7.42 (t, *J* = 7.6 Hz, 3H), 7.19 – 7.27 (m, 2H), 7.03 (d, *J* = 8.1 Hz, 2H), 6.91 (t, *J* = 7.4 Hz, 1H), 4.23 – 4.14 (m, 4H, $PO(OCH_2CH_3)_2$), 1.31 (t, *J* = 7.0 Hz, 6H, $PO(OCH_2CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 142.7 (C), 136.0 (d, *J* = 239.9 Hz, C=N), 129.9 (d, *J* = 22.6 Hz, C), 129.5, 129.4 (x2), 129.0 (x2), 128.50, 128.46, 121.6, 113.4 (x2), 62.8 (d, *J* = 6.1 Hz, $P(OCH_2CH_3)_2$), 16.2 (t, *J* = 6.7 Hz, $P(OCH_2CH_3)_2$). FT-IR (cm^{-1}): 3220, 2981, 1600, 1548, 1502, 1228, 1019, 970, 752, 695.
- *(E)-diethyl (2-phenylhydrazono) (p-tolyl) methylphosphonate* 2b: Yellow oil, R_f= 0.46 (1:1, hexane:EtOAc). ^{1}H ($CDCl_3$, 400 MHz, ppm): δ 8.22 (s, 1H, NHPh), 7.31 (s, 4H), 7.23 (dd, *J* = 8.5, 7.2 Hz, 2H), 7.04 (d, *J* = 7.5 Hz, 2H), 6.90 (t, *J* = 7.4 Hz, 1H), 4.24 – 4.08 (m, 4H, $PO(OCH_2CH_3)_2$), 2.34 (s, CH_3), 1.33 (dt, *J* = 11.0, 7.1 Hz, 6H, $PO(OCH_2CH_3)_2$). ^{13}C NMR (101 MHz, *CDCl*$_3$, ppm): δ 142.8 (C), 139.6 (C), 136.3 (d, *J* = 237.9 Hz, C=N), 130.1 (x2), 128.4 (x2), 128.37, 128.32, 126.8 (d, *J* = 22.8 Hz, C), 121.4, 113.3 (x2), 62.8 (d, *J* = 6.1 Hz, $P(OCH_2CH_3)$), 61.6 (d, *J* = 5.8 Hz, $P(OCH_2CH_3)_2$), 21.3 (CH_3), 16.2 (t, *J* = 6.5 Hz, $P(OCH_2CH_3)_2$). FT-IR (cm^{-1}): 3224, 2981, 1604, 1546, 1502, 1228, 1027, 970, 752, 662.
- *(E)-diethyl (2-phenylhydrazono) (4-bromophenyl) methylphosphonate* 2c: Yellow oil, R_f= 0.58 (1:1 hexane:EtOAc). ^{1}H ($CDCl_3$, 400 MHz, ppm): δ 8.15 (s, 1H, NHPh), 7.46 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 7.9 Hz, 2H), 7.21 (d, *J* = 7.8 Hz, 2H), 7.03 (d, *J* = 7.8 Hz, 2H), 6.90 (t, *J* = 7.3 Hz, 1H), 4.19–4.05 (m, 4H, $PO(OCH_2CH_3)_2$), 1.30 (t, *J* = 8.0 Hz, 6H, $PO(OCH_2CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 142.6 (C), 135.6 (C-Cl), 134.8 (d, *J* = 242.3 Hz, C=N), 130.15, 130.11, 129.8 (x2), 129.1 (x2), 128.4 (d, *J* = 21.8 Hz, C), 121.9, 113.5 (x2), 62.9 (d, *J* = 6.1 Hz, $P(OCH_2CH_3)_2$), 61.7 (d, *J* = 5.6 Hz, $P(OCH_2CH_3)_2$), 16.2 (t, *J* = 6.8 Hz, $P(OCH_2CH_3)_2$). FT-IR (cm^{-1}): 3221, 2982, 1604, 1548, 1496, 1229, 1025, 972, 751, 656.

- *(E)-diethyl (2-phenylhydrazono) (4-chlorophenyl) methylphosphonate* 2d: Yellow oil, R_f= 0.46 (1:1 hexane:EtOAc). ^{1}H ($CDCl_3$, 400 MHz, ppm): δ 8.15 (s, 1H, NHPh), 7.54 (d, J = 8.3 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 7.13 (t, J = 8.0 Hz, 2H), 6.96 (d, J = 7.5 Hz, 2H), 6.82 (t, J = 7.3 Hz, 1H), 4.12–3.97 (m, 4H, $PO(OCH_2CH_3)_2$), 1.24 (t, J = 7.8 Hz, 6H, $PO(OCH_2CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 142.6 (C), 134.6 (d, J = 242.1 Hz, C=N), 132.7 (x2), 130.34, 130.30, 129.1 (x2), 128.8 (d, J = 23.0 Hz, C), 123.9 (C-Br), 121.8, 113.5 (x2), 62.9 (d, J = 6.2 Hz, $P(OCH_2CH_3)_2$), 61.7 (d, J = 5.6 Hz, $P(OCH_2CH_3)_2$), 16.1 (t, J = 6.7 Hz, $P(OCH_2CH_3)_2$). FT-IR (cm^{-1}): 3217, 2981, 1605, 1548, 1236, 1024, 972, 755, 696.

- *(E)-diethyl (2-phenylhydrazono) (4-nitrophenyl) methylphosphonate* 2e: Light brown oil, R_f= 0.62 (2:1 hexane:EtOAc). ^{1}H ($CDCl_3$, 400 MHz, ppm): δ 12.4 (s, 1H, NHPh), 8.11 (d, J = 8.5 Hz, 2H), 7.87 (d, J = 8.7 Hz, 2H), 7.30–7.15 (m, 4H), 6.94 (d, J = 7.1 Hz, 1H), 4.18–3.99 (m, 4H, $PO(OCH_2CH_3)_2$), 1.25 (t, J = 6.4 Hz, 6H, $PO(OCH_2CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 146.3, 143.1 (d, J = 26.8 Hz), 142.7, 129.7, 128.9, 126.1, 124.8 (d, J = 236.7 Hz, C=N), 123.4, 114.8, 113.8, 62.9 (d, J = 4.4 Hz, $P(OCH_2CH_3)_2$), 16.1 (t, J = 5.4 Hz, $P(OCH_2CH_3)_2$). FT-IR (cm^{-1}): 3162, 2963, 1594, 1466, 1330, 1264, 1013, 964.

- *(E)-dimethyl (2-phenylhydrazono) (phenyl) methylphosphonate* 2f: Yellow oil, R_f= 0.38 (2:1 Hexane:EtOAc). ^{1}H ($CDCl_3$, 400 MHz, ppm): δ 8.23 (s, 1H, NHPh), 7.49 (d, J = 7.1 Hz, 2H), 7.41 (t, J = 8.1 Hz, 3H), 7.21 (t, J = 8.0 Hz, 2H), 7.02 (d, J = 8.6 Hz, 2H), 6.89 (t, J = 7.3 Hz, 1H), 3.80 (d, J = 11.0 Hz, $PO(OCH_3)_2$, 6H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 142.6, 135.2 (d, J = 240.1 Hz, C=N), 129.8, 129.6, 129.5 (x2), 129.1 (x2), 128.4 (d, J = 4.0 Hz, x2), 121.7, 113.4 (x2), 53.4 (d, J = 4.0 Hz, $P(OCH_3)_2$). FT-IR (cm^{-1}): 3197, 2952, 1702, 1546, 1226, 1179, 1017, 831, 753, 692.

- *(E)-dimethyl (2-phenylhydrazono) (p-tolyl) methylphosphonate* 2g: Yellow oil, R_f= 0.25 (1:1 hexane:EtOAc). ^{1}H ($CDCl_3$, 400 MHz, ppm): δ 8.15 (s, 1H, NHPh), 7.26 (s, 4H), 7.18 (dd, J = 8.6, 7.3 Hz, 2H), 6.98 (d, J = 7.5 Hz, 2H), 6.86 (t, J = 7.4 Hz, 1H), 3.77 (d, J = 11.0 Hz, 6H, $PO(OCH_3)_2$), 2.34 (s, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 142.8 (C), 139.9 (C), 135.6 (d, J = 240.0 Hz, C=N), 130.6, 130.2, 129.4, 129.0, 128.6 (d, J = 4.0 Hz), 128.3 (d, J = 4.0 Hz), 126.7 (d, J = 22.7 Hz, C), 121.8 (d, J = 59.4 Hz), 113.5 (d, J = 60.2 Hz), 53.7 (d, J = 6.9 Hz, $P(OCH_3)_2$), 53.4 (d, J = 5.4 Hz, $P(OCH_3)_2$), 21.4 (CH_3). FT-IR (cm^{-1}): 3208, 2950, 1600, 1501, 1502, 1233, 1025, 834, 753.

- *(E)-dimethyl (2-phenylhydrazono) (4-bromophenyl) methylphosphonate* 2h: Yellow oil, R_f= 0.38 (1:1 hexane:EtOAc). ^{1}H ($CDCl_3$, 400 MHz, ppm): δ 8.15 (s, 1H, NHPh), 7.59 (t, J = 8.5 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 7.00 (d, J = 8.1 Hz, 2H), 6.88 (t, J = 7.3 Hz, 1H), 3.78 (d, J = 11.0 Hz, 3H, $P(OCH_3)_2$), 3.71 (d, J = 11.6 Hz, 3H, $P(OCH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 142.6 (C), 133.9 (d, J = 242.2 Hz, C=N), 132.9, 130.5, 130.1, 129.5, 129.0, 128.8, 128.6, 124.2, 122.1 (d, J = 56.4 Hz), 113.7 (d, J = 57.4 Hz), 53.7 (d, J = 6.8 Hz, $P(OCH_3)_2$), 53.4 (d, J = 5.8 Hz, $P(OCH_3)_2$). FT-IR (cm^{-1}): 3200, 2953, 1599, 1478, 1260, 1023, 791.

- *(E)-dimethyl (2-phenylhydrazono) (4-chlorophenyl) methylphosphonate* 2i: Yellow oil, R_f=0.39 (1:1 hexane:EtOAc). ^{1}H ($CDCl_3$, 400 MHz, ppm): δ 8.20 (s, 1H, NHPh), 7.48 (d, J = 8.5 Hz, 2H), 7.37 (d, J = 8.7 Hz, 2H), 7.28 – 7.18 (m, 2H), 7.05 (d, J = 7.5 Hz, 2H), 6.93 (t, J = 7.3 Hz, 1H), 3.82 (d, J = 11.0 Hz, 6H, $PO(OCH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 142.6 (s, C), 135.8, 133.9 (d, J = 242.2 Hz, C=N), 130.5, 130.3, 130.1, 129.8, 129.71, 129.66, 128.7, 128.2 (d, J = 23.2 Hz), 122.1 (d, J = 56 Hz), 113.1 (d, J = 22.5 Hz), 53.4 (d, J = 3.7 Hz, $P(OCH_3)_2$). FT-IR (cm^{-1}): 3174, 2946, 1603, 1528, 1478, 1260, 1013, 792.

- *(E)-dimethyl (2-phenylhydrazono) (4-nitrophenyl) methylphosphonate* 2j: Light brown oil, R_f= 0.38 (2:1 hexane:EtOAc). ^{1}H ($CDCl_3$, 400 MHz, ppm): δ 12.3 (s, 1H, NHPh), 8.11 (d, J = 9.0 Hz, 2H), 7.84 (d, J = 9.2 Hz, 2H), 7.27 (t, J = 7.4 Hz, 2H), 7.23–7.17 (m, 2H), 6.96 (t, J = 7.2 Hz, 1H), 3.72 (d, J = 11.5 Hz, 6H,

$PO(OCH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 146.6, 143.1 (d, J = 26.9 Hz), 142.8, 130.0, 129.2, 126.2, 124.9 (d, J = 234.0 Hz, C=N), 124.0, 115.1, 114.2, 53.1 (d, J = 7.4 Hz, $P(OCH_3)_2$). FT-IR (cm^{-1}): 3179, 2958, 1595, 1466, 1330, 1265, 1013, 851.

3.2. DFT Calculation of E/Z Form of Compounds 2a and 2f

Theoretical calculations utilized Gaussian 09, and visualization was conducted with GaussView 5.0 [15]. Geometry optimization for the *E* form of **2a** and **2f** and Z form of **2a** and **2f** molecules was carried out using the 6-31+G(d,p) basis set functional integrated with B3LYP in the DFT method. Molecules were determined by three structural parameters: bond length, bond angle and dihedral angle. In Figure S1 and Table S1-S4 (the data is given in the supporting information), the numbered arrangement of atoms in the molecules after geometric optimization, and the corresponding data for angles and bond lengths between these atoms are provided. The isomers can transform by rotating the nitrogen group 180°. The potential for hydrogen bonding between the hydrogen on nitrogen in the trans position and phosphorus results in the fixation of the nitrogen group and resistant to rotate (Figure 1). Therefore, the zero-point vibrational energy (ZPE) is approximately 0.21 kcal/mol and 0.10 kcal/mol higher for *Z*-configurations in *Z*-**2f** and *Z*-**2a**, respectively. These energy differences may be significant in terms of molecular stability and reactivity, as small energy changes in specific conformations can dictate the preferred pathway of chemical reactions.

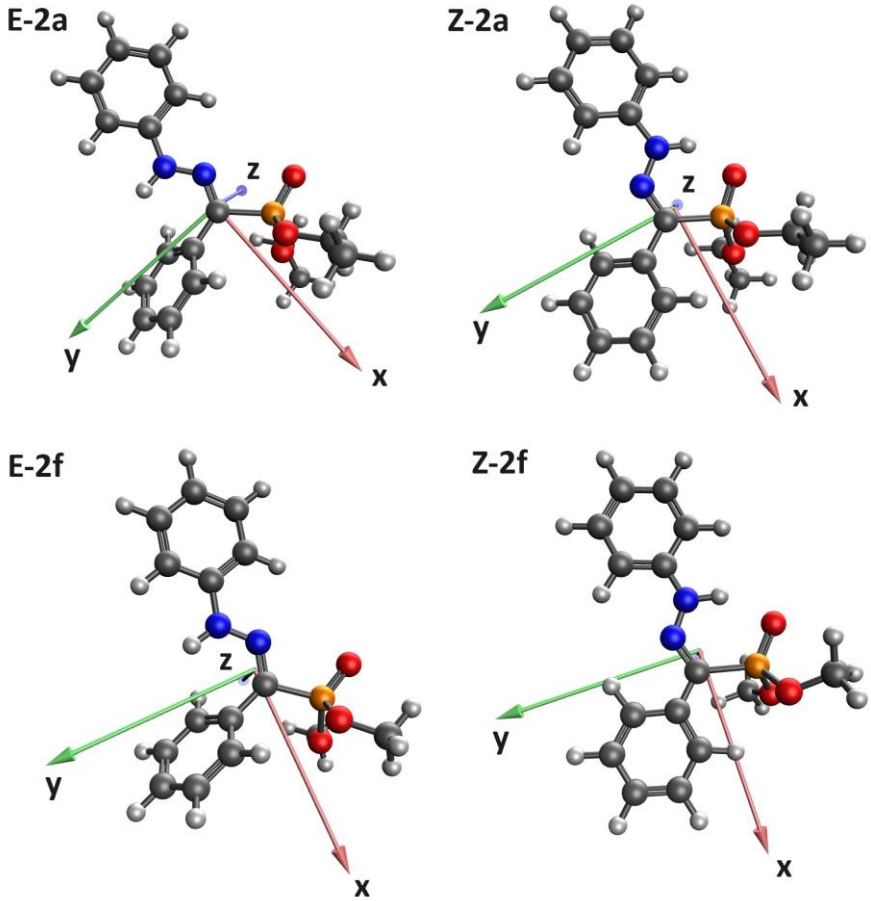


Figure 1. Images of molecules *E*-**2a** and *Z*-**2a**; *E*-**2f** and *Z*-**2f** from different perspectives after geometric optimization

The DFT analysis reveals that in the examined molecular structures, the Highest Occupied Molecular Orbital (HOMO) and Lowest Unoccupied Molecular Orbital (LUMO) exhibit charge distribution patterns along the entire molecular structure (Figure 2). Specifically, in *E*- configurations such as *E*-**2f** and *E*-**2a**, the phenyl units

are positioned in closer proximity, influencing the charge distribution. On the other hand, *Z*- configurations like *Z*-**2f** and *Z*-**2a** show phenyl units that are more distant from each other and adopt a planar arrangement. Despite these structural variations, the charge distribution appears to be consistently and homogeneously delocalized across the entirety of the systems studied. In addition, it has been observed that the band gap values of *Z*- configurations in both molecules are lower compared to the *E*- configurations. The fact that the LUMO level of the *Z*- configuration is lower than that of the *E*- configuration implies that the energy levels, and consequently, electron behavior, are more accessible in the *Z*- configuration. It is considered that the positions of the phenyl groups in the *E*-configuration create steric hindrance, while the planarity of the phenyl groups in the *Z*-configuration facilitates charge movement. Additionally, the interaction between the hydrogen attached to nitrogen in the *Z*-configuration and the electrophilic phosphorus atom in the phosphonate group has supported this situation. As a result, *Z*- configurations are energetically more stable for both molecules. The lower LUMO level in the *Z*- configuration suggests that the molecule can accept electrons at a lower energy, potentially making it more efficient in electron transfer processes.

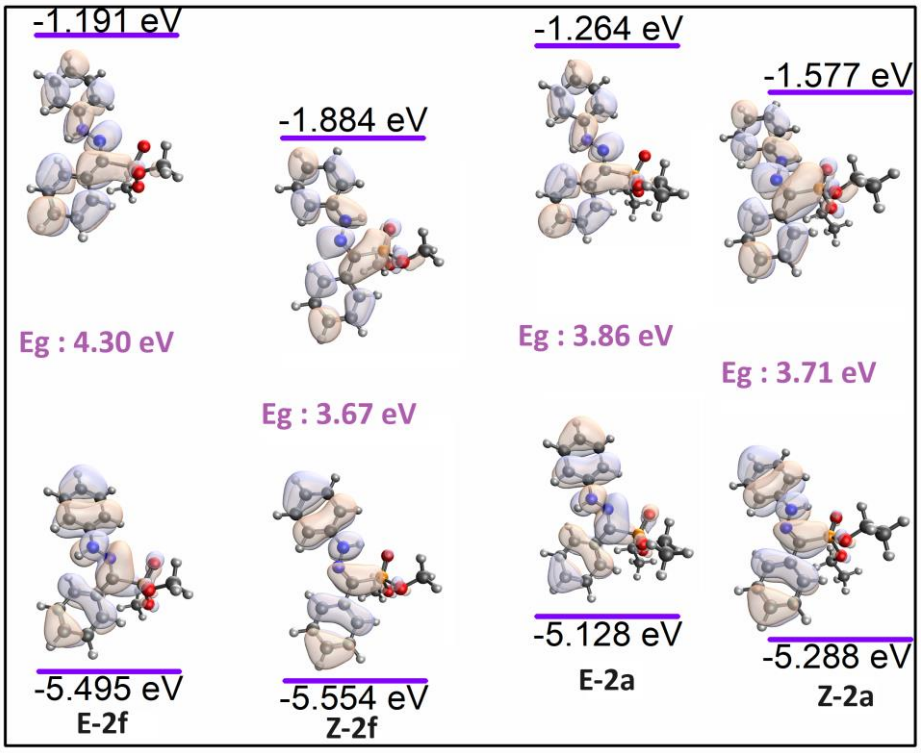


Figure 2. Theoretical charge distribution of HOMO-LUMO in *E*-**2f** and *Z*-**2f**; *E*-**2a** and *Z*-**2a** structures at the B3LYP/6-31G(d,p) level

In addition, the interaction between nucleophilic and electrophilic groups plays a vital role in chemical reactions, and understanding their contributions to factors like HOMO-LUMO and band structures is important [16]. According to the total density calculation, electrophilic phosphonates, a common group in structures, contribute directly to the LUMO of molecules since they tend to accept electrons (act as acceptors). The color scale of the phosphonate groups in trans configurations indicates their higher electronegativity, providing evidence for their lower energy levels (Figure 3).

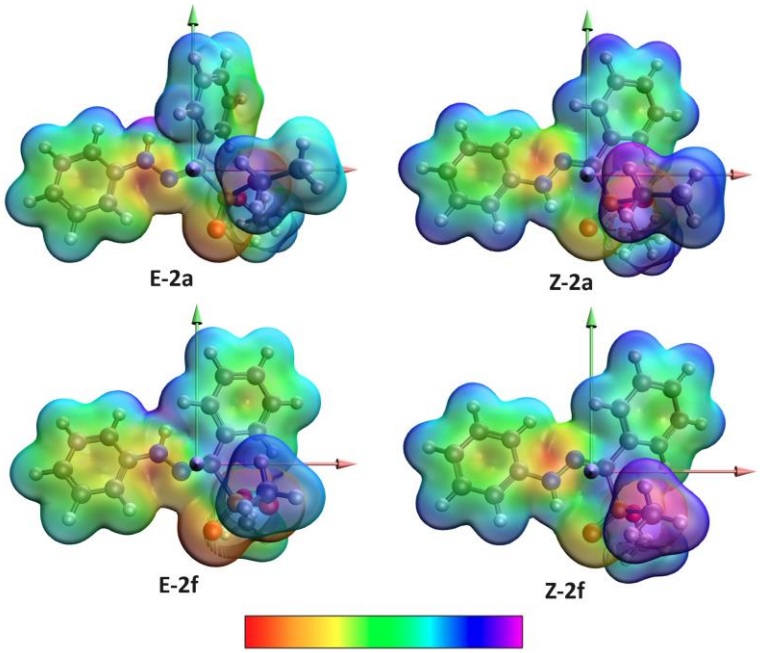


Figure 3. Electron density of *E*-**2a**/*Z*-**2a** and *E*-**2f**/*Z*-**2f**

4. Conclusion

The synthesis of exclusively the *E*-isomer of *α*-hydrazone phosphonates has been achieved in good yields through the nucleophilic addition of triethyl phosphite and trimethyl phosphite to NI derivatives. The dechlorination of compound **1** to form the corresponding NI's *in situ* was achieved by using triethylamine. The *α*-hydrazone phosphonates were obtained exclusively in *E* form rather than *Z* form. Nucleophilic addition of trialkyl phosphite prefers to attack NI derivatives from the less hindered site to give exclusively *E*-isomer of *α*-hydrazone phosphonate derivatives. *Z*-isomer of *α*-hydrazone phosphonate is stable due to H-bonding, but *E* configuration *α*-hydrazone phosphonate is sterically less hindered. We have also performed the DFT calculation for compounds **2a** and **2f** for both *E* and *Z* forms. After the geometric optimization, we have determined the three structural parameters bond length and angle along with the dihedral angle provided in supporting information. There is a potential H-bonding between the hydrogen atom connected to the *N*-atom and the *O*-atom in the phosphonate group in the *Z* geometry of compounds **2a** and **2f**. This makes the compounds **2a** and **2f** resistant to rotation (Fig. 1). This results in a higher zero-point vibrational energy (ZPE) and the value is about 0.21 kcal/mol and 0.10 kcal/mol higher for *Z*-configurations in compounds **2f** and **2a**, respectively. We have also determined the HOMO-LUMO energy levels for both *E* and *Z* isomer of compounds **2a** and **2f**. In *E* isomers of compound **2f** (Figure 2) and **2a** the phenyl groups are closely positioned affecting the charge distribution. However, in *Z*- isomer of compounds **2a** and **2f** phenyl units are spaced farther apart and adopt a planar arrangement. Due to H-bonding *Z*-configurations of both compounds **2a** and **2f** are found to be energetically more stable. To that end, the titled compounds *α*-hydrazone phosphonates will be converted into their *α*-hydrazone phosphonic acid forms and the investigation for the biological activity tests in due course.

Author Contributions

The first author designed and performed the synthesis and wrote the paper. The second author performed the DFT calculation of the titled compounds. They all read and approved the final version of the paper.

Conflicts of Interest

All the authors declare no conflict of interest.

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