ChemPubSoc Europe

DOI: 10.1002/open.201900376

Open Access ChemistryOPEN Full Papers

Reactions of 1,2,4-Oxadiazole[4,5-*a*]piridinium Salts with Alcohols: the Synthesis of Alkoxybutadienyl 1,2,4-Oxadiazoles

Mattia Moiola, Marco Leusciatti, and Paolo Quadrelli*[a]

1,2,4-Oxadiazole[4,5-*a*]piridinium salts add alcohols and alkoxides to undergo electrocyclic ring opening affording alkoxybutadienyl 1,2,4-oxadiazole derivatives. The pyridinium salts represent a special class of Zincke salts that are prone to rearrange to give alkoxybutadienyl 1,2,4-oxadiazoles when treated with suitable nucleophiles or, alternatively, to give pyridones in the presence of bicarbonate. The pivotal tuning of the experimental conditions leads to a straightforward synthesis of valuable 1,2,4-oxadiazole derivatives. The mechanism is also discussed in the light of previous observations.

1. Introduction

The great interest in 1,2,4-oxadiazoles[1] in organic synthesis can be ascribed both to the versatility of these heterocycles with respect to their preparationf and elaboration in other synthons as well as to their biological activities, specifically in drug discovery where oxadiazoles are often hydrolysis-resisting bioisosteric replacements for amide or ester functionalities. Some derivatives can also act as bioisosteres of the carboxylic acid functionality.[2] Compounds containing the oxadiazole ring were found to be anti-inflammatory or antiviral agents, agonists of muscarinic receptors, peptidomimetics, antitumor agents[3] or partial agonists for a class of peroxisome proliferator-activated receptors.[4] Moreover, 1,2,4- and 1,3,4-oxadiazoles containing flexible alkoxy chains were also found to display liquid crystalline and emissive properties.[5]

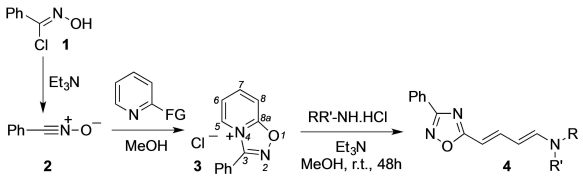
A number of conventional and unconventional methodologies and several methods are reported in the literature regarding the synthesis of these heterocycles.[1,2] In the search of new method for the preparation of functionalized 1,2,4-oxadiazoles, we pursued in our traditional interest in the 1,3-dipolar cycloaddition approach through nitrile oxide chemistry.[6]

Recently, we have detailed the remarkable behavior of the 1,2,4-oxadiazole[4,5-*a*]piridinium salts **3** with amines;[7] synthesized from nitrile oxides of type **2** and suitably 2-substituted pyridines, the 1,2,4-oxadiazole[4,5-*a*]piridinium salts **3** undergo an electrocyclic ring-opening in the presence of *in situ* generated amines (from their hydrochlorides) to afford in excellent yield the 5-dienamino derivatives of type **4** (Scheme 1). The scope of this methodology, thoroughly investigated in the light of the mechanism proposed, aimed to set up the protocol for obtaining single products with reliable and positive impacts on the synthetic field.

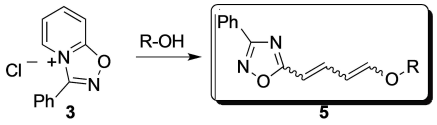
Expanding our investigation on the reactivity of nitrile oxides and 2-substituted pyridines as well as that of their oxadiazole-pyridinium salts, we studied the chemical behavior of these latters in the presence of alcohols and alkoxides identifying an interesting route to 5-alkoxybutadienyl substituted 1,2,4-oxadiazoles of type **5** (Scheme 2). Scope and limitations of the protocol are discussed in the light of the proposed mechanism.

2. Results and Discussion

3-Phenyl-1,2,4-Oxadiazole[4,5-*a*]piridinium chloride **3** was prepared according to the known procedure.[7] Compound **3** is stable for days in water solution but unstable in the presence of 5% solution $NaHCO_3$ affording the insoluble *N*-substituted 2-pyridone **6** through oxadiazole ring-opening reaction.[7] The



Scheme 1. Benzonitrile oxide reactions with 2-substituted pyridines and reaction pathway to 5-dienamino 1,2,4-oxadiazoles. FG, functional groups.



Scheme 2. Reaction of the salt **3** with alcohols to afford 5-alkoxybutadienyl 1,2,4-oxadiazoles **5**.

[a] *Dr. M. Moiola, Dr. M. Leusciatti, Prof. Dr. P. Quadrelli*
Department of Chemistry
University of Pavia
Viale Taramelli 12, 27100 – Pavia (Italy)
E-mail: paolo.quadrelli@unipv.it

Supporting information for this article is available on the WWW under https://doi.org/10.1002/open.201900376

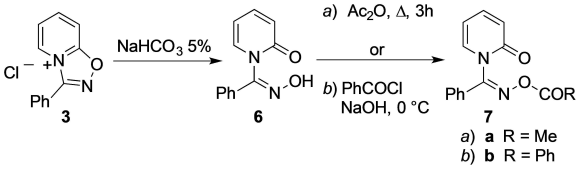
reaction takes place almost immediately and is quantitative after one day (Scheme 3).[8–10] Acylation of compound **6** with acetic anhydride or benzoyl chloride afforded the *O*-acyl derivatives **7a**, **b**, respectively in 63% and 62% yields, according to the well-established methods for amidoximes acylation reported in literature.[11]

The behavior of salt **3** with slightly basic water solutions somewhat suggests to investigate the reactions with alcohols and alkoxides.

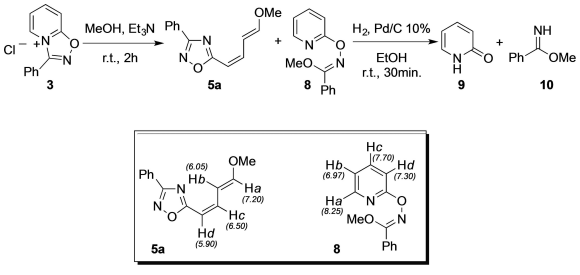
The salt **3** is soluble in methanol and in general in polar solvents and indefinitely stable in their solutions. However, when 1–2 equivalents Et_3N are added to the methanol solution, compound **3** disappears after few hours to leave the methoxybutadienyl-1,2,4-oxadiazole derivative **5a** (15% yield) and the hydroximic ester **8** as major product (75% yield) (Scheme 4).

The structures of the reaction products were attributed on the basis of the corresponding analytical and spectroscopic data. The ^1H NMR ($CDCl_3$) of the methoxybutadienyl-1,2,4-oxadiazole **5a** shows the typical signals diene moiety; in the inset of Scheme 4 the chemical shifts of **5a** are reported showing that the H*b* and H*d* proton signals are quite shielded as expected for an alkoxydiene with respect to the H*a* and H*c* signals. The geometry of the double bond was determined on the basis of the relative coupling constants (*J*); The double bond close to the oxadiazole ring has a typical (*Z*) geometry with a $J = 11$ Hz while the vinyl ether portion has a larger $J =$ 13 Hz, accounting for a (*E*) configuration.

The hydroximic ester **8** shows in its ^1H NMR ($CDCl_3$) spectrum the typical pyridine proton array, quite deshieded and with increasing *J* values moving from H*a* to the H*d*, as expected for this type of heterocycles. In the specific case, the structure of **8** was furtherly demonstrated upon catalytic hydrogenation that afforded quantitatively an equimolecular mixture of 2-pyridone **9** and methyl benzimidate[12] **10**.



Scheme 3. Reaction of salt **3** with $NaHCO_3$ 5% water solution and acylation reactions of compound **6**.



Scheme 4. Reaction of the salt **3** with methanol in the presence of Et_3N and hydrogenation reaction of compound **8**.

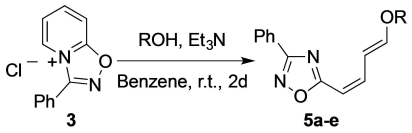
With the aim to set-up properly the reaction conditions in order to obtain as single product of the reaction the alkoxybutadienyl-1,2,4-oxadiazole derivatives of type **5**, we took advantage of the method applied for the reaction with amines,[7] *i.e.* by suspending the salt **3** in benzene as solvent in the presence of 4 mmol of alcohols and adding 5 mmol Et_3N to establish a low-concentration equilibrium with the nucleophilic species (Scheme 5). The reactions proceed slowly and take 2 day for complete disappearance of the salt **3**, affording the desired products **5a–e** in very good yields (80–92%). From the crude mixtures traces of the corresponding hydroximic ester of type **8** could be detected not isolable due to their very low amounts.

The structures of products **5b–e** were attributed on the basis of the corresponding analytical and spectroscopic data. In the ^1H NMR ($CDCl_3$) spectra the trend shown for compound **5a** is confirmed for the new products regarding the diene moieties. The signals of the protons located on the (*Z*) double bond are found shielded in the range δ 5.4–7.0 ppm with coupling constant values $J = 11$ Hz. On the other side, she signals of the protons located on the (*E*) double bond are found slightly deshielded in the range δ 6.0–7.5 ppm with coupling constant values $J = 13$ Hz. A complete characterization is reported in the experimental section.

The obtained results clearly show a different behavior of the salt **3** in dependence of the concentration of alcohols; upon increasing the MeOH/Benzene ratio (1%, 5%, 20%, 50% V/V) in the reactions with salt **3**, the yields of compound **5a** decrease steadily (NMR determinations) to reach the 8% for compound **5a** and 79% for compound **8** in pure MeOH as solvent, consistent with previous results.

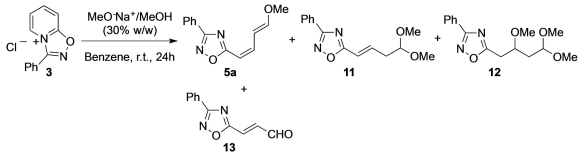
To better understand the reactivity of salt **3** and for sake of comparison with free amine reactions previously reported,[7] we investigated the reactions with the methoxide anion; the reaction was conducted by using a 30% w/w solution MeO^-Na^+/MeOH (2 equiv.) in a benzene suspension of salt **3**. After one day at room temperature the worked-up reaction mixture was submitted to chromatographic separation to obtain the products whose structures are shown in Scheme 6.

Compound **5a** was isolated in modest yield (6%) along with the new products **11** and **12** derived from the multiple addition of the methoxide anion to the diene moiety, respectively



5	R	Y (%)
a	Me	80
b	Et	90
c	*n*Pr	92
d	iPr	91
e	*n*Bu	92

Scheme 5. Reactions of the salt **3** with alcohols/Et_3N in benzene suspensions.



Scheme 6. Reaction of salt **3** with MeO^-Na^+/MeOH in benzene as solvent.

obtained in 10% and 34% yields, and an oxidative cleavage product **13** in 36% yield. For products **11**–**13** the structures were attributed on the basis of their analytical and spectroscopic data. Specifically in the ^{1}H NMR ($CDCl_3$) of compound **11** the presence of a single double bond is testified by the presence of two signals at δ 6.56 and 7.10 coupled with a J = 16 Hz, accounting for a (*E*) geometry of the C=C double bond, while two methoxy groups are found at δ 3.40, geminally linked to the acetalic CH whose proton resonate at δ 4.57. The parent compound **12** possesses as additional methoxy group (δ 3.41) and a methylene adjacent to the oxadiazole ring whose proton are found at δ 3.19. Finally, in the ^{1}H NMR ($CDCl_3$) of the α,β-unsaturated aldehyde **13** the aldehyde proton is found at δ 9.90 as a doublet, coupled with the C=C double bond protons found at δ 7.37 and 7.43.

The use of stronger bases seems to erode the reaction selectivity that is clearly guarantee by the ROH/R_3N/Benzene methodology conditions.

The results here reported add intriguing aspects in the reactivity of the oxadiazole-pyridinium salts **3** with nucleophiles. These monocycloadducts obtained through a pseudo-pericyclic[13] addition of nitrile oxides to pyridine derivatives are a special type of Zincke salts[14] whose electrocyclic ring-opening is triggered by nucleophilic addition.[15] We have already accounted for this type of mechanism, detailing the various stereochemical features in a previous work using different amines as nucleophiles to conduct these synthetic transformations.[7]

The results shown in Scheme 5 can be easily explained in the light of previous observations: alcohols add the position 5 of the pyridinium salt **3** with the assistance of an organic base to give the adduct **14** that undergoes disrotatory electrocyclic ring-opening to afford the intermediate **15**. This latter partially isomerizes to give the stable isolated compounds **5a**–**e** in (*E,Z*) configurations (Scheme 7).

As these reactions proceeded at the earlier stage slower than the analogous reaction with amines, we found difficult to monitor experimentally the reaction pathway through NMR. Attempts were made but the output was not qualitatively and quantitatively satisfactory as previously demonstrated.[7] However, we reasonably propose the mechanism in Scheme 7 on the basis of the product outcome.

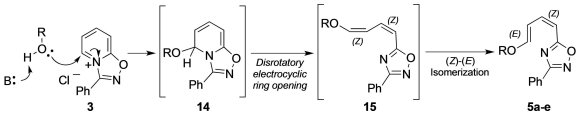
The formation of the hydromic esters of type **8** from alcoholic solutions of **3** can be explained on the basis of the proposed mechanism proposed in Scheme 8. At high concentration of alcohols or in pure alcohols as solvents, the reaction proceeded by addition to the electrophilic carbon atom C3 of the oxadiazole ring of **3** to give the intermediate **16** that, in the presence of organic bases, neutralized the pyridinium salt affording the hydroximic esters **8a**–**e**. In some cases, the *syn* and *anti* stereosiomers of **8** around the C=N double bond could be observed in the crude; the structure of **8** corresponds to the isolated compound.

Finally, Scheme 9 shows the proposed mechanism accounting the formation of the adducts **11** and **12**. The structures of these compounds do suggest the mechanism starting from the primary adduct **5a** that is prone to add a methoxide ion to give the intermediate **17** that gains its neutrality by extracting a proton from the solvent (MeOH) leaving product **11**. This latter is again prone to add a second methoxide ion in the same manner to afford the intermediate **18** before rearranging to product **12** in a similar way.

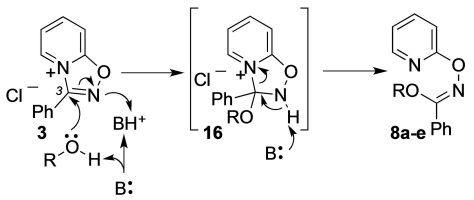
The presence in the reaction mixture of the α,β-unsaturated aldehyde **13** can be ascribed to oxidation occurring on compound **5a**; this phenomenon was also observed when **5a** was left in solution in open air (TLC monitor).

The use of pyridines for the preparation acyclic and heterocyclic compounds belonging to several classes of organic compounds remains a valuable topic of research and the application of the chemistry of Zincke salts[16] renovates a protocol dating back more than one century.[17] 1,2,4-Oxadiazole[4,5-*a*]piridinium salts of type **3** belong to the wide family of Zincke salts and display a remarkable chemical behavior, interesting and valuable on both mechanistic and applicative points of view. They can be easily prepared from a variety of 2-halogen substituted pyridines and aromatic or aliphatic nitrile oxides[18] expanding the synthetic possibilities from a single molecule to obtain variable functionalized oxadiazole derivatives.

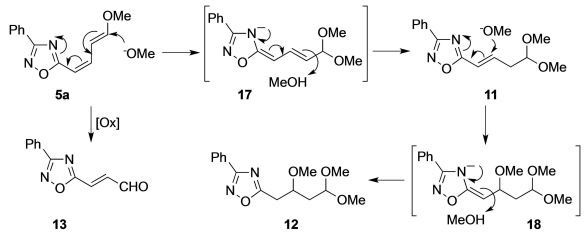
In our previous work we summarized the reactivity of salts **3** with amines in connection with the competitive dimerization processes involving the nitrile oxides, evidencing the compound stability aspects determining the accessibility of specific reaction pathways.[7] Hereby, we wish to conclude giving another comprehensive picture of the reactivity of salts **3** with



Scheme 7. Nucleophilic addition of alcohols to the salt **3** with disrotatory mechanism outcome of adduct **14** to give intermediate **15** and subsequent (*Z*)–(*E*) isomerization.



Scheme 8. Proposed mechanism for compounds **8a**–**e** formation.



Scheme 9. Proposed mechanism for the formation of compounds **11** and **12**.

alcohols and alkoxides as the experimental results here exposed allow to design (Scheme 10).

When the 1,2,4-Oxadiazole[4,5-*a*]piridinium chloride **3** is suspended in benzene and an amount of alcohols is added in the presence of an organic base, a disrotatory electrocyclic ring-opening starts from the adduct **14** affording the intermediate **15** that enters (*Z*)–(*E*) isomerization process to give the final compounds **5**. Important rule to trigger this reaction pathway: the amount of alcohols must remains below 1%. Upon the increasing this amount a competitive reaction pathway is enforced and speed-up by the alcohol concentration to give as major product the hydroximic ester **8**.

On the other side, the use of alkoxides, stronger bases even in low concentration, still activate the electrocyclic ring-opening but the alkoxybutadienyl derivatives undergo a further addition to the diene moiety, cancelling the reaction selectivity previously observed.

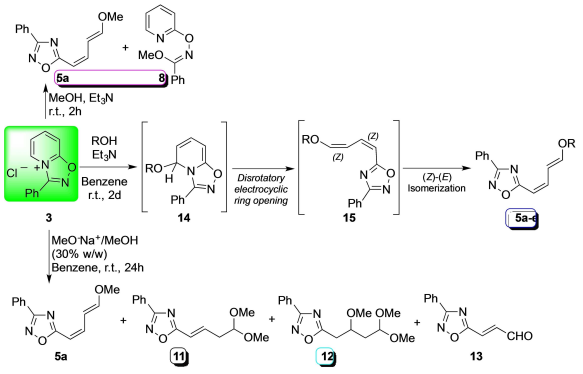
3. Conclusions

To sum up, a comparison with the salt **3** behaviour with amines seems to give a neat preference on the synthetic ground to the reactions with nitrogen containing derivatives rather than the alcohols. In particular the stability of secondary amine derivatives is indefinite while the alkoxybutadienyl derivative somewhat suffer a long-term oxidative degradation to aldehydes and related compounds.

Other targets and planned investigations will promise further developments in this topic as well as the use of some of these oxadiazole derivatives in biological investigations.

Experimental Section

All melting points (Mp) are uncorrected. Elemental analyses were done on a elemental analyzer available at the Department. ^{1}H and ^{13}C NMR spectra were recorded on a 300 MHz spectrometer (solvents specified). Chemical shifts are expressed in ppm from internal tetramethylsilane (δ) and coupling constants (*J*) are in Hertz (Hz): b, broad; s, singlet; bs, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet. IR spectra (nujol mulls) were recorded on a spectrophotometer Perkin-Elmer RX-1 available at the Department and absorptions (ν are in cm^{-1}. Column chromatography and tlc: silica gel H60 and GF_{254}, respectively; eluents: cyclohexane/ethyl acetate 9:1 to pure ethyl acetate.



Scheme 10. Mechanistic chart: from pyridinium salts **3** to alkoxybutadienyl oxadiazoles **5** through electrocyclic ring-opening. With high alcohol concentration competitive reaction affords the hydroximic ester **8**. With alkoxide ions, subsequent addition to the diene moiety furnishes the methoxy derivatives **11** and **12**.

Starting and Reference Materials

2-Hydroxypyridine, 2-chloropyridine, were purchased from Sigma-Aldrich (Merck). The alcohols used in this work were also purchased from Sigma-Aldrich (Merck).

Benzhydroximoyl chloride was obtained by treatment of benzaldoxime with sodium hypochlorite.[18] Addition of a slight excess of Et_3N to a DCM solution of benzhydroximoyl chloride furnished *in situ* BNO.

Solvents and all the other reagents were purchased from Sigma-Aldrich (Merck) and used without any further purification with the single exception of triethylamine that was carefully distilled and used in all the reactions, when requested.

Reaction of Salt 3 in Methanol with Triethylamine

A methanol solution (20 mL) of the pyridinium salt **3** 1.0 g (4.3 mmol) is left under stirring at room temperature and 1 mL (7.2 mmol) of freshly distilled triethylamine is added dropwise. After a couple of hours (TLC monitoring), methanol is removed at reduced pressure and the residues were taken up with benzene to ensure precipitation of insoluble chlorides. The organic phase was then evaporated to dryness and the residue were submitted to chromatographic separation to isolate the products **5a** and **8** that were fully characterized.

5-((1Z,3E)-4-Methoxybuta-1,3-dien-1-yl)-3-phenyl-1,2,4-oxadiazole ***5a***, 0.15 g (15%), dark yellow oil. IR: $\nu_{C=N}$ 1680, $\nu_{C\text{-}O}$ 1290 cm^{-1}. ^{1}H-NMR (C_6D_6) δ: 3.12 (s, 3H, OCH_3); 5.90 (d, 1H, *J* = 11 Hz, H*d*); 6.05 (dd, 1H, *J* = 13, 11 Hz, H*b*); 6.50 (d, 1H, *J* = 13 Hz, H*c*); 7.20 (m, 3H + 1H, arom. and H*a*); 8.33 (m, 2H, arom.). ^{13}C-NMR (DMSO) δ: 59.8, 105.7, 120.9, 125.3, 128.8, 129.9, 131.5, 137.8, 141.4, 146.1, 159.8. Anal. Calcd for $C_{13}H_{12}N_2O_2$ (228.25): C, 68.41; H, 5.30; N, 12.27. Found: C, 67.50; H, 5.35; N, 12.25.

Methyl N-(pyridin-2-yloxy)benzimidate ***8***, 0.74 g (75%), yellow oil. IR: $\nu_{C=N}$ 1630, ν_{OMe} 1100 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.03 (s, 3H, OCH_3); 6.97 (dd, 1H, *J* = 7, 5 Hz, H*b*); 7.30 (d, 1H, *J* = 8 Hz, H*d*); 7.50 (m, 3H, arom.); 7.70 (dd, 1H, *J* = 8, 7 Hz, H*c*); 7.85 (m, 2H, arom.); 8.25 (d, 1H, *J* = 5 Hz, H*a*). ^{13}C-NMR (DMSO) δ: 52.5, 96.1, 126.4, 126.9, 128.6, 130.5, 146.4, 152.5, 166.9, 176.9. Anal. Calcd for $C_{13}H_{12}N_2O_2$ (228.25): C, 68.41; H, 5.30; N, 12.27. Found: C, 67.29; H, 5.38; N, 12.30.

Catalytic Hydrogenation of 8

A solution of the compound **8** 210 mg (1.3 mmol) in 75 mL ethanol 96% are hydrogenated with 50 mg Pd/C 10% at room temperature (H_2 absorption 27 mL in 30 minutes). The catalyst is then removed by filtration and the solvent evaporated at reduced pressure to leave an oily residue. Upon addition of diethyl ether a crystalline solid corresponding to the 2-pyridone **9** separates off, found identical with an authentic specimen. The organic phase was then evaporated to dryness to leave an oil identified as the methyl benzimidate[12] **10**.

General Procedure for the Reactions of 3 with Alcohols and Triethylamine in Benzene

An anhydrous benzene suspension (100 mL) of the pyridinium salt **3** 0.7 g (3 mmol) is left under stirring at room temperature and 4 mmol of selected alcohols (methanol, absolute ethanol, *n*-propanol, isopropanol, *n*-butanol) are added along with 5 mmol of freshly distilled triethylamine. After a couple of days (TLC monitoring), the insoluble salts are filtered and the solvent is removed at reduced pressure to leave oily residues that were purified by chromatography or distillation and fully characterized.

5-((1Z,3E)-4-Ethoxybuta-1,3-dien-1-yl)-3-phenyl-1,2,4-oxadiazole **5b**, 0.65 g (90%), dark yellow oil. IR: $\nu_{C=N}$ 1681, ν_{C-O} 1289 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.95 (t, 3H, *J* = 7 Hz, CH_3), 3.05 (q, 2H, *J* = 7 Hz, CH_2), 4.22 (s, 3H, OCH_3); 5.40 (dd, 1H, *J* = 11 Hz, H*d*); 6.05 (d, 1H, *J* = 13 Hz, H*b*); 6.83 (dd, 1H, *J* = 13, 11 Hz, H*c*); 7.49 (m, 3H + 1H, arom. and H*a*); 8.09 (m, 2H, arom.). ^{13}C-NMR ($CDCl_3$) δ: 24.7, 45.4, 59.8, 97.3, 126.8, 127.3, 129.0, 130.9, 146.7, 148.6, 167.2, 177.3. Anal. Calcd for $C_{14}H_{14}N_2O_2$ (242.28): C, 69.41; H, 5.82; N, 11.56. Found: C, 69.40; H, 5.85; N, 11.55.

5-((1Z,3E)-4-Propoxybuta-1,3-dien-1-yl)-3-phenyl-1,2,4-oxadiazole **5c**, 0.71 g (92%), yellow oil. IR: $\nu_{C=N}$ 1660, ν_{C-O} 1290 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.03 (t, 3H, CH_3); 1.80 (sx, 2H, CH_2); 3.93 (t, 2H, OCH_2); 6.07 (d, 1H, *J* = 11 Hz, H*d*); 6.67 (dd, 1H, *J* = 13, 1 Hz, H*b*); 7.05 (m, 1H + 1H, H*a,c*); 7.40 (m, 3H, arom.); 8.39 (m, 2H, arom.). ^{13}C-NMR (DMSO) δ: 10.7, 24.7, 59.8, 97.3, 126.8, 127.3, 128.9, 130.9, 146.7, 148.5, 167.3, 177.3. Anal. Calcd for $C_{15}H_{16}N_2O_2$ (256.31): C, 70.30; H, 6.29; N, 10.93. Found: C, 70.20; H, 6.25; N, 10.95.

5-((1Z,3E)-4-Isopropoxybuta-1,3-dien-1-yl)-3-phenyl-1,2,4-oxadiazole **5d**, 0.70 g (91%), yellow oil. IR: $\nu_{C=N}$ 71 ν_{C-O} 1290 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.20 (d, 6H, CH_3); 4.40 (m, 1H, OCH); 6.07 (d, 1H, *J* = 11 Hz, H*d*); 6.67 (dd, 1H, *J* = 11, 1 Hz, H*b*); 6.93 (d, 1H, *J* = 13 Hz, H*c*); 7.10 (dd, 1H, *J* = 13, 1 Hz, H*a*); 7.30 (m, 3H, arom.); 8.20 (m, 2H, arom.). ^{13}C-NMR (DMSO) δ: 23.6, 25.2, 67.3, 96.3, 126.8, 127.3, 129.0, 130.9, 147.1, 151.8, 167.3, 177.2. Anal. Calcd for $C_{15}H_{16}N_2O_2$ (256.31): C, 70.30; H, 6.29; N, 10.93. Found: C, 70.33; H, 6.31; N, 10.91.

5-((1Z,3E)-4-Butoxybuta-1,3-dien-1-yl)-3-phenyl-1,2,4-oxadiazole **5e**, 0.75 g (92%), yellow oil. IR: $\nu_{C=N}$ 1640, ν_{C-O} 1290 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.99 (t, 3H, CH_3); 1.30–1.70 (m, 4H, CH_2); 4.00 (t, 2H, OCH_2); 6.07 (dd, 1H, *J* = 11, 1 Hz, H*d*); 6.67 (dd, 1H, *J* = 12, 11 Hz, H*b*); 7.03 (m, 1H + 1H, H*a,c*); 7.30 (m, 3H, arom.); 8.20 (m, 2H, arom.). ^{13}C-NMR (DMSO) δ: 23.6, 25.1, 53.2, 66.9, 96.3, 126.8, 127.3, 128.9, 130.9, 147.1, 151.8, 167.2, 177.2. Anal. Calcd for $C_{16}H_{18}N_2O_2$ (270.33): C, 71.09; H, 6.71; N, 10.36. Found: C, 71.10; H, 6.70; N, 10.35.

Reaction of 3 in Sodium Methoxide 30% Solution in benzene

Pyridinium salt **3** 2.0 g (8.6 mmol) are suspended in anhydrous benzene (100 mL) and 3.25 mL (17 mmol) MeONa/MeOH 30% solution were added under stirring at room temperature. After one day (TLC monitoring), the reaction is quenched with water and the organic phase separated and dried over anhydrous Na_2SO_4. The solvent is then removed at reduced pressure and the residue was submitted to chromatographic separation to isolate the products **5a**, **11**, **12** and **13** that were fully characterized.

(E)-5-(4,4-Dimethoxybut-1-en-1-yl)-3-phenyl-1,2,4-oxadiazole **11**, 0.22 g (10%), straw yellow oil. IR: $\nu_{C=N}$ 1665, ν_{C-O} 1071 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.68 (dd, 2H, *J* = 7, 6 Hz, CH_2); 3.40 (s, 6H, OCH_3); 4.57 (t, 1H, *J* = 6 Hz, O–CH–O); 6.56 (d, 1H, *J* = 16 Hz, CH=); 7.10 (dd, 1H, *J* = 16, 7 Hz, CH=); 7.49 (m, 3H, arom.); 8.11 (m, 2H, arom.). ^{13}C-NMR ($CDCl_3$) δ: 36.6, 53.2, 102.8, 115.9, 126.8, 127.3, 128.7, 131.0, 141.4, 168.4, 174.4. Anal. Calcd for $C_{14}H_{16}N_2O_3$ (260.29): C, 64.60; H, 6.20; N, 10.76. Found: C, 64.50; H, 6.15; N, 10.85.

3-Phenyl-5-(2,4,4-trimethoxybutyl)-1,2,4-oxadiazole **12**, 0.85 g (34%), straw yellow solid, m.p. 98 °C (dec.). IR: ν_{C-O} 1127 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.96 (dd, 2H, *J* = 7, 6 Hz, CH_2); 3.19 (d, 2H, *J* = 7 Hz, CH_2); 3.37 (s, 6H, OCH_3); 3.41 (s, 3H, OCH_3); 3.91 (dd, 1H, *J* = 12, 6 Hz, CH–O); 4.62 (t, 1H, *J* = 6 Hz, O–CH–O); 7.50 (m, 3H, arom.); 8.10 (m, 2H, arom.). ^{13}C-NMR ($CDCl_3$) δ: 31.1, 36.8, 52.4, 52.7, 57.0, 74.8, 101.2, 126.9, 128.3, 130.6, 130.7, 175.9, 176.8. Anal. Calcd for $C_{15}H_{20}N_2O_4$ (292.34): C, 61.63; H, 6.90; N, 9.58. Found: C, 61.58; H, 6.85; N, 9.65.

(E)-3-(3-Phenyl-1,2,4-oxadiazol-5-yl)acrylaldehyde **13**, 0.62 g (36%), straw yellow solid, m.p. 89–91 °C. IR: $\nu_{C=O}$ 1688, $\nu_{C=N}$ 1664 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.37 (dd, 1H, *J* = 16, 8 Hz, CH=); 7.43 (d, 1H, *J* = 16 Hz, CH=); 7.40 (m, 3H, arom.); 8.20 (m, 2H, arom.); 9.90 (d, 1H, *J* = 8 Hz, CHO). ^{13}C-NMR (DMSO) δ: 120.9, 125.3, 128.8, 129.9, 131.5, 137.8, 141.4, 146.1, 159.8, 199.2. Anal. Calcd for $C_{11}H_8N_2O_2$ (200.20): C, 66.00; H, 4.03; N, 13.99. Found: C, 66.08; H, 4.05; N, 14.05.

Acknowledgments

Financial support by the University of Pavia, MIUR is gratefully acknowledged. We also thank "VIPCAT – Value Added Innovative Protocols for Catalytic Transformations" project (CUP: E46D17000110009) for valuable financial support.

Keywords: Nitrile oxides · 1,3-dipolar cycloadditions · Zincke salts · oxadiazoles · alkoxybutadienyl derivatives

[1] P. Quadrelli, in *Modern Applications of Cycloaddition Chemistry*, Elsevier, Amsterdam, **2019**.
[2] G. Romeo, U. Chiacchio, *Modern Heterocyclic Chemistry*, J. Alvarez-Builla, J. J. Vaquero, J. Barluenga, Ed.; Wiley-VCH, Eds.: **2011**, pp. 1047–1252.
[3] S. Chama, S. Sanchit, *J. Drug Delivery Ther.* **2015**, *5*, 8–13.
[4] R. Shioi, S. Okazaki, T. Noguchi-Yachide, M. Ishikawa, M. Makishima, Y. Hashimoto, T. Yamaguchi, *Bioorg. Med. Chem. Lett.* **2017**, *27*, 3131–3134.
[5] M. Parra, P. Hidalgo, E. Carrasco, J. Barbera, L. Silvino, *Liq. Cryst.* **2006**, *33*, 875–882.
[6] P. Caramella, P. Grünanger, in *1,3-Dipolar Cycloaddition Chemistry*, Vol. 1, (Eds. A. Padwa), J. Wiley & Sons, New York, **1984**, p.291.
[7] S. Carella, M. G. Memeo, P. Quadrelli, *ChemistryOpen* **2019**, *8*, 1209–1221.
[8] A. Corsaro, G. Perrini, P. Caramella, F. Marinone Albini, T. Bandiera, *Tetrahedron Lett.* **1988**, *44*, 4917–4925.
[9] F. Marinone Albini, R. De Franco, T. Bandiera, P. Grünanger, P. Caramella, *Gazz. Chim. Ital.* **1990**, *120*, 1–7.
[10] P. Caramella, A. Gamba Invernizzi, E. Pastormerlo, P. Quadrelli, A. Corsaro, *Heterocycles* **1995**, *40*, 515–520.
[11] a) F. Eloy, R. Lenaers, *Chem. Rev.* **1962**, *62*, 155–183; b) F. Eloy, R. Lenaers, R. Buyle, *Bull. Soc. Chim. Belg.* **1964**, *73*, 518–531; c) J. A. Durden, D. L. Heywood, *J. Org. Chem.* **1965**, *30*, 4359–4361.
[12] B. Wu, Z. Yang, H. Zhang, L. Wang, X. Cui, *Chem. Commun.* **2019**, *55*, 4190–4193.
[13] P. von Ragué Schleyer, J. I. Wu, F. P. Cossio, I. Fernandez, *Chem. Soc. Rev.* **2014**, *43* 4909–4921.
[14] Th. Zincke, *Justus Liebigs Ann. Chem.* **1903**, *330*, 361–374.
[15] T. Focken, A. B. Charette, *Org. Lett.* **2006**, *8*, 2985–2988.
[16] W.-C. Cheng, M. J. Kurth, *Org. Prep. Proced. Int.* **2002**, *34*, 585–608.
[17] C. D. Vanderwal, *J. Org. Chem.* **2011**, *76*, 9555–9567.
[18] C. Grundmann, P. Grünanger, *The Nitrile Oxide,* Springer-Verlag: Heidelberg, **1971**.

Manuscript received: December 31, 2019
Revised manuscript received: January 13, 2020