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

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1,2,4-Oxadiazole[4,5-α]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 preparation and elaboration in other synths as well as to their biological activities, specifically in drug discovery where oxadiazoles are often hydrolysis-resistant bioisosteres 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.[6,7] 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-α]piridinium salts 3 with amines;[8] synthesized from nitrile oxides of type 2 and suitably 2-substituted pyridines, the 1,2,4-oxadiazole[4,5-α]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-α]piridinium chloride 3 was prepared according to the known procedure.[9] Compound 3 is stable for days in water solution but unstable in the presence of 5% solution NaHCO₃ affording the insoluble N-substituted 2-pyridone 6 through oxadiazole ring-opening reaction.[10]

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.
reaction takes place almost immediately and is quantitative after one day (Scheme 3). 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 Et₃N 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 (CDCl₃) 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 Hb and Hd proton signals are quite shielded as expected for an alkylidine with respect to the Ha and Hc 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 (CDCl₃) spectrum the typical pyridine proton array, quite deshielded and with increasing J values moving from Ha to the Hd, 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.

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,[11] i.e. by suspending the salt 3 in benzene as solvent in the presence of 4 mmol of alcohols and adding 5 mmol Et₃N 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 (CDCl₃) 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 3.5–4.7 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⁻/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 moieties, respectively.
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 $\delta$ 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 $\delta$ 3.40, geminally linked to the acetalic CH whose proton resonate at $\delta$ 4.57. The parent compound 12 possesses as additional methoxy group ($\delta$ 3.41) and a methylene adjacent to the oxadiazole ring whose proton are found at $\delta$ 3.19. Finally, in the $^1$H NMR (CDCl$_3$) of the $\alpha\beta$-unsaturated aldehyde 13 the aldehyde proton is found at $\delta$ 9.90 as a doublet, coupled with the C=C double bond protons found at $\delta$ 7.37 and 7.43.

The use of stronger bases seems to erode the reaction selectivity that is clearly guaranteed by the ROH/R$_3$N/Benzene methodology conditions.

The results here reported add intriguing aspects in the reactivity of the oxadiazole-pyridinium salts 3 with nucleophiles. These monocyloadducts 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.[9]

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 stereoisomers 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 $\alpha\beta$-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-$\alpha$]pyridinium 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
alcohols and alkoxybutadienyl derivatives undergo a further addition in low concentration, still activate the electrocyclic ring-opening by the alcohol concentration to give as major product the hydroximic ester 8.

On the other side, the use of alcohols, 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 usefulness 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. 1H and 13C 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.

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).

Benzyldioximoyl chloride was obtained by treatment of benzaldimine with sodium hypochlorite. Addition of a slight excess of Et3N 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 was submitted to chromatographic separation to isolate the products 5a and 8 that were fully characterized.

S-(1Z,3E)-4-Methoxybuta-1,3-dien-1-yl-3-phenyl-1,2,4-oxadiazole 5a, 0.15 g (15%), dark yellow oil. IR: νC=O 1680, νC–O 1290 cm⁻¹. 1H-NMR (CDCl3): δ: 1.42 (t, 3H, OCH3); 2.10 (d, 1H, J = 11 Hz, Hd); 6.05 (dd, 1H, J = 13, 11 Hz, Hb); 6.50 (d, 1H, J = 13 Hz, Hc); 7.20 (m, 3H + H1, arom. and H6); 8.33 (m, 2H, arom.). 13C-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 C19H16N2O2 (228.25): C, 74.49; H, 5.30; N, 12.27. Found: C, 74.70; H, 5.35; N, 12.25.

Methyl N-(pyridin-2-yl)benzimidate 8, 0.74 g (75%), yellow oil. IR: νC–N=O 1630, νO=O 1100 cm⁻¹. 1H-NMR (CDCl3): δ: 4.03 (s, 3H, OCH3); 6.97 (dd, 1H, J = 7, 5 Hz, Hb); 7.30 (d, 1H, J = 8 Hz, Hf); 7.50 (m, 3H, arom.); 7.70 (dd, 1H, J = 8, 7 Hz, Hc); 7.85 (m, 2H, arom.); 8.25 (d, 1H, J = 5 Hz, Hg). 13C-NMR (DMSO): δ: 52.5, 96.1, 126.4, 126.9, 128.6, 135.0, 146.4, 152.5, 159.8. Anal. Calcd for C12H13N2O2 (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 ethanolic 96% are hydrogenated with 50 mg Pd/C 10% at room temperature (H2 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 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 to reduce 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: ν: 5-((1Z,3E)-4-Ethoxybuta-1,3-dien-1-yl)-3-phenyl-1,2,4-oxadiazole

5-(1Z,3E)-4-Isopropoxybuta-1,3-dien-1-yl)-3-phenyl-1,2,4-oxadiazole 5c, 0.71 g (92 %), yellow oil. IR: ν: 5-((1Z,3E)-4-Isopropoxybuta-1,3-dien-1-yl)-3-phenyl-1,2,4-oxadiazole

5-(1Z,3E)-4-Butoxybuta-1,3-dien-1-yl)-3-phenyl-1,2,4-oxadiazole 5d, 0.70 g (91 %), yellow oil. IR: ν: 5-((1Z,3E)-4-Butoxybuta-1,3-dien-1-yl)-3-phenyl-1,2,4-oxadiazole

5-(1Z,3E)-4-(2,4,4-Trimethoxybutyl)-1,2,4-oxadiazole 5e, 0.75 g (92 %), yellow oil. IR: ν: 5-(1Z,3E)-4-(2,4,4-Trimethoxybutyl)-1,2,4-oxadiazole

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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 hour (TLC monitoring), the reaction is quenched with water and the organic phase separated and dried over anhydrous Na2SO4. The solvent is then removed at reduced pressure and the residue was subjected to chromatographic separation to isolate the products 5a, 5b, 11, 12 and 13 that were fully characterized.

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: 5-((1Z,3E)-4-Ethoxybuta-1,3-dien-1-yl)-3-phenyl-1,2,4-oxadiazole

5-(1Z,3E)-4-(2,4,4-Trimethoxybutyl)-1,2,4-oxadiazole 13, 0.62 g (36 %), straw yellow solid, m.p. 89–91 °C. IR: ν: 5-((1Z,3E)-4-(2,4,4-Trimethoxybutyl)-1,2,4-oxadiazole

(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: ν: 5-((1Z,3E)-4-(2,4,4-Trimethoxybutyl)-1,2,4-oxadiazole

3-(3-Phenyl-1,2,4-oxadiazol-5-yl)-4-ethyl-2-methylpentan-2-one 14, 0.62 g (36 %), yellow oil. IR: ν: 5-((1Z,3E)-4-(2,4,4-Trimethoxybutyl)-1,2,4-oxadiazole