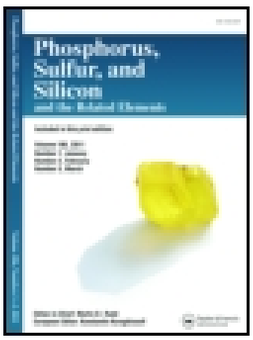

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ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/gpss20

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To cite this article: Sidika Polat-Cakir (2020): 1,3-Dipolar cycloaddition reactions of acyl phosphonates with nitrile oxides: synthesis of phosphonate-containing dioxazole derivatives, Phosphorus, Sulfur, and Silicon and the Related Elements, DOI: 10.1080/10426507.2020.1854259

To link to this article: https://doi.org/10.1080/10426507.2020.1854259

PHOSPHORUS, SULFUR, AND SILICON AND THE RELATED ELEMENTS
https://doi.org/10.1080/10426507.2020.1854259

1,3-Dipolar cycloaddition reactions of acyl phosphonates with nitrile oxides: synthesis of phosphonate-containing dioxazole derivatives

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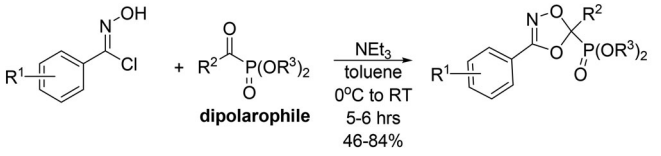
ABSTRACT

New phosphonate-containing five-membered heterocyclic dioxazole derivatives are synthesized via 1,3-dipolar cycloaddition reactions of nitrile oxides used as dipole with acyl phosphonates under basic conditions. Herein, acyl phosphonates take part in the cyclization process as a dipolarophile to afford the related dioxazole compounds in moderate-to-good yields (49–84%). Substituted aryl nitrile oxides and aroyl phosphonates were employed in the 1,3-dipolar cycloaddition reactions where triethylamine was the effective tertiary base. Alkyl version of acyl phosphonate also afforded the expected cycloadduct, that is, dimethyl 5-isopropyl-3-phenyl-1,4,2-dioxazol-5-yl-5-phosphonate. Diethyl/dimethyl 3,5-aryl-1,4,2-dioxazol-5-yl-5-phosphonate derivatives are fully characterized by using ^{1}H NMR, ^{13}C NMR, ^{31}P-NMR, and FT along with high-resolution mass spectroscopy.

ARTICLE HISTORY
Received 5 October 2020
Accepted 18 November 2020

KEYWORDS
1,3-Dipolar cycloaddition; acyl phosphonate; dioxazole; heterocyclic; dipole and dipolarophile

GRAPHICAL ABSTRACT



Introduction

1,3-Dipolar cycloaddition (DC) reactions between dipoles and dipolarophiles are one of the fundamental reactions of organic chemistry for the synthesis of five-membered heterocycles.[1,2] There are two types of 1,3-dipoles, that is, allyl anion and propargyl–allenyl anion.[1,2] Allyl anions are classified as having *N*-atom- and *O*-atom-centered dipoles. Some examples for the *N*-atom-centered allyl anions are azomethine ylides, nitro compounds, and nitrones. Carbonyl ylides and carbonyl imines are the examples for the *O*-atom-centered allyl anions. Alkenes and alkynes are the most common dipolarophiles used in the 1,3-DC reactions.

The *N*-atom-centered dipole such as nitrile oxide (R–C≡N^{+}– O^{-}), which is a propargyl–allenyl type dipole, has been utilized in the 1,3-DC reactions to construct five-membered *N*-heterocyclic compounds. Isoxazolidines are easily synthesized via 1,3-dipolar cycloaddition of nitrile oxides to alkenes.[3] Cycloaddition of nitrile oxides with alkynes offers a direct synthesis of isoxazoles. This type of dipole is easily obtained from readily available starting materials such as dehydrogenation of aldoximes[4] or dehydration of nitroalkanes.[5,6] A more practical way to form nitrile oxide is the addition of a base to hydroximoyl chloride.[7,8] The *in situ* formed nitrile oxides react immediately with a variety of dipolarophiles, because they are unstable and are very reactive intermediates.[9] Commercially available aldehydes are the precursor of corresponding nitrile oxides. Oxazoles and isoxazole structures are important structures in the field of medicinal chemistry, because they exhibit a wide range of biological activity.[10] Isoxazole-based drug called valdecoxib is used in the market to treat osteoarthritis and rheumatoid arthritis.[11]

The 1,3-DC reactions of nitrile oxides with alkenes as a dipolarophile are well documented.[12] Vinylphosphonate as dipolarophile was used in the 1,3-DC with nitrile oxides for the synthesis of phosphonate-containing isoxazole derivatives. This work was reported by Ye *et al.* where the phosphonyl isoxazolines were isolated in 47–69% yields.[13] In the literature, there are many examples of 1,3-DC reactions of nitrile oxides with alkenes for the synthesis of five-membered *N*-heterocycles, but the cyclization reactions with aldehydes as dipolarophiles are very limited. Huisgen *et al.* have reported the 1,3-DC reaction between nitrile oxide and benzaldehyde in the presence of a base where the corresponding dioxazole product was formed with 55% yield.[14] Azam *et al.* have also reported the synthesis of new dioxazole

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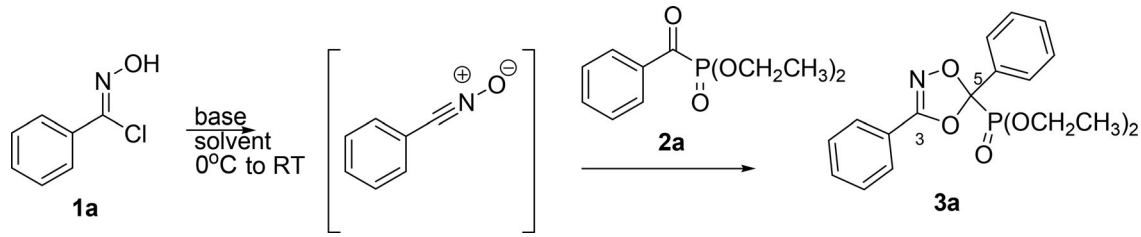
Supplemental data for this article can be accessed here.

Table 1. Investigation of bases in 1,3-DC reactions of benzohydroximoyl chloride **2a** and phenyl acyl phosphonate **1a**.



Entry	Base[a]	Solvent	Yield (%)[b]
1	NEt_3	DCM	40
2	NEt_3	Toluene	76
3	NEt_3	CH_3CN	38
4	NEt_3	MeOH	ND[c]
5	NEt_3	DMF	23
6	$NaHCO_3$	Toluene	NR[d]
7	$NaHCO_3$	DCM	NR[d]
8	Na_2CO_3	CH_3CN	67
9	DABCO	CH_3CN	ND[c]
10	DBU	CH_3CN	50

[a]The reactions were carried out with hydroximoyl chloride **2a** (2.0 equiv.), benzoyl acyl phosphonate **1a** (1 equiv.), and base (2.5 equiv.) at the specified temperature until the disappearance of benzoyl acyl phosphonate indicated by TLC.
[b]Isolated chemical yield.
[c]ND: not determined decomposed.
[d]NR: no reaction.

derivatives while testing them for potential antiviral activity.[15] In the latter work, various aldehydes were simply reacted with oxime under basic conditions to synthesize the dioxazoles.

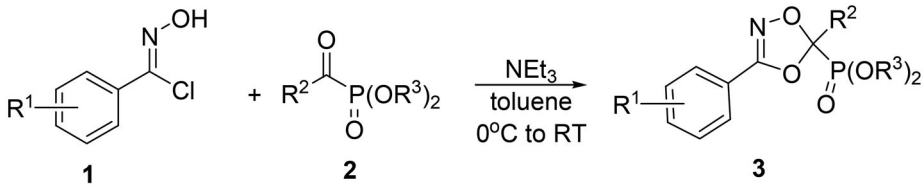
Acyl phosphonates are one of the useful members of the organophosphorous compounds, and they could be used as a reagent to access *P*-atom-containing organic structures. Having a phosphonate group in the structure may enhance the biological activity of a parent structure.[16] Acyl phosphonates are used in many reactions and even in hetero Diels–Alder reactions to synthesize glycosyl-type phosphonates where they act as a dienophile and easily react with electron-rich dienes.[17] Herein, acyl phosphonates are utilized in the 1,3-dipolar cyclization reaction of nitrile oxide under basic condition to synthesize phosphonate-containing new dioxazole five-membered heterocyclic compounds. In the 1,3-DC reactions, acyl phosphonates take part as a dipolarophile, which leads to the formation of the dioxazole cycloadducts possessing a phosphonate group.

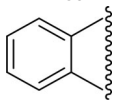
Results and discussion

To optimize the 1,3-dipolar cycloaddition reaction, benzohydroximoyl chloride **1a** precursor of nitrile oxide acting as dipole, and benzoyl acyl phosphonate **2a** acting as dipolarophile were chosen as the model substrates. Dechlorination of benzohydroximoyl chloride with a base led to the formation of nitrile oxide *in situ*. Benzoyl acyl phosphonate **2a** was easily prepared according to a literature procedure reported by Taylor *et al.*[18] Tertiary bases (i.e., NEt_3, DBU, and DABCO) and inorganic bases (i.e., Na_2CO_3 and $NaHCO_3$) in different solvent systems were tested as shown in Table 1. The dechlorination reaction of benzohydroximoyl chloride **1a** to synthesize the phosphonate-containing dioxazole compound **3a** was carried out in different solvents such as DCM, toluene, and acetonitrile. In the case of triethylamine in toluene, the 1,3-DC reaction between nitrile oxide **1a** and phenyl substituted acyl phosphonate **2a** proceeded smoothly at room temperature and offered the expected compound **3a** in 76% yield within 5–6 h. We have found that triethylamine was the most effective tertiary base for the cycloaddition reactions of acyl phosphonate with nitrile oxides.

The structure of **3a** was elucidated by spectral analyses of both proton and carbon NMRs along with DEPT and HSQC. In the proton NMR, the triplet was observed at 1.19 ppm corresponding to the protons $-CH_3$ of the phosphonate group. The protons of $-OCH_2$ in the phosphonate group appeared as multiples integrating for four hydrogens in the range $4.24 - 4.00$ ppm. These two signals clearly indicated the existence of diethyl phosphonate group in the structure. The aryl group signals in the dioxazole structure **3a** were observed at $7.81 - 7.30$ ppm range integrating for ten hydrogens. The carbon NMR spectra revealed ten signals for the phenyl groups where the four of them were assigned as quaternary C-atom by using DEPT-135 NMR. The quaternary carbon atom of $-C=N$ (C-3) was observed at 158.2 ppm. The quaternary C-atom corresponding to –OCO– (C-5) resonated at 118 ppm with a large coupling constant value ($J_{C\text{-}P}$ = 199.1 Hz) due to the neighboring P-atom.[17,19] This characteristic signal (C-5) has been observed in all synthesized phosphonate-containing dioxazole structures **3a**–**3o** in the range $109.2 - 116.0$ ppm obtained from carbon NMR. In the carbon NMR of **3a**, the signals at 64.7 and 64.5 ppm were assigned as $-OCH_2$ corresponding to the diethyl phosphonate group ($PO(O\underline{CH_2}CH_3)_2$) while the methyl group of the diethyl phosphonate resonated at 16.2 ppm. ^{31}P NMR clearly indicated the existence of phosphonate group in the corresponding

Table 2. Substrate scope of 1,3-DC reactions of nitrile oxides **1** with acyl phosphonates **2**.



Entry	R^1	R^2	R^3	Dioxazole[a]	Yield (%)[b]
1	H	Ph	OEt	**3a**	76
2	H	Ph	OMe	**3b**	74
3	H	4-MeC_6H_4-	OEt	**3c**	74
4	H	4-$MeOC_6H_4$-	OEt	**3d**	49
5	H	4-ClC_6H_4-	OEt	**3e**	78
6	H	4-FC_6H_4-	OEt	**3f**	60
7	H	2-ClC_6H_4-	OMe	**3g**	69
8	H	3-ClC_6H_4-	OMe	**3h**	77
9	H	$CH(CH_3)_2$	OMe	**3i**	59
10	4-Me	Ph	OEt	**3j**	61
11	4-Br	Ph	OEt	**3k**	84
12	4-Cl	Ph	OEt	**3l**	70
13	4-NO_2	Ph	OEt	**3m**	66
14	4-MeO	Ph	OEt	**3n**	58/60[c]
15		Ph	OEt	**3o**	84

[a]Reaction is monitored by TLC, and the reaction mixture subjected to purification until the disappearance of acyl phosphonates indicated by TLC.
[b]Isolated chemical yield. [c]Both NEt_3 (toluene) and Na_2CO_3 (acetonitrile) were used as a base.

dioxazole structure. In the cycloaddition reaction, benzoyl acyl phosphonate **2a** took part as a dipolarophile where the *in situ* formed planar nitrile oxide appeared as a dipole.

After determining the optimized reaction conditions, different aromatic hydroximoyl chlorides and acyl phosphonates were subsequently tested to examine the substrate scopes of those [3 + 2] 1,3-DC reactions. Both electron donating (ED) and electron withdrawing substituents (EW) for both dipole and dipolarophile were used. The required hydroximoyl chlorides were easily prepared according to a procedure given in the literature.[20,21] Acyl phosphonate derivatives were prepared via Arbuzov reaction by simply treating the parent chlorides with both triethyl and trimethyl phosphites.[18] As shown in Table 2, all of the tested substrates in 1,3-DC reactions gave the expected dioxazole cycloadducts **3a–3p**. Aroyl phosphonates having different positions on the phenyl ring and electronic properties were used in cycloaddition reactions (Table 2, entries 1–8). They all offered the corresponding phosphonate-containing dioxazole derivatives **3a**-**3j** in moderate yields. Methyl ester of benzoyl phosphonate **2b** used in the 1,3-DC reaction afforded the expected cycloadduct **3b** in similar yield of **3a** (entry 2). The electronic properties of aroyl phosphonates did not notably affect the chemical yields except dioxazole **3d** (Table 2, entry 4). The aroyl phosphonate **2d** having a strong electron donating group (MeO) on the phenyl group at the para position afforded the cycloadduct **3d** albeit in low yield. Electron withdrawing groups such as Cl and F on the phenyl ring also afforded the phosphonate-containing dioxazole compounds **3e–3h** in good yields (Table 2, entries 5-8). The alkyl version of acyl phosphonate **2a** was also utilized in the 1,3-DC reaction of nitrile oxide **1a** and corresponding dioxazole cycloadduct **3i** was obtained in 59% yield (Table 2, entry 9). Different substituted aromatic *N*-hydroximoyl chlorides with either ED (CH_3, MeO, naphthyl) or EW (Br, Cl, NO_2) substituent were used as substrates. The corresponding 1,3-DC reactions proceeded smoothly giving the expected products **3j–3o** in good yields (Table 2, entries 10-14). The reaction between the nitrile oxide **1n** having the strong ED group-MeO on the phenyl ring and the aroyl phosphonate **2a** proceeded well where the corresponding dioxazole **3n** was attained in moderate yield (Table 2, entry 14, 58% by using NEt_3 in toluene). When Na_2CO_3 was used as a base in acetonitrile, the yield of cycloadduct **3n** was improved slightly to 60%. Electron-deficient *N*-hydroximoyl chloride **1 m** furnished the dioxazole product **3 m** in 66% yield (entry 13). In addition, 1-naphthyl substituted *N*-hydroximoyl chloride **1o** was also used as a substrate and then the dioxazole cycloadduct **3o** was obtained in high yield (entry 15, 84%).

Conclusions

The nitriles oxides were generated *in situ* and were reacted with acyl phosphonate derivatives via 1,3-dipolar cycloaddition reactions. Acyl phosphonates served as a dipolarophile in the cyclization reaction, and the nitrile oxides were used as 1,3-dipole. Nitrile oxides having either electron donating or withdrawing substituent in the 1,3-DC reaction were easily prepared by using the corresponding hydroximoyl chlorides. The dehalogenation process was easily carried out by using triethylamine as a base. Both reactants in the 1,3-DC reaction could be synthesized from readily available starting

materials. A variety of substituted nitrile oxides and acyl phosphonates was employed to understand the effect of the substituent at different positions and the reactivity of the cycloadditions. In all cases, the expected phosphonate-containing dioxazole compounds **3a-3o** were obtained in moderate to good yields. Alkyl version of the acyl phosphonate was also tested as a dipolarophile in the 1,3-DC reaction. The related phosphonate-containing dioxazole compound **3i** was obtained in 59% isolated chemical yield.

Electron-rich and electron-poor *N*-hydroximoyl chlorides were also examined in the 1,3-DC reaction of acyl phosphonate, which furnished the dioxazole cycloadducts **3j-3o** in good yields. The electronic features of the aromatic moieties in the 1,3-dipole did not significantly affect the product yield. For example, both electron-rich arylhydroximoyl chloride with an electron-donating 4-CH_3O- (entry 14) and electron-poor arylhydroximoyl chloride with an electron-withdrawing group 4-NO_2- (entry 13) both gave similar yields (entry 13 with 66% yield and entry 14 with 60% yield). In the case of dipolarophile, the electron-rich aroyl phosphonate gave the dioxazole compound **3d** in low yield (entry 4, 49% yield) while the unsubstituted aroyl phosphonate **3a** was isolated in 76% yield (entry 1).

Herein, a practical method is described for the synthesis of phosphonate-containing dioxazole compounds via 1,3-dipolar cycloaddition of nitrile oxides to acyl phosphonates by using readily available starting materials. This work has also demonstrated that acyl phosphonates could serve as a dipolarophile in the 1,3-DC reactions with a dipole-nitrile oxide. To that end, the investigations for the biological activity of the newly synthesized phosphonate-containing dioxazoles are in progress.

Experimental

The chemical shift values for proton and carbon NMR were reported in parts per million (ppm) relative to residual solvent signal of $CDCl_3$ unless otherwise stated (7.26 ppm in proton NMR and 77.0 ppm in carbon NMR). JEOL NMR-500 MHz was used for ^{31}P analyses (202 MHz), and the chemical shift (δ) is reported in ppm relative to diethyl phosphite (%3) as external reference. Bruker AVANCE III 400 MHz NMR was used for proton and carbon NMR (400 MHz for proton and 100 MHz for carbon, respectively). HRMS analyses were performed by using Agilent 6224 High Resolution Mass at METU-Central Laboratory. Bruker Platinum ATR-IR instrument was used for IR spectra, and the data were reported in cm^{-1}. Silica gel 230-400-mesh was used for the column chromatography to purify cycloadducts. Ethyl acetate/hexane mixture was used as eluting solvent in column chromatography. All cycloaddition reactions were performed under nitrogen atmosphere. The progress of cycloaddition reactions was monitored by TLC using silica gel plates with fluorescent indicator. Phosphomolybdic acid in ethanol (PMA) solution was used as a dying solution to visualize the spots. Toluene was distilled from Na/benzophenone and was used freshly in 1,3-DC reactions. Acyl chlorides, the precursor of acyl phosphonates, and aldehydes for the synthesis of hydroximoyl chloride derivatives were all readily available starting materials, and all of them were purchased from the suppliers. Both the derivatives of acyl phosphonates and hydroximoyl chlorides were easily synthesized according to the literature procedures.[18,20,21] The Supplemental Materials contain sample ^{1}H, ^{13}C, and ^{31}P NMR spectra of products 3 (Figures S1–S47).

General procedure for the synthesis of phosphonate-containing dioxazole derivatives 3a–3p

To a solution of hydroximoyl chloride (2.5 equiv.) in toluene (10 mL) at 0 °C under a nitrogen atmosphere was added triethylamine (2.5 equiv) dropwise to generate *in situ*-related nitrile oxide. Then, the dipolarophile acyl phosphonate (1 equiv.) was added to this mixture under vigorous stirring. The resulting mixture was continued to stir vigorously at room temperature until the completion of reaction controlled by TLC usually for 5–6 h. The crude mixture was filtrated, evaporated, and subjected to column chromatography for purification by using hexane:EtOAc mixtures. The synthesized phosphonate-containing dioxazole derivatives were obtained as oil after the column chromatography.

Diethyl 3,5-diphenyl-1,4,2-dioxazol-5-yl-5-phosphonate 3a

Oily compound, R_f = 0.42 (3:1 hexane:EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.81 – 7.74 (m, 2H), 7.70 – 7.65 (m, 2H), 7.44 – 7.38 (m, 1H), 7.39 – 7.30 (m, 5H), 4.24 – 4.00 (m, 4H, $PO(O\underline{CH_2}CH_3)_2$), 1.19 (q, J = 6.9 Hz, 6H, $PO(OCH_2\underline{CH_3})_2$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.2 (d, $J_{C\text{-}P}$ = 5.4 Hz, C = N), 134.8 (d, $J_{C\text{-}P}$ = 19.4 Hz, C), 131.8 (CH), 129.8 (CH), 128.6 (CH), 128.2 (CH), 126.9 (CH), 126.1 (d, $J_{C\text{-}P}$ = 2.6 Hz, CH), 121.9 (C), 110.8 (d, $J_{C\text{-}P}$ = 199.1 Hz, –OCO–), 64.7 (d, $J_{C\text{-}P}$ = 7.7 Hz, $PO(O\underline{CH_2}CH_3)_2$), 64.5 (d, $J_{C\text{-}P}$ = 6.9 Hz, $PO(O\underline{CH_2}CH_3)_2$), 16.2 (t, $J_{C\text{-}P}$ = 5.9 Hz, $PO(OCH_2\underline{CH_3})_2$). ^{31}P NMR ($CDCl_3$, 202 MHz): δ 9.25. IR (cm^{-1}): 2983, 1348, 1258, 1223, 1016, 969, 689. HRMS-EI (m/z): calculated for $C_{18}H_{21}NO_5P$ [M + H]: 362.1157 and found: 362.1158.

Dimethyl 3,5-diphenyl-1,4,2-dioxazol-5-yl-5-phosphonate 3 b

Oily compound, R_f = 0.58 (1:1 hexane:EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.87 (d, J = 7.1 Hz, 2H), 7.80 – 7.73 (m, 2H), 7.55 – 7.49 (m, 1H), 7.48 – 7.42 (m, 5H), 3.84 (d, J = 9.2 Hz, 3H, $PO(OCH_3)_2$), 3.82 (d, J = 9.2 Hz, 3H, $PO(OCH_3)_2$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.3 (d, $J_{C\text{-}P}$ = 5.1 Hz, C = N), 134.7 (d, $J_{C\text{-}P}$ = 19.5 Hz), 132.0, 130.0, 128.7, 128.4, 127.0, 126.0, 121.8, 110.9 (d, $J_{C\text{-}P}$ = 199.3 Hz, –OCO–), 55.0 (d, $J_{C\text{-}P}$ = 7.0 Hz, $PO(OCH_3)_2$), 54.8 (d, $J_{C\text{-}P}$ = 7.1 Hz, $PO(OCH_3)_2$). ^{31}P NMR ($CDCl_3$, 202 MHz): δ 11.55. IR (cm^{-1}): 2963, 1349, 1262, 1021, 962, 837, 752, 688. HRMS-EI (m/z): calculated for $C_{16}H_{16}NNaO_5P$ [M + Na]: 356.0664 and found: 356.0666.

Diethyl 3-phenyl-5-p-tolyl-1,4,2-dioxazol-5-yl-5-phosphonate 3c

Oily compound, R_f = 0.44 (3:1 hexane:EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.78 (d, J = 7.0 Hz, 2H), 7.57 (dd, J = 8.3, 1.7 Hz, 2H), 7.37 (d, J = 7.7 Hz, 2H), 7.16 (d, J = 7.6 Hz, 3H), 4.19 – 4.01 (m, 4H, PO(OCH_2CH_3)$_2$), 2.29 (s, 3H, CH_3), 1.20 (td, J = 7.0, 5.7 Hz, 6H, PO(OCH_2CH_3)$_2$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.9 (d, $J_{C\text{-}P}$ = 5.2 Hz, C = N), 139.6 (d, $J_{C\text{-}P}$ = 2.2 Hz), 132.0 (d, $J_{C\text{-}P}$ = 18.8 Hz), 131.5, 128.6, 128.4, 126.6, 125.8 (d, $J_{C\text{-}P}$ = 2.6 Hz), 121.7, 110.7 (d, $J_{C\text{-}P}$ = 199.4 Hz, –OCO–), 64.3 (d, $J_{C\text{-}P}$ = 7.0 Hz, PO(OCH_2CH_3)$_2$), 64.2 (d, $J_{C\text{-}P}$ = 7.3 Hz, PO(OCH_2CH_3)$_2$), 20.8 (CH_3), 16.0 (t, $J_{C\text{-}P}$ = 5.9 Hz, PO(OCH_2CH_3)$_2$). ^{31}P NMR ($CDCl_3$, 202 MHz): δ 9.39. IR (cm^{-1}): 2983, 1348, 1258, 1098, 1015, 970, 818, 689. HRMS-EI (m/z): calculated for $C_{19}H_{23}NO_5P$ [M + H]: 376.1314 and found: 376.1315.

Dimethyl 5-(4-methoxyphenyl)-3-phenyl-1,4,2-dioxazol-5-yl-5-phosphonate 3d

Oily compound, R_f = 0.50 ((1:1) hexane:EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.87 (d, J = 7.0 Hz, 2H), 7. 70 (dd, J = 8.9, 1.7 Hz, 2H), 7.52 (d, J = 7.4 Hz, 1H)), 7.46 (t, J = 7.5 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 3.85 (d, J = 10.5 Hz, 3H, PO(OCH_3)$_2$), 3.84 (d, J = 10.2 Hz, 3H, PO(OCH_3)$_2$), 3.83 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.7, 158.0 (d, $J_{C\text{-}P}$ = 5.2 Hz, C = N), 128.4, 127.31, 127.29, 126.7, 126.2 (d, J $J_{C\text{-}P}$ = 19.8 Hz), 121.5, 113.5, 110.7 (d, $J_{C\text{-}P}$ = 201.0 Hz, –OCO–), 54.9 (OCH_3), 54.6 (d, $J_{C\text{-}P}$ = 7.0 Hz, PO(OCH_3)$_2$), 54.5 (d, $J_{C\text{-}P}$ = 7.1 Hz, PO(OCH_3)$_2$). ^{31}P NMR ($CDCl_3$, 202 MHz): δ 11.73. IR (cm^{-1}): 2958, 1348, 1252, 1010, 837, 757, 689. HRMS-EI (m/z): calculated for $C_{17}H_{18}NNaO_6P$ [M + Na]: 386.0769 and found: 386.0769.

Diethyl 5-(4-chlorophenyl)-3-phenyl-1,4,2-dioxazol-5-yl-5-phosphonate 3e

Oily compound, R_f = 0.50 (3:1 hexane:EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.77 (d, J = 7.0 Hz, 2H), 7.62 (dd, J = 8.6, 1.7 Hz, 2H), 7.47 – 7.36 (m, 3H), 7.33 (d, J = 8.0 Hz, 2H), 4.22 – 4.04 (m, 4H, PO(OCH_2CH_3)$_2$), 2.29 (s, 3H, CH_3), 1.22 (t, J = 7.0 Hz, 3H, PO(OCH_2CH_3)$_2$), 1.20 (t, J = 7.1 Hz, 3H, PO(OCH_2CH_3)$_2$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.1 (d, $J_{C\text{-}P}$ = 5.4 Hz, C = N), 135.9 (d, $J_{C\text{-}P}$ = 2.4 Hz), 133.4 (d, $J_{C\text{-}P}$ = 19.8 Hz), 131.9, 128.6, 128.4, 127.6 (d, $J_{C\text{-}P}$ = 2.6 Hz), 126.8, 121.5, 110.2 (d, $J_{C\text{-}P}$ = 200.0 Hz, –OCO–), 64.7 (d, $J_{C\text{-}P}$ = 7.2 Hz, PO(OCH_2CH_3)$_2$), 64.5 (d, $J_{C\text{-}P}$ = 7.4 Hz, PO(OCH_2CH_3)$_2$), 16.2 (t, $J_{C\text{-}P}$ = 5.7 Hz, PO(OCH_2CH_3)$_2$). ^{31}P NMR ($CDCl_3$, 202 MHz): δ 8.81. IR (cm^{-1}): 2983, 1347, 1262, 1090, 1014, 968, 824, 687. HRMS-EI (m/z): calculated for $C_{18}H_{20}ClNO_5P$ [M + H]: 396.0768 and found: 396.0768.

Diethyl 5-(4-fluorophenyl)-3-phenyl-1,4,2-dioxazol-5-yl-5-phosphonate 3f

Oily compound, R_f = 0.44 (3:1 hexane:EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.90 – 7.83 (m, 2H), 7.77 (ddt, J = 6.9, 5.3, 1.7 Hz, 2H), 7.58 – 7.49 (m, 1H), 7.51 – 7.40 (m, 2H), 7.13 (t, J = 8.8 Hz, 2H), 4.34 – 4.11 (m, 4H, PO(OCH_2CH_3)$_2$), 1.32 (t, J = 7.0 Hz, 3H, PO(OCH_2CH_3)$_2$), 1.28 (t, J = 7.0 Hz, 3H, PO(OCH_2CH_3)$_2$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.4 (dd, $J_{C\text{-}F}$ = 249.4 Hz, $J_{C\text{-}P}$ = 2.1 Hz, CF), 158.0 (d, $J_{C\text{-}P}$ = 5.4 Hz, C = N), 131.8, 130.7 (dd, $J_{C\text{-}P}$ = 19.8 Hz and $J_{C\text{-}F}$ = 3.1 Hz), 128.5, 128.2 (dd, $J_{C\text{-}F}$ = 8.7 Hz and $J_{C\text{-}P}$ = 2.6 Hz), 126.4, 121.5, 115.1 (d, $J_{C\text{-}F}$ = 21.9 Hz), 110.2 (d, $J_{C\text{-}P}$ = 200.8 Hz, –OCO–), 64.6 (d, $J_{C\text{-}P}$ = 7.4 Hz, PO(OCH_2CH_3)$_2$), 64.5 (d, $J_{C\text{-}P}$ = 7.2 Hz, PO(OCH_2CH_3)$_2$), 16.1 (t, $J_{C\text{-}P}$ = 5.8 Hz, PO(OCH_2CH_3)$_2$). ^{31}P NMR ($CDCl_3$, 202 MHz): δ 8.98. IR (cm^{-1}): 2983, 1347, 1260, 1228, 1095, 1015, 971, 837, 688. HRMS-EI (m/z): calculated for $C_{18}H_{20}FNO_5P$ [M + H]: 380.1063 and found: 380.1061.

Dimethyl 5-(2-chlorophenyl)-3-phenyl-1,4,2-dioxazol-5-yl-5-phosphonate 3 g

Oily compound, R_f = 0.50 (3:1 hexane:EtOAc). ^{1}H NMR (*d*-acetone, 400 MHz): δ 7.80 – 7.71 (m, 3H), 7.54 – 7.29 (m, 6H), 3.74 (d, J = 4.1 Hz, 3H, PO(OCH_3)$_2$), 3.72 (d, J = 4.2 Hz, 3H, PO(OCH_3)$_2$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.4 (d, $J_{C\text{-}P}$ = 5.5 Hz, C = N), 132.3, 132.1 (d, $J_{C\text{-}P}$ = 19.9 Hz), 131.8, 131.3, 131.0, 129.1, 128.5, 126.9, 126.4, 121.5, 110.9 (d, $J_{C\text{-}P}$ = 202.1 Hz, –OCO–), 54.9 (d, $J_{C\text{-}P}$ = 7.2 Hz, PO(OCH_3)$_2$), 54.7 (d, $J_{C\text{-}P}$ = 7.2 Hz, PO(OCH_3)$_2$). ^{31}P NMR ($CDCl_3$, 202 MHz): δ 10.89. IR (cm^{-1}): 2962, 1348, 1265, 1067, 1022, 762, 685. HRMS-EI (m/z): calculated for $C_{16}H_{16}ClNO_5P$ [M + H]: 368.0455 and found: 368.0455.

Dimethyl 5-(3-chlorophenyl)-3-phenyl-1,4,2-dioxazol-5-yl-5-phosphonate 3 h

Oily compound, R_f = 0.50 (3:1 hexane:EtOAc). ^{1}H NMR (*d*-acetone, 400 MHz): δ 7.93 (dd, J = 7.2, 1.6 Hz, 2H), 7.78 – 7.71 (m, 2H), 7.69 – 7.63 (m, 1H), 7.62 – 7.54 (m, 4H), 3.88 (d, J = 6.5 Hz, 3H, PO(OCH_3)$_2$), 3.85 (d, J = 6.5 Hz, 3H, PO(OCH_3)$_2$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.0 (d, $J_{C\text{-}P}$ = 5.2 Hz, C = N), 136.6 (d, $J_{C\text{-}P}$ = 19.9 Hz), 134.2, 131.9, 130.0, 129.6, 128.6, 126.8, 126.0 (d, $J_{C\text{-}P}$ = 2.8 Hz), 124.2 (d, $J_{C\text{-}P}$ = 2.2 Hz), 121.2, 109.9 (d, $J_{C\text{-}P}$ = 199.9 Hz, –OCO–), 54.9 (d, $J_{C\text{-}P}$ = 6.9 Hz, PO(OCH_3)$_2$), 54.7 (d, $J_{C\text{-}P}$ = 7.2 Hz, PO(OCH_3)$_2$). ^{31}P NMR ($CDCl_3$, 202 MHz): δ 10.98. IR (cm^{-1}): 2958, 1346, 1267, 1026, 1022, 765, 686. HRMS-EI (m/z): calculated for $C_{16}H_{16}ClNO_5P$ [M + H]: 368.0455 and found: 368.0457.

Dimethyl 5-isopropyl-3-phenyl-1,4,2-dioxazol-5-yl-5-phosphonate 3j

Oily compound, R_f = 0.34 ((1:1) hexane:EtOAc). NMR ($CDCl_3$, 400 MHz): δ 7.80 (d, J = 7.1 Hz, 2H), 7.54–7.41 (m, 3H), 3.89 (d, J = 10.3 Hz, 3H, PO(OCH_3)$_2$), 3.83 (d,

$J = 10.4$ Hz, 3H, PO(OCH$_3$)$_2$), 2.50 (pd, $J = 6.9$ and 5.0 Hz, 1H, CH(CH$_3$)$_2$), 1.15 (dd, $J = 6.9$ and 2.6 Hz, 6H, CH(CH$_3$)$_2$). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 158.3 (C = N), 131.5, 128.5, 126.5, 121.6, 116.0 (d, $J_{C\text{-}P}$ = 190.8 Hz, –OCO–), 54.3 (d, $J_{C\text{-}P}$ = 7.1 Hz, PO(OCH$_3$)$_2$), 53.8 (d, $J_{C\text{-}P}$ = 7.3 Hz, PO(OCH$_3$)$_2$), 33.0 (d, $J_{C\text{-}P}$ = 22.7 Hz, CH(CH$_3$)$_2$), 15.2 (d, $J_{C\text{-}P}$ = 4.2 Hz, CH(CH$_3$)$_2$). ^{31}P NMR (CDCl$_3$, 202 MHz): 13.12. δ IR (cm^{-1}): 2958, 1352, 1263, 1024, 832, 762, 689. HRMS-EI (m/z): calculated for $C_{13}H_{19}NO_5P$ [M + H]: 300.1001 and found: 300.1001.

Diethyl 5-phenyl-3-p-tolyl-1,4,2-dioxazol-5-yl-5-phosphonate 3k

Oily compound, R_f = 0.35 (2:1 hexane:EtOAc). ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.71 – 7.64 (m, 4H), 7.38 – 7.32 (m, 3H), 7.17 (d, $J = 8.0$ Hz, 2H), 4.20 – 4.01 (m, 4H, PO(OCH$_2$CH$_3$)$_2$), 2.32 (s, 3H, CH$_3$), 1.19 (q, $J = 6.8$, 6H, PO(OCH$_2$CH$_3$)$_2$). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 158.3 (d, $J_{C\text{-}P}$ = 5.3 Hz, C = N), 142.4, 134.9 (d, $J_{C\text{-}P}$ = 19.6 Hz), 129.8, 129.3, 128.1, 126.9, 126.1 (d, $J_{C\text{-}P}$ = 2.6 Hz), 119.0, 110.6 (d, $J_{C\text{-}P}$ = 198.2 Hz, –OCO–), 64.6 (d, $J_{C\text{-}P}$ = 7.3 Hz, PO(OCH$_2$CH$_3$)$_2$), 64.5 (d, $J_{C\text{-}P}$ = 7.1 Hz, PO(OCH$_2$CH$_3$)$_2$), 21.4 (CH$_3$), 16.20 (d, $J_{C\text{-}P}$ = 7.4 Hz, PO(OCH$_2$CH$_3$)$_2$), 16.19 (d, $J_{C\text{-}P}$ = 7.1 Hz, PO(OCH$_2$CH$_3$)$_2$). ^{31}P NMR (CDCl$_3$, 202 MHz): δ 9.32. IR (cm^{-1}): 2982, 1344, 1261, 1016, 967, 744, 696. HRMS-EI (m/z): calculated for $C_{19}H_{23}NO_5P$ [M + H]: 376.1314 and found: 376.1319.

Diethyl 3-(4-bromophenyl)-5-phenyl-1,4,2-dioxazol-5-yl-5-phosphonate 3 l

Oily compound, R_f = 0.29 (3:1 hexane:EtOAc). ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.78 – 7.73 (m, 4H), 7.64 – 7.59 (m, 2H), 7.49 – 7.44 (m, 3H), 4.30 – 4.09 (m, 4H, PO(OCH$_2$CH$_3$)$_2$), 1.30 (t, $J = 7.3$ Hz, 3H, PO(OCH$_2$CH$_3$)$_2$), 1.28 (t, $J = 7.0$ Hz, 3H, PO(OCH$_2$CH$_3$)$_2$). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 157.5 (d, $J_{C\text{-}P}$ = 5.1 Hz, C = N), 134.4 (d, $J_{C\text{-}P}$ = 19.3 Hz), 131.9, 129.8, 128.2, 128.1, 126.3, 125.9 (d, $J_{C\text{-}P}$ = 2.9 Hz), 120.7, 111.0 (d, $J_{C\text{-}P}$ = 199.0 Hz, –OCO–), 64.5 (d, $J_{C\text{-}P}$ = 7.4 Hz, PO(OCH$_2$CH$_3$)$_2$), 64.4 (d, $J_{C\text{-}P}$ = 6.9 Hz, PO(OCH$_2$CH$_3$)$_2$), 16.1 (t, $J_{C\text{-}P}$ = 7.5 Hz, PO(OCH$_2$CH$_3$)$_2$). ^{31}P NMR (CDCl$_3$, 202 MHz): δ 9.08. IR (cm^{-1}): 2973, 1345, 1260, 1229, 1098, 1008, 976, 836, 700. HRMS-EI (m/z): calculated for $C_{18}H_{20}BrNO_5P$ [M + H]: 440.0262 and found: 440.0262.

Diethyl 3-(4-chlorophenyl)-5-phenyl-1,4,2-dioxazol-5-yl-5-phosphonate 3 m

Oily compound, R_f = 0.50 ((2:1) hexane:EtOAc). ^{1}H NMR (*d*-acetone, 400 MHz): δ 7.95 – 7.90 (m, 2H), 7. 78 – 7.75 (m, 2H), 7.66 – 7.58 (m, 2H), 7.53 – 7.49 (m, 3H), 4.27 – 4.03 (m, 4H, PO(OCH$_2$CH$_3$)$_2$), 1.26 (t, $J = 7.1$ Hz, 3H, PO(OCH$_2$CH$_3$)$_2$), 1.25 (t, $J = 7.1$ Hz, 3H, PO(OCH$_2$CH$_3$)$_2$). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 157.7 (d, $J_{C\text{-}P}$ = 5.5 Hz, C = N), 138.1, 134.7 (d, $J_{C\text{-}P}$ = 19.0 Hz), 130.0, 129.1, 128.3, 126.1 (d, $J_{C\text{-}P}$ = 2.8 Hz), 120.5, 111.2 (d, $J_{C\text{-}P}$ = 199.6 Hz, –OCO–), 64.7 (d, $J_{C\text{-}P}$ = 7.8 Hz, PO(OCH$_2$CH$_3$)$_2$), 64.6 (d, $J_{C\text{-}P}$ = 7.3 Hz, PO(OCH$_2$CH$_3$)$_2$), 16.3 (t, $J_{C\text{-}P}$ = 5.8 Hz, PO(OCH$_2$CH$_3$)$_2$), 16.2 (t, $J_{C\text{-}P}$ = 6.0 Hz, PO(OCH$_2$CH$_3$)$_2$). ^{31}P NMR (CDCl$_3$, 202 MHz): δ 9.10. IR (cm^{-1}): 2983, 1343, 1259, 1014, 968, 797, 696. HRMS-EI (m/z): calculated for $C_{18}H_{20}ClNO_5P$ [M + H]: 396.0768 and found: 396.0769.

Diethyl 3-(4-nitrophenyl)-5-phenyl-1,4,2-dioxazol-5-yl-5-phosphonate 3n

Oily compound, R_f = 0.49 ((1:1) hexane:EtOAc). ^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.31 (d, $J = 8.9$ Hz, 2H), 8.05 (d, $J = 8.9$ Hz, 2H), 7.71 – 7.79 (m, 2H), 7.49 – 7.44 (m, 3H), 4.32 – 4.07 (m, 4H, PO(OCH$_2$CH$_3$)$_2$), 1.31 (t, $J = 7.1$ Hz, 3H, PO(OCH$_2$CH$_3$)$_2$), 1.27 (t, $J = 7.1$ Hz, 3H, PO(OCH$_2$CH$_3$)$_2$). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 157.0 (d, $J_{C\text{-}P}$ = 4.9 Hz, C = N), 149.5, 134.1 (d, $J_{C\text{-}P}$ = 18.7 Hz), 130.2, 128.3, 127.9, 125.9 (d, $J_{C\text{-}P}$ = 2.9 Hz), 123.9, 118.4, 112.0 (d, $J_{C\text{-}P}$ = 199.5 Hz, –OCO–), 64.9 (d, $J_{C\text{-}P}$ = 7.6 Hz, PO(OCH$_2$CH$_3$)$_2$), 64.8 (d, $J_{C\text{-}P}$ = 6.6 Hz, PO(OCH$_2$CH$_3$)$_2$), 16.2 (t, $J_{C\text{-}P}$ = 6.2 Hz, PO(OCH$_2$CH$_3$)$_2$). ^{31}P NMR (CDCl$_3$, 202 MHz): δ 8.70. IR (cm^{-1}): 2983, 1525, 1341, 1221, 1015, 974, 846, 712, 692. HRMS-EI (m/z): calculated for $C_{18}H_{20}N_2O_7P$ [M + H]: 407.1008 and found: 407.1008.

Diethyl 3-(4-methoxyphenyl)-5-phenyl-1,4,2-dioxazol-5-yl-5-phosphonate 3o

Oily compound, R_f = 0.36 (1:1 hexane:EtOAc). ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.80 (d, $J = 8.9$ Hz, 2H), 7.78 – 7.71 (M, 3H), 7.49 – 7.38 (m, 3H), 6.94 (d, $J = 8.9$ Hz, 2H), 4.29 – 4.08 (m, 4H, PO(OCH$_2$CH$_3$)$_2$), 3.85 (s, 3H, OCH$_3$), 1.29 (t, $J = 7.3$ Hz, 3H, PO(OCH$_2$CH$_3$)$_2$), 1.25 (t, $J = 7.2$ Hz, 3H, PO(OCH$_2$CH$_3$)$_2$). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 162.3, 158. 0 (d, $J_{C\text{-}P}$ = 5.3 Hz, C = N), 134.9 (d, $J = 19.5$ Hz), 129.7, 128.6, 128.0, 126.0 (d, $J = 2.9$ Hz), 114.0, 110.3 (d, $J = 198.9$ Hz, –OCO–), 64.5 (d, $J_{C\text{-}P}$ = 6.9 Hz, PO(OCH$_2$CH$_3$)$_2$), 64.4 (d, $J_{C\text{-}P}$ = 7.3 Hz, PO(OCH$_2$CH$_3$)$_2$), 55.1 (OCH$_3$), 16.1 (t, $J_{C\text{-}P}$ = 6.6 Hz, PO(OCH$_2$CH$_3$)$_2$). ^{31}P NMR (CDCl$_3$, 202 MHz): δ 9.41. IR (cm^{-1}): 2981, 1607, 1514, 1346, 1256, 1016, 967, 837, 651. HRMS-EI (m/z): calculated for $C_{19}H_{23}NO_6P$ [M + Na]: 414.1082 and found: 414.1082.

Diethyl 3-(naphthalen-1-yl)-5-phenyl-1,4,2-dioxazol-5-yl-5-phosphonate 3p

Oily compound, R_f = 0.48 ((1:1) hexane:EtOAc). ^{1}H 7.89 – 7.84 (m, 3H)NMR (CDCl$_3$, 400 MHz): δ 8.89 (d, $J = 8.6$ Hz, 1H), 8.09 (d, $J = 7.3$ Hz, 3H), 7.76 (d, $J = 8.2$ Hz, 1H), 7.54 (t, $J = 7.7$ Hz, 1H), 7.47 – 7.34 (m, 5H), 4.32 – 4.06 (m, 4H, PO(OCH$_2$CH$_3$)$_2$), 1.24 (t, $J = 7.1$ Hz, 6H, PO(OCH$_2$CH$_3$)$_2$). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 157.8 (d, $J = 5.4$ Hz, C = N), 134.7 (d, $J = 19.7$ Hz), 133.1, 132.5, 129.6, 129.5, 128.3 (d, $J = 5.8$ Hz), 128.0, 127.5, 126.2, 125.9 (d, $J = 2.7$ Hz), 125.7, 124.3, 118.2, 109.2 (d, $J_{C\text{-}P}$ = 199.0 Hz, –OCO–), 64.3 (d, $J_{C\text{-}P}$ = 7.0 Hz, PO(OCH$_2$CH$_3$)$_2$), 64.2 (d, $J_{C\text{-}P}$ = 7.2 Hz, PO(OCH$_2$CH$_3$)$_2$), 16.0 (t, $J_{C\text{-}P}$ = 5.1 Hz,

$PO(OCH_2\underline{CH_3})_2$). ^{31}P NMR ($CDCl_3$, 202 MHz): δ 9.56. IR (cm^{-1}): 2982, 1259, 1016, 974, 805, 773, 696. HRMS-EI (*m*/*z*): calculated for $C_{22}H_{23}NO_5P$ [M + H]: 412.1314 and found: 412.1313.

Acknowledgment

The author thanks to Canakkale Onsekiz Mart University for financing this research and also thanks to Middle East Technical University (METU), Department of Chemistry.

Funding

This work was supported by Canakkale Onsekiz Mart University, the Scientific Research Coordination Unit (Project number: FBA-2020-3281).

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