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# *N,O*-Nucleosides from Ene Reactions of Nitrosocarbonyl Intermediates with the 3-Methyl-2-buten-1-ol

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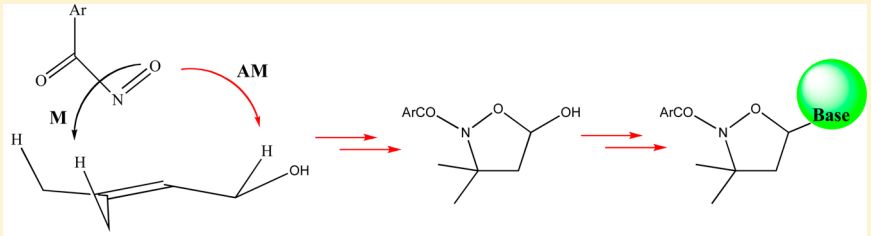
Supporting Information




| Ar | Markovnikov path (M) | Anti-Markovnikov path (AM) |
|---|---|---|
| **Ph** | ***60*** | ***0*** |
| **Mes** | ***50*** | ***25*** |
| **Anthra** | ***27*** | ***52*** |

**ABSTRACT:** Nitrosocarbonyl intermediates undergo ene reactions with allylic alcohols, affording regioisomeric adducts in fair yields. Nitrosocarbonyl benzene reacts with 3-methyl-2-buten-1-ol and follows a Markovnikov orientation and abstracts preferentially the twix hydrogens over the lone ones. With the more sterically demanding nitrosocarbonyl mesitylene and anthracene, the Markovnikov directing effect is relieved and lone abstraction is observed, affording the 5-hydroxy-isoxazolidines that serve as synthons for the preparation of *N,O*-nucleoside analogues according to the Vorbrüggen protocol.

## INTRODUCTION

The discovery of several new series of nucleosides analogues with antiviral activity altered the classical way of thinking about nucleosides analogues as antiviral agents.[1] These derivatives play a fundamental role in viral chemotherapy and modification of the sugar fragment and its replacement with a carbocyclic moiety resulted in the syntheses of interesting nucleosides analogues that have shown remarkable activity toward a variety of viruses.[2]

Methods for the synthesis of sugar- and sugar-modified and carbocyclic-nucleosides were studied extensively.[3] However, various synthetic problems were frequently encountered, such as low yields, low stereoselectivity, and toxicity problems of the obtained compounds, which are just some of the problems that characterize these synthetic approaches.

Among the various synthetic strategies, the heteroatom substitution produced a series of compounds where the sugar moiety was replaced by alternative heterocyclic rings. Furthermore, the introduction of a side chain on the sugar led to several branched nucleosides that were found to be potential antitumoral or antiviral agents.[4] In this field, the Chiacchio and Romeo groups have described the synthesis of 4′-$\alpha$-C-branched *N,O*-nucleosides based on the 1,3-dipolar cycloadditions of nitrones with vinyl acetate, followed by coupling with silylated nucleobases. The obtained compounds were evaluated for their activity against various viruses as well as cytoxicity and apoptotic activity.[5]

Recently, we have proposed the synthesis of a new class of carbocyclic nucleosides starting from cyclopentadiene using the nitrosocarbonyl intermediates (RCONO, **1**) chemistry.[6] These intermediates, generated by the mild oxidation of nitrile oxides with tertiary amine *N*-oxides or by oxidation of hydroxamic acids, are efficiently trapped by cyclopentadiene (Scheme 1) to afford the hetero Diels−Alder (HDA) cycloadducts **2** that are highly reactivity dipolarophiles and were employed to synthesize the conformationally restricted carbocyclic moiety aminols **4** through amide hydrolysis and N−O bond cleavage of the cycloadducts **3**.[7] Aminols **4** were useful for the linear construction of purine and pyrimidine nucleosides **5**. These nucleosides are characterized by the presence of a secondary hydroxy group on the cyclopentane moiety and by an isoxazoline ring fused to the carbocyclic unit and were found moderately active against human Herpes (types 1 and 2) and Varicella viruses.[8] Recently, anthryl derivatives were found active with no cellular toxicity at the dose tested against the Human Papilloma virus (HPV).[9]

Applications of nitrosocarbonyls to the syntheses of biologically active molecules are well-known, essentially due, first, to the variety of generating methods available (oxidation of hydroxamic acids[10] and nitrile oxides[11] and thermal[12] or photochemical[13] cycloreversions of 1,2,4-oxadiazole-4-oxides)

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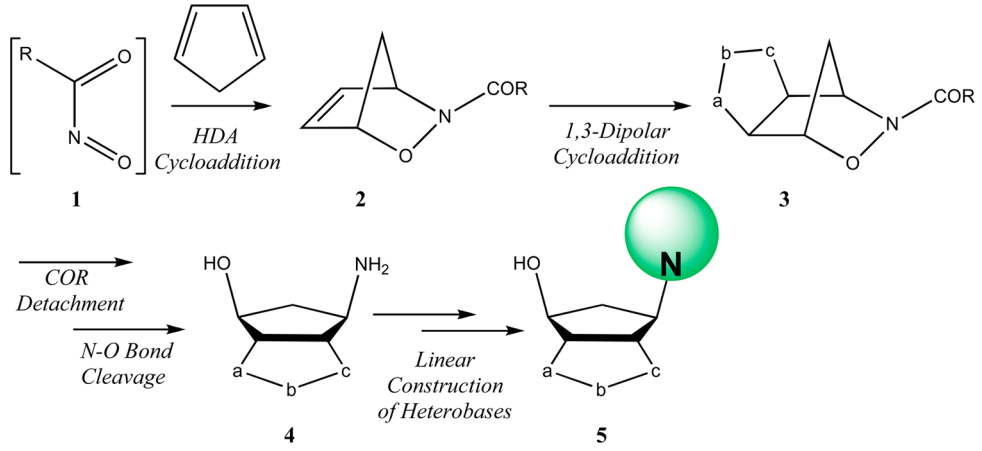
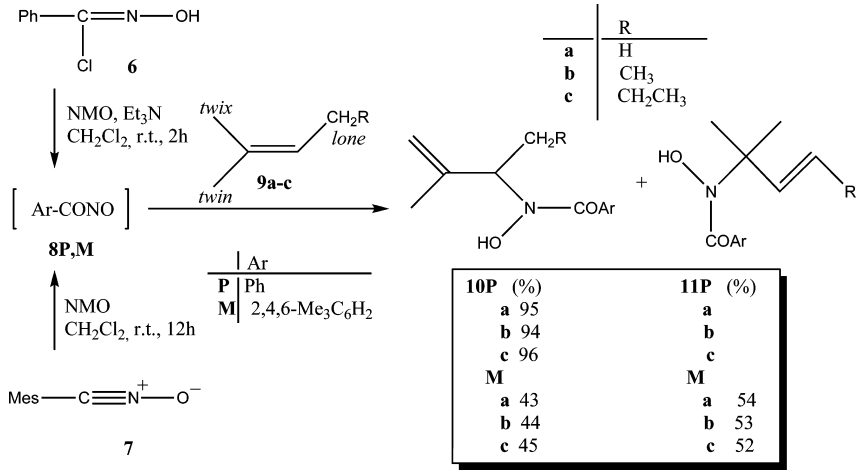
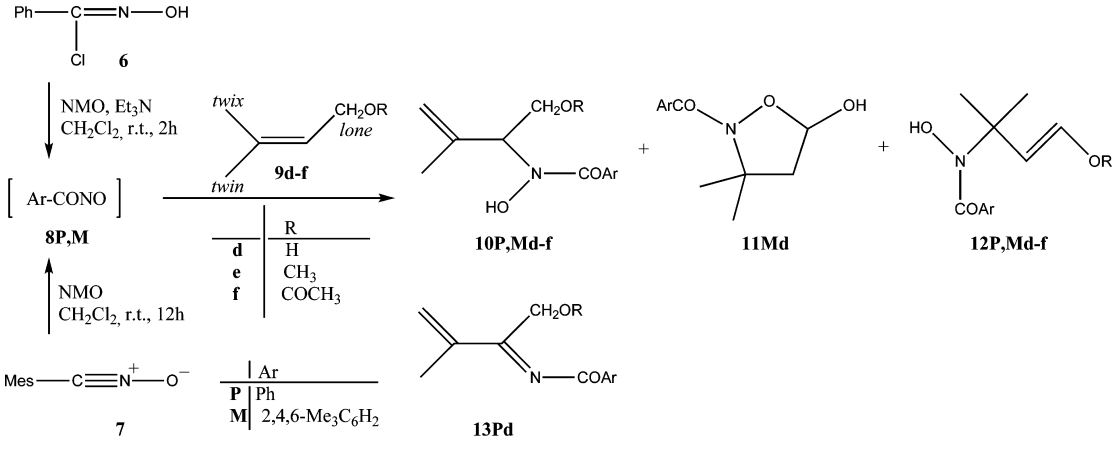
**Scheme 1. Synthetic Pathway of Isoxazoline-Carbocyclic Nucleosides through Nitrosocarbonyl Chemistry and Linear Construction of the Heterobases**




**Scheme 2. Ene Reactions of Aromatic Nitrosocarbonyl Intermediates with Trisubstituted Olefins**




**Scheme 3. Ene Reactions of Aromatic Nitrosocarbonyl Intermediates with the 3-Methyl-2-buten-1-ol and Its Methyl Ether and Acetyl Derivatives**




and, second, to the exceptional reactivity of these intermediates in HDA reactions. Nevertheless, nitrocarbonyl intermediates are also powerful enophiles,[14] but no applications of ene reactions toward the synthesis of nucleosides are actually reported.[15] We have detailed that nitrosocarbonyl intermediates, generated at r.t. by the mild oxidation of nitrile oxides, undergo clean ene reactions with trisubstituted olefins **9**. Allylic hydrogens on the more congested side of the alkene are exclusively abstracted (the "cis effect"), thus resembling the singlet oxygen behavior. Nitrosocarbonyl benzene **8P** (P = phenyl) follows a Markovnikov (M) orientation and abstracts preferentially the twix hydrogens over the lone ones. With the more sterically demanding nitrosocarbonyl mesitylene **8M** (M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= mesityl), the M-directing effect is relieved and comparable twix and lone abstraction are observed (Scheme 2).[16]

On pursuing our research in nitrosocarbonyl ene reactions, we extended the studies to other trisubstituted olefins and, in particular, to allylic alcohols (R = OH). The 3-methyl-2-buten-1-ol was found to be the proper model to investigate the selectivity outcome in the ene reaction with nitrosocarbonyls bearing more sterically demanding substituents. An unexpected isoxazolidine deriving from the anti-Markovnikov (AM) addition to the alcohol is presented as a valuable synthon toward the preparation of new *N*,*O*-nucleoside analogues through the Vonbrüggen protocol.

## RESULTS

**Ene Reactions with Nitrosocarbonyl Benzene and Mesitylene.** Addition of a dichloromethane (DCM) solution of benzohydroximoyl chloride **6** to a stirred solution of *N*-methyl-morpholine *N*-oxide (NMO, 1.1 equiv) and $Et_3N$ (1 equiv or a catalytic amount) in DCM in the presence of an excess (5 equiv) of 3-methyl-2-buten-1-ol **9d** afforded, after standing overnight at r.t., the ene adducts **10Pd** and **13Pd** (Scheme 3) that were isolated upon chromatographic separation of the reaction mixture in the reported yields (Table 1). The same procedure was followed for the allylic ether **9e**[17] and acetate **9f**,[18] which were prepared according to the reported syntheses.

**Table 1. Yields of Adducts in the Reactions of Nitrosocarbonyls 8P,M with Alkenes 9d−9f**

| Ar-CONO | alkene | 10 | 11 | 12 | 13 |
|---|---|---|---|---|---|
| **8P** | **9d** | 50 | | | 8 |
| | **9e** | 70 | | | |
| | **9f** | 60 | | | |
| **8M** | **9d** | 50 | 25 | | |
| | **9e** | 63 | | 35 | |
| | **9f** | 56 | | 32 | |

The structures of all isolated ene adducts rely upon the corresponding analytical and spectroscopic data. In the $^1$H NMR spectra, the typical olefinic methylene signals are found in the range between 5.00 and 5.43 $\delta$ for adducts **10Pd−10Pf** and more shielded between 4.89 and 5.00 $\delta$ for the derivative **13Pd**. The N-OH group is evident when the spectrum is recorded in DMSO and is found strongly deshielded in the range 8.2−8.4 $\delta$ for **10Pd−10Pf** and even more (9.3−9.5 $\delta$) for adduct **13Pd**. In the reaction with the allylic alcohol **9d**, compound **13Pd** is related to **10Pd** and both derive from the addition of the nitrosocarbonyl benzene **8P** to the less-substituted carbon atom of the double bond, in full accordance with a M orientation.[14,16] Adduct **13Pd** derives from **10Pd** simply upon water elimination.

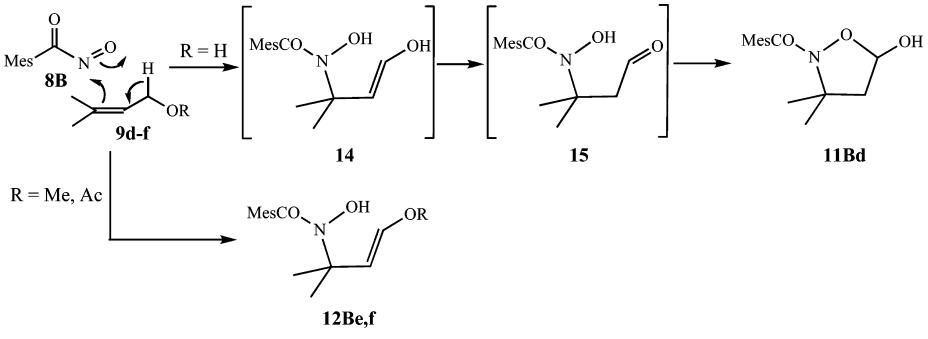
When the hydroxy group of the alcohol **9d** is protected as an ether in **9e** or an ester in **9f**, the ene reactions with the nitrosocarbonyl benzene **8P** proceed straight to single ene adducts **10Pe** and **10Pf**, respectively, which are obtained in good yields according to the addition of the nitrosocarbonyl electrophilic nitrogen to the alkene in an M fashion.[19]

Moving to the nitrosocarbonyl mesitylene **8M** case, the experimental conditions were even simpler and cleaner. Mesitonitrile oxide **7** was added to a stirred solution of NMO (1.1 equiv) in DCM in the presence of an excess (5 equiv) of 3-methyl-2-buten-1-ol **9d** at r.t. After stirring overnight and column chromatographic separation, the ene adduct **10Md** was isolated in 50% yield along with an unexpected second compound, **11Md**, in only, but remarkable, 25% yield.

Compound **10Md** is the M adduct, and its structure is in accordance with the analytical and spectroscopic data. The structure of **11Md** was not immediately clear. The $^1$H NMR spectrum indicates the presence of one deshielded proton at 5.44 $\delta$ coupled with two protons at 2.14 and 2.35 $\delta$, while an OH group gives a singlet at 6.98 $\delta$, as confirmed by the corresponding IR spectrum. The $^{13}$C NMR spectrum presents a signal at 95.3 $\delta$ resembling an acetal-type carbon atom. The structure assignment as shown in Scheme 3 came from the X-ray analysis (see the Supporting Information). These types of 5-hydroxy-isoxazolidines are usually prepared by reaction of hydroxamic acids and $\alpha,\beta$-unsaturated aldehydes.[20] The origin of the isoxazolidine **11Md** was undoubtedly attributed to a relief in the M addition determined by the more sterically demanding mesityl group that activates the AM path.[16] As the addition of the nitrosocarbonyl moiety occurs on the more substituted carbon atom of the allylic alcohol **9d**, the primary adduct is the enol **14** that evolves into the nonisolable aldehyde **15**, which undergoes cyclization to the hemiacetal **11Md** (Scheme 4). In fact, when the protected alcohols **9e,f** were used and the reactions were carried out in the same conditions, adducts **10Me** and **10Mf** were obtained in 63% and 56% yields, respectively, along with the enol ethers **12Me** and **12Mf** in 35% and 32% yields, respectively (Scheme 3 and Table 1).

The structures of the adducts obtained from alkenes **9e,f** rely upon their analytical and spectroscopic data. The $^1$H NMR spectra of adducts **10Me** and **10Mf** show the olefinic methylenes as singlets at 4.90 and 5.00 $\delta$ for **10Me** and at 4.96 and 5.04 $\delta$ for **10Mf**. The N-OH singlets are found at 9.07

**Scheme 4. AM Pathway: The Formation of Isoxazolidine Ring**





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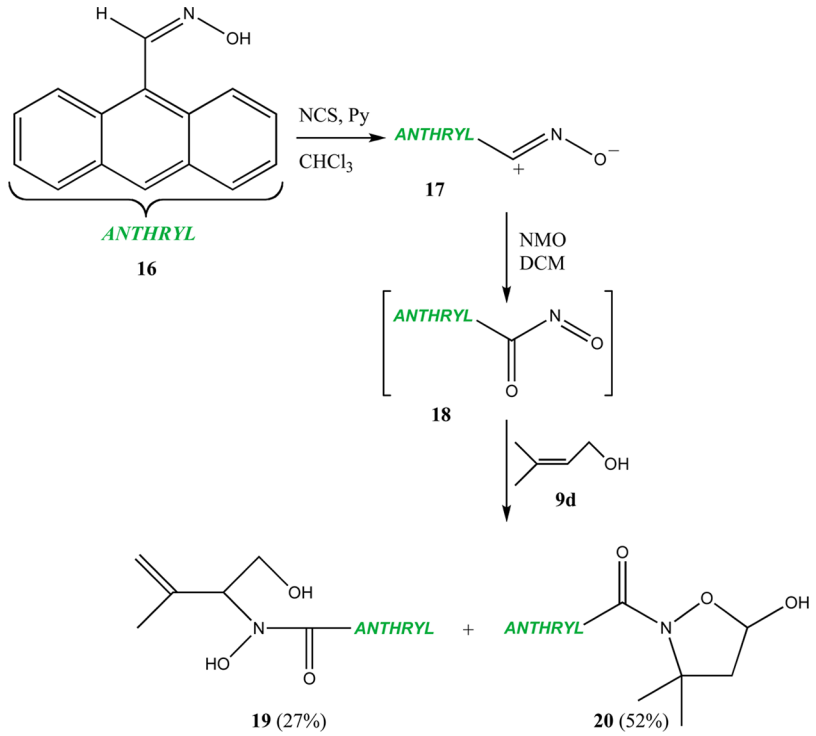
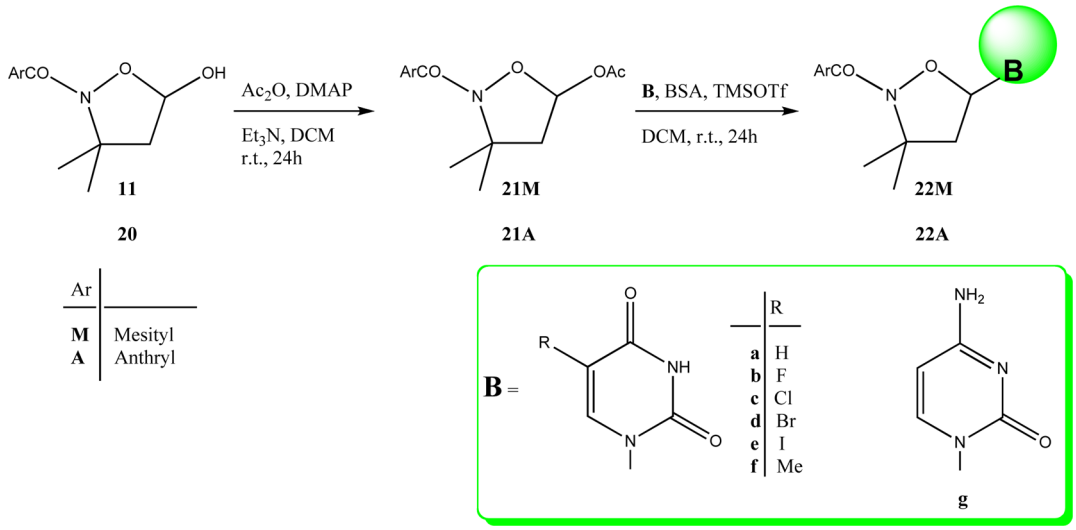
**Scheme 5. Ene Reaction of Anthryl Nitrosocarbonyl Intermediate with the 3-Methyl-2-buten-1-ol**




**Scheme 6. Synthesis of Isoxazolidine-Nucleoside Analogues through the Vorbrüggen Protocol**




and 9.27 $\delta$ for the two products, respectively. The enol-ether **12Me** showed the double bond signals at 5.23 and 6.52 $\delta$ and the N-OH singlet at 9.10 $\delta$ while the enol-acetate **12Mf** showed the double bond signals at 5.88 and 7.21 $\delta$ and the N-OH singlet at 9.38 $\delta$.

The results of the reactions of nitrosocarbonyls **8P**,**M** and olefins **9d**−**9f** seem to show that hydrogen bonding is ineffective with respect to the selectivity. To verify experimentally the influence of the substitution pattern on the reactivity of the double bond, we performed control experiments by means of intermolecular competition reactions of the alkenes **9d** versus **9e** and **9f**, respectively, in the presence of the nitrosocarbonyl benzene **8P** and mesitylene **8M**. The results showed that the expected compounds (as shown in Table 1) from the competitive reactions were isolated in all the cases with the same ratios (see the Experimental Section). The allylic alcohol **9d** was not found somehow more reactive than the others, and the selectiviy outcomes were maintained.

**Enforcing the AM Path.** We explored the ene reaction of another typical stable nitrile oxide,[21] the anthracenenitrile oxide **17** obtained from the 9-anthraldeyde oxime **16** according to the preparation reported in the literature[22] by treating a chloroform solution of **16** with NCS and catalytic pyridine at 0 °C for 2 h. The solid nitrile oxide **17** was added portionwise to a stirred DCM solution of 5 equiv of the allylic alcohol **9d** in the presence of 2 equiv of NMO at r.t. for 48 h. After the usual workup, the residue was submitted to column chromatography, and two products were isolated and identified as compounds **19** and **20** in 27% and 52% yields, respectively (Scheme 5).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Their structures rely upon the relative spectroscopic data. In particular, the $^1$H NMR spectrum of the major compound **20** showed a deshielded proton as a triplet at 5.22 $\delta$, coupled with two protons at 2.20 and 2.44 $\delta$. Just before the aromatic signals (7.5−8.6 $\delta$), a doublet was found at 6.84 $\delta$ corresponding to the OH group (exchange with $D_2O$) and whose presence was confirmed by the IR spectrum ($\nu_{OH}$ = 3200 cm$^{-1}$). The $^{13}$C NMR spectrum showed significantly the acetal-type carbon at 95.8 $\delta$.

The experiment performed with anthracene nitrosocarbonyl **18** and alcohol **9d** confirms the relief of the M control observed in the addition of **8M** to enes **9d**−**9f** (Table 1), and the results show the remarkable influence of the nitrosocarbonyl substituent on the selectivities. The approach of the bulkier anthracene group determines a strong steric hindrance that disfavors the M path enforcing the AM selectivity.

**Synthesis of *N,O*-Nucleosides.** The 5-hydroxy-isoxazolidines **11Bd** and **20** obtained from the ene reaction of nitrosocarbonyl mesitylene **8M** and nitrosocarbonyl anthracene **18** with the allylic alcohol **9d** were used as synthons to prepare *N,O*-nucleoside analogues by adapting the Vorbrüggen protocol[23] as well as the Chiacchio's procedures for similar compounds.[5,24] The acetyl derivatives of **21M,A** were prepared according to standard procedures (Scheme 6).[25] The acetylated compound was obtained in nearly quantitative yield and fully characterized. In the $^1$H NMR spectrum of **21M**, the presence of the acetyl group is shown by the presence of a singlet at 2.09 $\delta$ while the OH signal, previously found at 6.98 $\delta$, disappeared. Similarly, in the $^1$H NMR spectrum of **21A**, the acetyl group is found as a singlet at 2.15 $\delta$ while the OH signal at 6.84 $\delta$ is now absent.

The Vorbrüggen protocol can be applied on both previously silylated heterobases or commercial compounds in the presence of silylating agents.[23,26] In the cases at hand, we report the syntheses conducted on commercial heterobases of the uracil family used in the presence of the in situ silylating agent, the bis(trimethylsilyl)acetamide (BSA), and trimethylsilyl trifluoromethanesulfonate (TMSO-Tf) as reaction promoter.[27] The acetylated isoxazolidine **21M,A** were added under a nitrogen atmosphere at r.t. to a solution of the selected heterobases (2 equiv) and BSA (2 equiv), and the solutions became clear after boiling in DCM for a couple of hours. The mixtures were then ice-cooled at 0 °C, TMSO-Tf was added, and the reactions were refluxed overnight (Scheme 6). The desired compounds **22M,A**(**a**−**g**) were obtained as white solids by simple crystallization or column chromatographic purification.

Nucleoside analogues **22M,A**(**a**−**g**) were isolated from good to excellent yields (48−99%), and their structures rely upon the analytical and spectroscopic data. All the reactions gave single products belonging to the family of uracil derivatives.

The uracil derivative **22Ma** is representative of a general trend in the $^1$H NMR spectra of this type of compound, and the doublets ($J$ = 8 Hz) at 5.67 and 7.64 $\delta$ are clearly related to the uracil double bond while the imide NH is found highly deshielded at 10.10 $\delta$ as a singlet. The same features were found in cytosine derivative **22Mg**. When, in the uracil ring, the =CH−C proton is replaced by a halogen (**b**, **c**, **d**, **e**) or by a methyl, as in the case of tymine (**f**), a single proton corresponding to the N−CH= is observed in the range of 7.43−7.80 $\delta$, while the imide NH singlets remain strongly deshielded in the range of 10.08−10.51 $\delta$.

In $^1$H NMR spectra of nucleosides **22A**(**a**−**g**), the signals corresponding to the anthracene and isoxazolidine moieties are easily detectable. In the $^1$H NMR spectrum of the uracil derivative **22Aa**, the doublets ($J$ = 8 Hz) at 5.49 and 7.86 $\delta$ are clearly related to the uracil double bond while the imide NH is found highly deshielded at 11.22 $\delta$ as a singlet. In the $^1$H NMR spectrum of the cytosine derivative **22Mg**, the double bond doublets ($J$ = 8 Hz) are found at 5.53 and 7.39 $\delta$. Again, when, in the uracil ring, the =CH−C proton is replaced by a halogen (**b**, **c**, **d**, **e**) or by a methyl, as in the case of tymine (**f**), a single proton corresponding to the N−CH= is observed in the range of 7.29−7.86 $\delta$, while the imide NH singlets remain strongly deshielded in the range of 11.23−11.75 $\delta$.

Nucleoside analogues **22M,A** can be submitted for biological evaluation without any further structural modification, either for their antiviral behavior or, in other cases, in order to compare their activities with those of reported carbocyclic and heterocyclic structures.[5,8,24,28] In particular, in nucleoside analogues **22A**, the presence of an anthracene ring adds fluorescent properties to these compounds, a further tool for our future studies. The use of fluorescent moieties in the nucleoside synthesis has attracted the interest of various research groups as marker molecules or in the field of imaging to follow their path inside the cells in order to achieve a better understanding of the "in vivo" mechanisms.[29] Fluorescent structures can be considered "molecular labels"[30] to be assembled in specific oligofluorosides, as sensors[31] or indicators of the behavior of the DNA.[32] New fluorophores are constantly developed as well as their applications.[33] Fluorescent polyaromatic groups may be active through their ability to establish $\pi$-stacking interactions with themselves[34] as well as DNA intercalators;[35] these mechanisms are in action in different cases depending upon the biological targets.

## DISCUSSION AND CONCLUSIONS

We have investigated the ene reactions of aromatic nitrosocarbonyls, generated through the mild oxidative protocol with NMO, with allylic alkoxy olefins. The faster oxidation process of nitrile oxide to nitrosocarbonyl intermediate prevents a possible side reaction, that is, the addition of the allylic alcohol to the electrophilic nitrile oxide. From the reaction mixtures, the presence of adducts between the aromatic nitrile oxides and the 3-methyl-2-buten-1-ol **9d** was not observed.

The nitrosocarbonyl benzene **8P** adds the 3-methyl-2-buten-1-ol **9d**, affording adducts **10Pd** and **13**, which derive from the preferred M path in ene reactions of trisubstituted olefins.[13,16] If hydroxy-protected allylic ether **9e** or ester **9f** are used, the reactions proceed straightforwardly to single ene adducts **10Pe,f** in accordance with the prevailing HOMO$_{(olefin)}$−LUMO$_{(nitrosocarbonyl)}$ interaction, somewhat enforced by the polarization of the C=C double bond induced by the $CH_2OR$ group.[36] Furthermore, no hydrogen-bonding effects are found in directing the selectivity in the reactions at hand.

When bulkier substituents replace the phenyl group (Figure 1), as in nitrosocarbonyl intermediates **8M** and **18**, in the ene reactions with the 3-methyl-2-buten-1-ol **9d**, the M path is risen energetically because of a steric effect and the AM path is favored, affording a mixture of regioisomeric compounds. We have recently detailed the selectivity outcome in ene reactions of nitrosocarbonyl mesitylene **8M** with trisubstituted olefins,[16] and the results show the remarkable influence of the nitrosocarbonyl substituent on the selectivities in ene reactions. Model calculations on the reaction of **8P,M** with tetramethylethylene (TME) shed light on the factors involved in the


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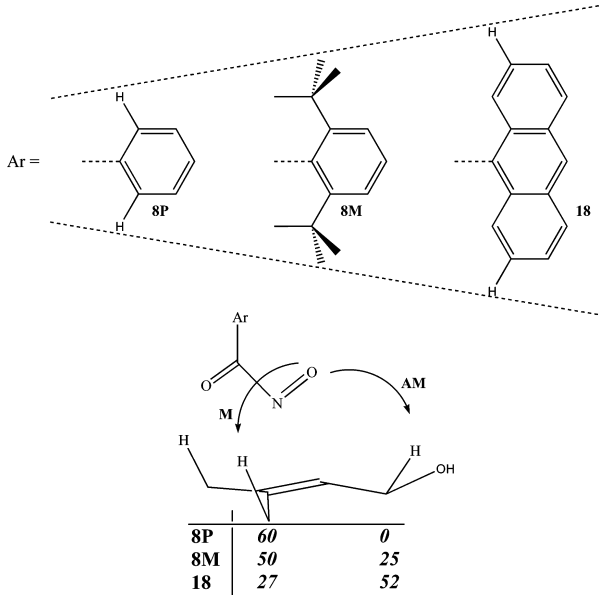


**Figure 1.** Effect of substituents on ene reaction selectivity.

varying selectivities. In these reactions of trimethylethylenes, the M path is favored in the case of nitrosocarbonyl benzene **8P** while steric hindrance in the approach of **8M** compensates somewhat its electronic preference, and mixtures of M and AM adducts are formed. This mechanism is at work also in the case of 3-methyl-2-buten-1-ol **9d** as well as the corresponding hydroxy-protected derivatives **9e**,**f** (Figure 2) and remarkably influences and enforces the selectivity in the reaction of nitrosocarbonyl anthracene **18** with 3-methyl-2-buten-1-ol **9d**.

The steric hindrance produced by the anthracene group reverses the selectivity in the ene reaction, and the corresponding 5-hydroxy-isoxazolidine becomes the major product and a convenient intermediate for nucleoside analogue synthesis.

As we have demonstrated,[16] in the reactions of nitrosocarbonyl **8P** with TME, the transition structure (TS) of the addition step of **8P** to TME shows no special hindrance between the addends, whereas in the TS of **8M**, the mesityl group is twisted out of the nitrosocarbonyl plane as usual, causing unfavorable steric crowding between its *ortho* methyl and the "trans" distal TME methyl, as depicted in Figure 2.

This crowding should slow down the M approach of **8M** to a trisubstituted ethene and compensates somewhat the M electronic bias. Figure 3 reports the same features in the case of the allylic alcohol **9d**. From the M approach point of view, it seems quite clear that the OH group is not playing any role in directing the addition of the nitrosocarbonyl intermediates, both in the cases depicted in the TS **M** and **M′**, as the top view of the structures shows (Figure 3).

The steric clashes at work in the M case drift the addition to the **AM** path that is the prelude to the enol formation and subsequent cyclization to the isoxazolidine structures.

The structures of the 5-hydroxy-isozaxolidine **11** and **20** resemble those obtainable through nitrone additions to vinyl ether derivatives and constitute useful synthons toward the prepartion of *N*,*O*-nucleoside analogues. By adapting the Vorbrüggen protocol[23] as well as known procedures for similar compounds,[5,24] we have prepared a selection of uracil derivatives **22M**,**A**(**a**−**g**) from good to excellent yields. These products constitute a new class of nucleoside analogues with a variety of different heterobases, easily inserted on the isoxazolidine ring. Their potentialities in terms of biological activity are totally unexplored, but we believe in future promising results if we compare the new nucleoside structures with those of known compounds, both hetero- and carbocyclic, recently reported in the literature, which were found to be interesting adenosine receptor agonists.[37] The insertion of a fluorecent chromophore allows for planning future applications as fluorescent markers in different biological targets.

The uracil derivatives **22M**,**A**(**a**−**g**) were sent to the Southern Research Institute (SRI) of Birmingham (AL, USA) within the Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF) program and tested against the *Mycobacterium tuberculosis* H37Rv in BACTEC 12B medium using the microplate Alamar Blue Assay.[38] The minimum inhibition concentration (MIC $\mu$g/mL) was found to be >6.25 for all the compounds with the %Inh in the range of 22−34. Further antiviral and antitumoral tests are currently under evaluation.

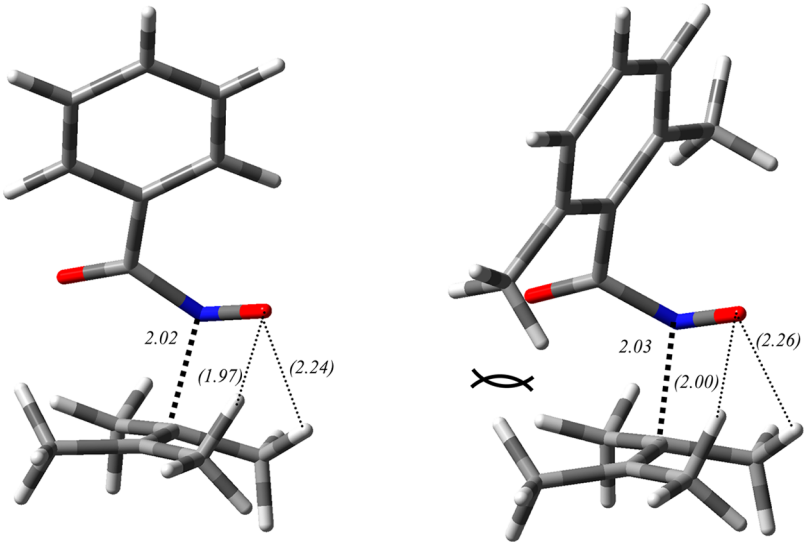


**Figure 2.** Side view of the B3LYP/6-31G* TS's for the reactions of tetramethylethylene with nitrosocarbonyl benzene and 2,6-dimethylbenzene.[16]


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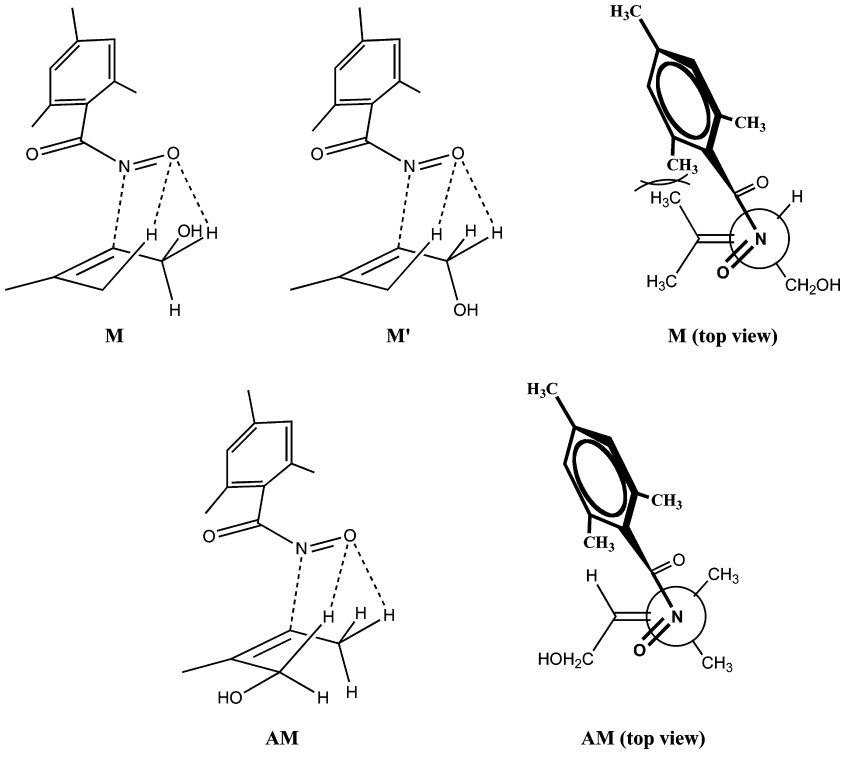


**Figure 3.** Side views and top views of the M and AM ene additions to the 3-methyl-2-buten-1-ol of the nitrosocarbonyl mesitylene.

## EXPERIMENTAL SECTION

All melting points (mp's) are uncorrected. Elemental analyses were done on n elemental analyzer available at the Departmen of Chemistryt. $^1$H and $^{13}$C NMR spectra were recorded on a 300 MHz spectrometer (solvents specified). Chemical shifts are expressed in parts per million (ppm) from internal tetramethylsilane ($\delta$), and coupling constants ($J$) are in hertz (Hz): b, broad; s, singlet; bs, broad singlet; d, doublet; t, triplet; m, multiplet. IR spectra (Nujol mulls) were recorded on a spectrophotometer available at the Department, and absorbtions ($\nu$) are in cm$^{-1}$. Column chromatography and tlc: silica gel H60 and $GF_{254}$, respectively. Eluants: cyclohexane/ethyl acetate 9:1 to pure ethyl acetate; pure $CHCl_3$ to $CHCl_3$/MeOH 9/1 for the nucleoside syntheses. The identification of samples from different experiments was secured by mixed mp's and superimposable IR spectra.

**Starting and Reference Materials.** 3-Methyl-2-buten-1-ol (99%) **9d** was purchased from chemical suppliers.

3-Methyl-2-butenyl methyl ether **9e** was prepared from 4-bromo-2-methyl-2-butene and MeONa according to the reported synthesis.[17]

1-Acetoxy-3-methyl-2-butene **9f** was prepared from the alcohol **9d** and acetic anhydride as reported.[18]

Benzhydroximoyl chloride was obtained by treatment of benzaldoxime with sodium hypochlorite.[39] Addition of a slight excess of $Et_3N$ to a DCM solution of benzhydroximoyl chloride furnished in situ BNO.

Mesitonitrile oxide **7** was obtained by oxidation of 2,4,6-trimethylbenzaldoxime with bromine.[21]

The 9-anthraldeyde oxime **16** has been purchased from chemical suppliers.

**General Procedure for the Ene Reactions of Nitrosocarbonyl Benzene 8A with Alkenes 9d−9f.** To an ice-cooled DCM (200 mL) solution of alkenes **9d−9f** (5 equiv) were added 1.9 g (1.3 equiv) of NMO and 2 mL (1.1 equiv) of $Et_3N$ under stirring. A solution of 2.0 g (12.9 mmol) of benzhydroxymoyl chloride **6** in 100 mL of DCM was added dropwise, and the reaction was left under stirring at r.t. for 24 h. After dilution with an equivalent volume of DCM, the organic phase was washed with water and dried over anhydrous $Na_2SO_4$. After filtration, the solvent was then evaporated and the reaction mixture was separated by column chromatography, affording the ene adducts.

**10Pd**: (1.42 g, 50%) White crystals from ethanol, mp 157−159 °C. IR: $\nu_{OH}$ 3450, $\nu_{C=O}$ 1715 cm$^{-1}$. $^1$H NMR (DMSO) $\delta$: 1.70 (s, 3H, $CH_3$); 4.70 (m, 2H, $CH_2$-O); 5.15 (s, 1H + 1H, $CH_2$); 5.30 (m, 1H, CH-N); 7.2−7.9 (m, 5H, Ph); 8.21 (s, 1H, OH). $^{13}$C NMR (DMSO) $\delta$: 23.8; 66.0; 79.9; 120.4; 132.6; 132.9; 133.1; 133.2; 137.5; 142.7; 169.0. Anal. Calcd for $C_{12}H_{15}NO_3$ (221.25): C, 65.14; H, 6.83; N, 6.33. Found: C, 65.15; H, 6.83; N, 6.25.

**10Pe**: (2.12 g, 70%) Yellowish oil. IR: $\nu_{OH}$ 3203, $\nu_{C=O}$ 1626 cm$^{-1}$. $^1$H NMR (DMSO) $\delta$: 1.75 (s, 3H, $CH_3$); 3.33 (s, 3H, $OCH_3$); 3.56 (dd, $J$ = 10, 4 Hz, 2H, CH-N); 3.74 (t, $J$ = 10 Hz, 2H, $CH_2$-O); 4.89 and 4.97 (s, 1H + 1H, $CH_2$); 7.3−7.6 (m, 5H, Ph); 9.50 (s, 1H, OH). $^{13}$C NMR (DMSO) $\delta$: 21.0; 58.1; 69.2; 113.4; 126.0; 127.8; 128.0; 128.2; 128.5; 129.2; 135.4; 140.9; 169.2. Anal. Calcd for $C_{13}H_{17}NO_3$ (235.27): C, 66.36; H, 7.28; N, 5.95. Found: C, 66.35; H, 7.25; N, 5.94.

**10Pf**: (1.81 g, 60%) Yellowish oil. IR: $\nu_{OH}$ 3206, $\nu_{C=O}$ 1742, 1612 cm$^{-1}$. $^1$H NMR (DMSO at 80 °C) $\delta$: 1.80 (s, 3H, $CH_3$); 2.01 (s, 3H, $CH_3CO$); 4.35 (d, $J$ = 7 Hz, 2H, CH-O); 4.91 and 5.00 (s, 1H + 1H, $CH_2$); 5.03 (m, 1H, CH-N); 7.39 (m, 3H, arom.); 7.57 (m, 2H, arom.); 9.35 (s, 1H, OH). $^{13}$C NMR (DMSO at 80 °C) $\delta$: 13.5; 20.4; 57.8; 61.9; 113.5; 126.0; 128.3; 128.7; 129.1; 130.0; 140.6; 165.5; 171.5. Anal. Calcd for $C_{13}H_{17}NO_3$ (235.27): C, 66.36; H, 7.28; N, 5.95. Found: C, 66.34; H, 7.25; N, 5.94.

**13Pd**: (0.21 g, 8%) Yellowish oil. IR: $\nu_{OH}$ 3393, $\nu_{C=O}$ 1723 cm$^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$: 1.90 (s, 3H, $CH_3$); 5.22 (m, 2H, $CH_2$); 5.32 and 5.43 (s, 1H + 1H, $CH_2$); 7.2−8.0 (m, 5H, Ph). $^{13}$C NMR ($CDCl_3$) $\delta$: 19.3; 54.1; 118.6; 128.3; 129.3; 129.6; 133.0; 138.5; 154.9; 166.1. Anal. Calcd for $C_{12}H_{13}NO_2$ (203.23): C, 70.91; H, 6.45; N, 6.89. Found: C, 70.85; H, 6.45; N, 6.85.

**General Procedure for the Ene Reactions of Nitrosocarbonyl Mesitylene 8M with Alkenes 9d−9f.** To an ice-cooled DCM (200 mL) solution of alkenes **9d−9f** (5 equiv) was added 1.8 g (1.3 equiv) of NMO under stirring. A solution of 2.0 g (12.4 mmol) of mesitonitrile oxide **7** in 100 mL of DCM was added dropwise, and the reaction was left under stirring at r.t. for 24 h. After dilution with an equivalent volume of DCM, the organic phase was washed with water and dried over anhydrous $Na_2SO_4$. After filtration, the solvent was


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then evaporated and the reaction mixture was separated by column chromatography, affording the ene adducts.

**10Md**: (1.63 g, 50%) White crystals from ethanol, mp 162−163 °C. IR: $\nu_{OH}$ 3163, $\nu_{C=O}$ 1618 cm$^{-1}$. $^1$H NMR (DMSO) $\delta$: 1.78 (s, 3H, $CH_3$); 2.14, 2.18, and 2.21 (s, 9H, 3$CH_3$-Ar); 3.72 (dd, $J$ = 7, 6 Hz, 2H, $CH_2$-O); 4.68 (m, 1H, CH-N); 4.97 (bs, 1H + 1H, $CH_2$); 5.06 (t, $J$ = 7 Hz, 1H, OH); 6.80 (m, 2H, Ph); 9.04 (s, 1H, OH). $^{13}$C NMR (DMSO) $\delta$: 18.8; 18.9; 20.6; 21.4; 58.8; 60.5; 113.4; 127.3; 133.3; 133.5; 134.6; 136.5; 141.2; 170.0. Anal. Calcd for $C_{15}H_{21}NO_3$ (263.33): C, 68.41; H, 8.04; N, 5.32. Found: C, 68.47; H, 8.05; N, 5.25.

**11Md**: (0.82 g, 25%) White crystals from benzene, mp 157−158 °C. IR: $\nu_{OH}$ 3150, $\nu_{C=O}$ 1612 cm$^{-1}$. $^1$H NMR (DMSO) $\delta$: 1.55 and 1.72 (s, 6H, 2$CH_3$); 2.13, 2.19, and 2.22 (s, 9H, 3$CH_3$−Ar); 2.14 and 2.35 (s, 1H + 1H, $CH_2$); 5.44 (m, 1H, CH); 6.79 (m, 2H, Ph); 6.98 (s, 1H, OH). $^{13}$C NMR (DMSO) $\delta$: 18.3; 20.6; 25.5; 26.4; 50.2; 60.6; 95.3; 127.2; 127.5; 132.8; 132.9; 134.9; 136.7; 163.2. Anal. Calcd for $C_{15}H_{21}NO_3$ (263.33): C, 68.41; H, 8.04; N, 5.32. Found: C, 68.47; H, 8.06; N, 5.26.

**10Me**: (2.17 g, 63%) White crystals from ethanol, mp 127−128 °C. IR: $\nu_{OH}$ 2920, $\nu_{C=O}$ 1603 cm$^{-1}$. $^1$H NMR (DMSO) $\delta$: 1.79 (s, 3H, $CH_3$); 2.16, 2.17, and 2.21 (s, 9H, 3$CH_3$-Ar); 3.29 (s, 3H, $CH_3$-O); 3.70 (m, 2H, $CH_2$-O); 4.90 and 5.00 (s, 1H + 1H, $CH_2$); 5.24 (m, 1H, CH-N); 6.81 (m, 2H, Ph); 9.07 (s, 1H, OH). $^{13}$C NMR (DMSO) $\delta$: 18.6; 18.8; 20.1; 20.6; 21.3; 56.8; 57.8; 68.9; 113.4; 127.3; 133.3; 133.5; 134.5; 136.5; 140.7; 170.0. Anal. Calcd for $C_{16}H_{23}NO_3$ (277.35): C, 69.28; H, 8.36; N, 5.05. Found: C, 69.26; H, 8.25; N, 5.08.

**12Me**: (1.20 g, 35%) White crystals from ethanol, mp 133−135 °C. IR: $\nu_{OH}$ 2920, $\nu_{C=O}$ 1656 cm$^{-1}$. $^1$H NMR (DMSO) $\delta$: 1.51 (s, 6H, $CH_3$); 2.12 and 2.20 (s, 9H, 3$CH_3$-Ar); 3.46 (s, 3H, $CH_3$-O); 5.23 (d, $J$ = 13 Hz, 1H, C-CH); 6.52 (d, $J$ = 13 Hz, 1H, O-CH); 6.80 (m, 2H, Ph); 9.10 (s, 1H, OH). $^{13}$C NMR (DMSO) $\delta$: 18.5; 20.6; 26.6; 55.5; 61.0; 108.6; 127.2; 132.5; 133.7; 135.9; 136.4; 146.8; 154.5; 170.8. Anal. Calcd for $C_{16}H_{23}NO_3$ (277.35): C, 69.28; H, 8.36; N, 5.05. Found: C, 69.25; H, 8.37; N, 5.07.

**10Mf**: (2.12 g, 56%) White crystals from ethanol, mp 103−104 °C. IR: $\nu_{OH}$ 3086, $\nu_{C=O}$ 1747, 1658 cm$^{-1}$. $^1$H NMR (DMSO) $\delta$: 1.80 (s, 3H, $CH_3$); 2.00 (s, 3H, $CH_3$CO); 2.18 and 2.22 (s, 9H, 3$CH_3$-Ar); 4.25 and 4.41 (AB syst, 2H, $CH_2$-O); 4.96 and 5.04 (s, 1H + 1H, $CH_2$); 5.30 (dd, $J$ = 10, 4 Hz, 1H, CH-N); 6.82 (m, 2H, Ph); 9.27 (s, 1H, OH). $^{13}$C NMR (DMSO) $\delta$: 18.7; 18.8; 20.6; 20.7; 21.2; 56.4; 60.8; 114.0; 127.3; 127.4; 133.3; 133.4; 134.2; 136.7; 140.0; 170.1; 170.2. Anal. Calcd for $C_{17}H_{23}NO_4$ (305.36): C, 66.86; H, 7.59; N, 4.59. Found: C, 66.87; H, 7.58; N, 5.00.

**12Mf**: (1.21 g, 32%) White crystals from ethanol, mp 108−109 °C. IR: $\nu_{OH}$ 3098, $\nu_{C=O}$ 1754, 1667 cm$^{-1}$. $^1$H NMR (DMSO) $\delta$: 1.52 (s, 6H, $CH_3$); 2.12 and 2.20 (s, 9H, 3$CH_3$-Ar); 2.12 (s, 3H, $CH_3$CO); 5.88 (d, $J$ = 13 Hz, 1H, C-CH); 6.79 (m, 2H, Ph); 7.21 (d, $J$ = 13 Hz, 1H, O-CH); 9.38 (s, 1H, OH). $^{13}$C NMR (DMSO) $\delta$: 18.5; 20.5; 20.6; 25.8; 60.4; 120.3; 127.2; 132.7; 134.5; 135.9; 136.2; 168.0; 170.8. Anal. Calcd for $C_{17}H_{23}NO_4$ (305.36): C, 66.86; H, 7.59; N, 4.59. Found: C, 66.85; H, 7.55; N, 5.00.

**Ene Reaction of Anthracenenitrile Oxide 18 with 3-Methyl-2-Buten-1-ol 9d.** To an anhydrous DCM (80 mL) solution of 3-methyl-2-buten-1-ol **9d** (5 equiv) and NMO (2 equiv) was added 2.0 g (9 mmol) of anthracenenitrile oxide **18** portionwise under stirring at r.t. After 48 h, the organic phase was washed with brine and dried over anhydrous $Na_2SO_4$. After filtration and evaporation of the solvent, the residue was submitted to column chromatography. The two main fractions were identified as the adducts **19** and **20**, which were characterized as below:

**19**: (0.79 g, 27%) Pale yellow crystals from ethanol, mp 179−181 °C. IR: $\nu_{OH}$ 3254, $\nu_{C=O}$ 1603 cm$^{-1}$. $^1$H NMR (DMSO) $\delta$: 1.80 (s, 3H, $CH_3$); 3.35 (s, 2H, $CH_2$OH); 4.41 (m, 3H, OH); 4.67 (m, 2H, $CH_2$); 5.49 (b, 1H, CH); 7.57 (m, 4H, arom.); 8.11 (m, 4H, arom.); 8.59 (s, 1H, arom.); 9.71 (s, 1H, OH). $^{13}$C NMR (DMSO) $\delta$: 17.9; 25.5; 61.1; 119.6; 123.6; 125.5; 125.7; 126.0; 126.7; 128.4; 129.1; 131.3; 134.6; 155.6. Anal. Calcd for $C_{20}H_{19}NO_3$ (321.38): C, 74.75; H, 5.96; N, 4.36. Found: C, 74.69; H, 5.94; N, 4.36.

**20**: (1.52 g, 52%) Straw yellow crystals from ethanol, mp 229 °C (dec.). IR: $\nu_{OH}$ 3200, $\nu_{C=O}$ 1588 cm$^{-1}$. $^1$H NMR (DMSO) $\delta$: 1.83 (s, 3H, $CH_3$); 1.97 (s, 3H, $CH_3$); 2.22 (d, 1H, $J$ = 13 Hz, CH); 2.44 (dd, 1H, $J$ = 13, 5 Hz, CH); 5.23 (b, 1H, *CH*-OH); 6.84 (b, 1H, OH, exch. with $D_2O$); 7.56 (m, 4H, arom.); 7.89 (m, 1H, arom.); 7.99 (m, 1H, arom.); 8.11 (m, 2H, arom.); 8.62 (s, 1H, arom.). $^{13}$C NMR (DMSO) $\delta$: 25.7; 26.6; 50.0; 61.6; 95.8; 124.8; 125.3; 125.5; 125.6; 126.3; 126.4; 126.6; 126.7; 126.8; 128.2; 128.4; 130.6; 130.8; 131.9; 161.8. Anal. Calcd for $C_{20}H_{19}NO_3$ (321.38): C, 74.75; H, 5.96; N, 4.36. Found: C, 74.76; H, 6.00; N, 4.37.

**Synthesis of the *N*-Mesitoyl-3,3-dimethyl-5-acetoxy-1,2-isoxazolidine 21M.** To an ice-cooled anhydrous DCM (50 mL) solution of *N*-mesitoyl-3,3-dimethyl-5-hydroxy-1,2-isoxazolidine **11Md** (3.60 g, 14 mmol.) was added 2.2 equiv of $Ac_2O$ added under stirring along with 0.34 equiv of DMAP and 2.2 equiv of $Et_3N$. The reaction was left under stirring at r.t. for 24 h. After dilution with an equivalent volume of DCM, the organic phase was washed with a saturated solution of $NaHCO_3$ and dried over anhydrous $Na_2SO_4$. After filtration, the solvent was evaporated and a solid was obtained. The acetyl derivative **21M** (3.68 g) was obtained in 86% yield and recrystallized from methanol: mp 105−107 °C. IR: $\nu_{C=O}$ 1760 cm$^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$: 1.74 and 1.88 (s, 6H, 2$CH_3$); 2.09 (s, 3H, $CH_3$CO); 2.28 (s, 9H, 3$CH_3$-Ar); 2.50 (m, 2H, $CH_2$); 6.23 (d, $J$ = 6 Hz, 1H, O-CH-OAc); 6.80 (m, 2H, Ph). $^{13}$C NMR ($CDCl_3$) $\delta$: 18.4; 18.6; 20.9; 21.0; 49.8; 60.6; 93.9; 127.7; 127.8; 132.8; 133.5; 138.0; 165.1; 169.1. Anal. Calcd for $C_{17}H_{23}NO_4$ (305.36): C, 66.86; H, 7.59; N, 4.59. Found: C, 66.75; H, 7.56; N, 4.58.

**Synthesis of the *N*-Anthracenoyl-3,3-dimethyl-5-acetoxy-1,2-isoxazolidine 21A.** To an ice-cooled anhydrous DCM (50 mL) solution of *N*-anthracenoyl-3,3-dimethyl-5-hydroxy-1,2-isoxazolidine **20** (1.40 g, 4.78 mmol.) was added 2.2 equiv of $Ac_2O$ under stirring along with 0.34 equiv of DMAP and 2.2 equiv of $Et_3N$. The reaction was left under stirring at r.t. for 24 h. After dilution with an equivalent volume of DCM, the organic phase was washed with a saturated solution of $NaHCO_3$ and dried over anhydrous $Na_2SO_4$. The solvent was then evaporated, and a solid was obtained. The acetyl derivative **21A** (1.63 g) was obtained in 94% yield and recrystallized from ethanol: mp 200−201 °C. IR: $\nu_{C=O}$ 1748 cm$^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$: 1.84 and 1.97 (s, 3H + 3H, $CH_3$); 2.15 (s, 3H, $CH_3$CO); 2.47 (d, 1H, $J$ = 13 Hz, H-CH); 2.64 (dd, 1H, $J$ = 13, 5 Hz, H-CH); 6.04 (d, 1H, $J$ = 5 Hz, O-CH-O); 7.51 (m, 4H, arom.); 8.04 (m, 4H, arom.); 8.47 (m, 1H, arom.). $^{13}$C NMR ($CDCl_3$) $\delta$: 20.8; 26.0; 27.2; 49.5; 61.5; 93.5; 124.7; 124.9; 125.3; 125.8; 126.4; 127.0; 127.5; 127.8; 128.5; 128.6; 130.7; 130.9; 131.1; 164.0; 168.8. Anal. Calcd for $C_{22}H_{21}NO_4$ (363.40): C, 72.71; H, 5.82; N, 3.85. Found: C, 72.71; H, 5.81; N, 3.89.

**General Procedure for the Synthesis of Nucleosides 22 by Coupling of Isoxazolidines 21M,A and Heterobases B(a−g).** A solution of 2 equiv of heterobases **B** and 2 equiv of bis(trimethylsilyl)-acetamide (BSA) in anhydrous DCM (50 mL) is refluxed under a nitrogen atmosphere for 15−20 min until it becomes clear and hence cooled to ambient. A solution in DCM (10 mL) of isoxazolidines **21M,A** (0.20 g, 0.65 mmol) is added dropwise and cooled to 0 °C and additioned of 0.12 mL (1 equiv) of TMSO-Tf. The reaction is refluxed under stirring overnight and finally quenched with a saturated solution of $NaHCO_3$ at pH = 7. The mixture is diluted with an equivalent volume of DCM and washed with water and finally dried over $Na_2SO_4$. From the residues, nucleosides **22M,A(a−g)** are isolated upon crystallization or column chromatographic purification.

**22Ma**: (0.22 g, 95%) White solid from ethanol, mp 215 °C (dec.). IR: $\nu_{NH}$ 3166, $\nu_{C=O}$ 1690, 1642 cm$^{-1}$. $^1$H NMR ($CD_3COCD_3$) $\delta$: 1.75 and 1.89 (s, 6H, 2$CH_3$); 2.22 and 2.25 (s, 9H, 3$CH_3$-Ar); 2.72 and 2.90 (dd, $J$ = 14, 7 Hz, 2H, $CH_2$); 5.67 (d, $J$ = 8 Hz, 1H, CO-CH); 6.40 (t, $J$ = 7 Hz, 1H, CH); 6.82 (m, 2H, Ph); 7.64 (d, $J$ = 8, 1H, CH-N); 10.10 (bs, 1H, NH). $^{13}$C NMR ($CD_3COCD_3$) $\delta$: 19.5; 21.4; 25.4; 26.9; 48.8; 64.3; 83.4; 103.9; 129.0; 134.4; 134.9; 139.1; 140.5; 151.6; 154.5; 163.4; 168.0; 170.0. Anal. Calcd for $C_{19}H_{23}N_3O_4$ (357.40): C, 63.85; H, 6.48; N, 11.76. Found: C, 63.83; H, 6.45; N, 11.75.

**22Mb**: (0.24 g, 97%) White crystals from acetone, mp 210 °C (dec.). IR: $\nu_{NH}$ 3167, $\nu_{C=O}$ 1709 cm$^{-1}$. $^1$H NMR ($CD_3COCD_3$) $\delta$:


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1.74 and 1.88 (s, 6H, $2CH_3$); 2.24, 2.25, and 2.28 (s, 9H, $3CH_3$-Ar); 2.76 and 2.90 (dd, $J$ = 14, 7 Hz, 2H, $CH_2$); 6.35 (dt, $J$ = 7, 1 Hz, 1H, CH); 6.84 (m, 2H, Ph); 7.70 (d, $J$ = 7 Hz, 1H, CH-N); 10.50 (bs, 1H, NH). $^{13}$C NMR ($CD_3COCD_3$) $\delta$: 19.4; 19.5; 21.5; 25.3; 26.9; 49.0; 64.3; 84.1; 124.3; 124.8; 129.1; 134.4; 135.0; 135.4; 139.2; 140.5; 143.6; 150.2; 157.5; 157.8; 167.9. Anal. Calcd for $C_{19}H_{22}N_3O_4F$ (375.40): C, 60.79; H, 5.91; N, 11.19. Found: C, 60.81; H, 5.91; N, 11.21.

**22Mc**: (0.24 g, 93%) White crystals from acetone, mp 208−211 °C. IR: $\nu_{NH}$ 3167, $\nu_{C=O}$ 1709 cm$^{-1}$. $^1$H NMR ($CD_3COCD_3$) $\delta$: 1.73 and 1.87 (s, 6H, $2CH_3$); 2.25, 2.26, and 2.31 (s, 9H, $3CH_3$-Ar); 2.83 and 2.95 (dd, $J$ = 14, 7 Hz, 2H, $CH_2$); 6.29 (dt, $J$ = 7, 1 Hz, 1H, CH); 6.85 and 6.89 (1, 1H + 1H, Ph); 7.68 (s, 1H, CH-N); 10.60 (bs, 1H, NH). $^{13}$C NMR ($CD_3COCD_3$) $\delta$: 19.4; 19.5; 21.5; 25.1; 49.7; 64.2; 84.5; 109.8; 129.1; 129.2; 134.2; 135.0; 135.3; 137.3; 139.3; 150.6; 159.6; 168.2. Anal. Calcd for $C_{19}H_{22}N_3O_4Cl$ (391.85): C, 58.24; H, 5.66; N, 10.72. Found: C, 58.22; H, 5.69; N, 10.71.

**22Md**: (0.27 g, 95%) White crystals from methanol, mp 114−120 °C. IR: $\nu_{NH}$ 3168, $\nu_{C=O}$ 1700 cm$^{-1}$. $^1$H NMR ($CD_3COCD_3$) $\delta$: 1.72 and 1.86 (s, 6H, $2CH_3$); 2.25 and 2.32 (s, 9H, $3CH_3$-Ar); 2.84 and 2.96 (dd, $J$ = 14, 7 Hz, 2H, $CH_2$); 6.28 (t, $J$ = 6 Hz, 1H, CH); 6.87 (m, 2H, Ph); 7.74 (s, 1H, CH-N); 10.51 (bs, 1H, NH). $^{13}$C NMR ($CD_3COCD_3$) $\delta$: 19.5; 19.6; 21.5; 25.1; 26.9; 49.8; 64.2; 84.6; 97.8; 129.0; 129.3; 134.2; 135.0; 135.3; 139.3; 139.8; 150.8; 159.6; 168.3. Anal. Calcd for $C_{19}H_{22}N_3O_4Br$ (436.30): C, 52.31; H, 5.08; N, 9.63. Found: C, 52.25; H, 5.09; N, 9.55.

**22Me**: (0.29 g, 91%) White crystals from methanol, mp 106−110 °C. IR: $\nu_{NH}$ 3169, $\nu_{C=O}$ 1690 cm$^{-1}$. $^1$H NMR ($CD_3COCD_3$) $\delta$: 1.72 and 1.87 (s, 6H, $2CH_3$); 2.25 and 2.34 (s, 9H, $3CH_3$-Ar); 2.82 and 2.96 (dd, $J$ = 14, 7 Hz, 2H, $CH_2$); 6.27 (t, $J$ = 6 Hz, 1H, CH); 6.85 (m, 2H, Ph); 7.80 (s, 1H, CH-N); 10.45 (bs, 1H, NH). $^{13}$C NMR ($CD_3COCD_3$) $\delta$: 19.5; 19.8; 21.5; 25.0; 26.9; 49.9; 64.2; 69.9; 84.4; 129.0; 129.4; 134.1; 135.0; 135.3; 139.2; 144.7; 151.2; 160.8; 168.4. Anal. Calcd for $C_{19}H_{22}N_3O_4I$ (483.30): C, 47.22; H, 4.59; N, 8.69. Found: C, 47.15; H, 4.55; N, 8.49.

**22Mf**: (0.19 g, 78%) White crystals from ethyl acetate, mp 99−104 °C. IR: $\nu_{NH}$ 3170, $\nu_{C=O}$ 1700 cm$^{-1}$. $^1$H NMR ($CD_3COCD_3$) $\delta$: 1.74 and 1.88 (s, 6H, $2CH_3$); 1.83 (s, 3H, $CH_3$-C); 2.22, 2.25, and 2.27 (s, 9H, $3CH_3$-Ar); 2.74 and 2.86 (dd, $J$ = 14, 7 Hz, 2H, $CH_2$); 6.39 (t, $J$ = 7 Hz, 1H, CH); 6.82 (m, 2H, Ph); 7.43 (d, $J$ = 1 Hz, 1H, CH-N); 10.08 (bs, 1H, NH). $^{13}$C NMR ($CD_3COCD_3$) $\delta$: 12.8; 19.5; 21.4; 25.3; 26.9; 48.6; 64.3; 83.3; 112.1; 129.0; 134.3; 134.9; 135.5; 135.8; 139.0; 151.6; 164.2; 167.7. Anal. Calcd for $C_{20}H_{25}N_3O_4$ (371.42): C, 64.67; H, 6.78; N, 11.31. Found: C, 64.65; H, 6.75; N, 11.25.

**22Mg**: (0.11 g, 46%) White crystals from ethyl acetate, mp 107−110 °C. IR: $\nu_{NH2}$ 3360, 3170, $\nu_{C=O}$ 1640 cm$^{-1}$. $^1$H NMR ($CD_3COCD_3$) $\delta$: 1.75 and 1.83 (s, 6H, $2CH_3$); 2.21, 2.24, and 2.26 (s, 9H, $3CH_3$-Ar); 2.60 and 2.83 (dd, $J$ = 14, 7 Hz, 2H, $CH_2$); 5.88 (d, $J$ = 8 Hz, 1H, CH); 6.43 (t, $J$ = 7 Hz, 1H, CH); 6.81 (m, 2H, Ph); 7.38 (s, 2H, $NH_2$); 7.56 (d, $J$ = 8 Hz, 1H, CH-N). $^{13}$C NMR ($CD_3COCD_3$) $\delta$: 19.5; 21.4; 23.6; 25.6; 27.1; 49.5; 64.0; 84.2; 95.7; 128.8; 128.9; 129.0; 129.5; 134.3; 134.9; 135.5; 139.0; 141.4; 156.1; 167.3. Anal. Calcd for $C_{19}H_{24}N_4O_3$ (356.41): C, 64.02; H, 6.79; N, 15.72. Found: C, 63.90; H, 6.65; N, 15.55.

**22Aa**: (0.26 g, 97%) White solid from ethanol, mp > 200 °C. IR: $\nu_{NH}$ 3167, $\nu_{C=O}$ 1686 cm$^{-1}$. $^1$H NMR (DMSO) $\delta$: 1.84 (s, 3H, $CH_3$); 2.03 (s, 3H, $CH_3$); 2.79 (m, 2H, $CH_2$); 5.49 (d, 1H, $J$ = 8 Hz, CH-CO); 6.17 (dd, 1H, $J$ = 7, 6 Hz, O-CH-N); 7.59 (m, 5H, arom.); 7.86 (d, 1H, $J$ = 8 Hz, N-CH); 7.99 (m, 1H, arom.); 8.12 (m, 2H, arom.); 8.66 (s, 1H, arom.); 11.22 (s, 1H, NH). $^{13}$C NMR (DMSO) $\delta$: 25.1; 25.8; 46.2; 63.6; 82.3; 102.3; 124.3; 124.7; 125.6; 126.3; 126.7; 126.8; 126.9; 127.8; 128.5; 128.6; 130.4; 130.5; 140.0; 150.1; 162.6; 164.4. Anal. Calcd for $C_{24}H_{21}O_4N_3$ (415.43) C, 69.38; H, 5.10; N, 10.12. Found: C, 69.39; H, 5.05; N, 10.13

**22Ab**: (0.26 g, 93%) White solid from ethanol, mp > 200 °C. IR: $\nu_{NH}$ 3168, $\nu_{C=O}$ 1720 cm$^{-1}$. $^1$H NMR (DMSO) $\delta$: 1.83 (s, 3H, $CH_3$); 2.04 (s, 3H, $CH_3$); 2.79 (m, 2H, $CH_2$); 6.16 (t, 1H, $J$ = 7 Hz, O-CH-N); 7.58 (m, 4H, arom.); 7.81 (d, 1H, $J$ = 7 Hz, N-CH); 7.86 (d, 1H, $J$ = 9 Hz, arom.); 8.04 (m, 1H, arom.); 8.13 (m, 2H, arom.); 8.67 (s, 1H, arom.); 11.75 (s, 1H, NH). $^{13}$C NMR (DMSO) $\delta$: 24.9; 25.7; 45.9; 63.8; 82.7; 124.0; 124.3; 124.4; 124.6; 125.7; 126.4; 126.6; 126.8; 126.9; 127.8; 128.5; 129.6; 130.5; 130.6; 138.2; 138.4; 141.5; 148.8; 156.5; 156.8; 164.2. Anal. Calcd for $C_{24}H_{20}O_4N_3F$ (433.42) C, 66.51; H, 4.65; N, 9.70. Found: C, 66.51; H, 4.64; N, 9.71.

**22Ac**: (0.29 g, 97%) White solid from ethanol, mp 185−188 °C. IR: $\nu_{NH}$ 3067, $\nu_{C=O}$ 1728 cm$^{-1}$. $^1$H NMR (DMSO) $\delta$: 1.83 (s, 3H, $CH_3$); 2.03 (s, 3H, $CH_3$); 2.84 (m, 2H, $CH_2$); 6.12 (1H, t, $J$ = 6 Hz, O-CH-N); 7.58 (m, 4H, arom.); 7.72 (s, 1H, N-CH); 7.86 (d, 1H, $J$ = 8 Hz, arom.); 8.00 (d, 1H, $J$ = 8 Hz, arom.); 8.12 (m, 2H, arom.); 8.67 (s, 1H, arom.); 11.78 (s, 1H, NH). $^{13}$C NMR (DMSO) $\delta$: 24.8; 25.7; 46.3; 63.7; 83.1; 107.9; 124.3; 125.6; 125.7; 126.4; 126.8; 126.9; 127.9; 128.6; 130.4; 130.5; 130.6; 136.7; 149.2; 158.6; 164.4. Anal. Calcd for $C_{24}H_{20}O_4N_3Cl$ (449.89) C, 64.07; H, 4.48; N, 9.34. Found: C, 64.08; H, 4.49; N, 9.31.

**22Ad**: (0.31 g, 95%) White solid from ethanol, mp 167−170 °C. IR: $\nu_{NH}$ 3058, $\nu_{C=O}$ 1726 cm$^{-1}$. $^1$H NMR (DMSO) $\delta$: 1.83 (s, 3H, $CH_3$); 2.03 (s, 3H, $CH_3$); 2.85 (m, 2H, $CH_2$); 6.12 (t, 1H, $J$ = 6 Hz, O-CH-N); 7.57 (m, 4H, arom.); 7.81 (s, 1H, N-CH); 7.86 (d, 1H, $J$ = 8 Hz, arom.); 7.97 (d, 1H, $J$ = 8, 4 Hz, arom.); 8.13 (m, 2H, arom.); 8.67 (s, 1H, arom.); 11.73 (s, 1H, NH). $^{13}$C NMR (DMSO) $\delta$: 24.9; 25.7; 46.1; 63.7; 83.1; 96.5; 124.3; 125.6; 126.4; 126.9; 127.8; 128.6; 130.4; 130.5; 139.2; 149.4; 158.7; 164.4. Anal. Calcd for $C_{24}H_{20}O_4N_3Br$ (494.33) C, 58.31; H, 4.08; N, 8.50. Found: C, 58.31; H, 4.11; N, 8.51.

**22Ae**: (0.35 g, 99%) White solid from ethanol, mp 164−166 °C. IR: $\nu_{NH}$ 3059, $\nu_{C=O}$ 1724 cm$^{-1}$. $^1$H NMR (DMSO) $\delta$: 1.83 (s, 3H, $CH_3$); 2.03 (s, 3H, $CH_3$); 2.86 (m, 2H, $CH_2$); 6.13 (t, 1H, $J$ = 6 Hz, O-CH-N); 7.58 (m, 4H, arom.); 7.85 (d, 2H, $J$ = 7 Hz, arom.); 7.86 (s, 1H, N-CH); 7.96 (d, 1H, $J$ = 8 Hz, arom.); 8.13 (m, 2H, arom.); 8.67 (s, 1H, arom.); 11.60 (s, 1H, NH). $^{13}$C NMR (DMSO) $\delta$: 25.0; 25.7; 45.9; 63.7; 70.6; 82.8; 124.3; 125.6; 126.4; 126.9; 127.0; 127.8; 128.6; 130.4; 130.5; 143.9; 149.8; 160.1; 164.4. Anal. Calcd for $C_{24}H_{20}O_4N_3I$ (541.32) C, 53.25; H, 3.72; N, 7.76. Found: C, 53.22; H, 3.72; N, 7.80.

**22Af**: (0.24 g, 86%) White solid from ethanol, mp 155−157 °C. IR: $\nu_{NH}$ 3058, $\nu_{C=O}$ 1719 cm$^{-1}$. $^1$H NMR (DMSO) $\delta$: 1.63 (s, 3H, $CH_3$); 1.84 (s, 3H, $CH_3$); 2.05 (s, 3H, $CH_3$); 2.78 (m, 2H, $CH_2$); 6.19 (t, 1H, $J$ = 7 Hz, O-CH-N); 7.29 (d, 1H, $J$ = 1 Hz, N-CH); 7.59 (m, 4H, arom.); 7.86 (d, 1H, $J$ = 9 Hz); 8.04 (m, 1H, arom.); 8.13 (m, 2H, arom.); 8.66 (s, 1H, arom.); 11.23 (s, 1H, NH). $^{13}$C NMR (DMSO) $\delta$: 11.5; 24.4; 25.5; 45.9; 63.3; 81.6; 109.7; 123.9; 124.3; 125.2; 126.0; 126.2; 126.4; 126.5; 127.4; 128.1; 128.2; 130.0; 130.1; 134.4; 149.7; 162.9; 163.8. Anal. Calcd for $C_{25}H_{23}O_4N_3$ (429.46) C, 69.91; H, 5.40; N, 9.79. Found: C, 69.91; H, 5.41; N, 9.75.

**22Ag**: (0.04 g, 48%) White solid from ethanol, mp 188−191 °C. IR: $\nu_{NH2}$ 3362, 3171, $\nu_{C=O}$ 1664 cm$^{-1}$. $^1$H NMR (DMSO) $\delta$: 1.87 (s, 3H, $CH_3$); 1.98 (s, 1.98, $CH_3$); 2.59 e 2.84 (m, 1H + 1H, $CH_2$); 5.53 (d, 1H, $J$ = 7 Hz, CH-CN); 6.22 (t, 1H, $J$ = 6 Hz, O-CH-N); 7.18 (d, 2H, $NH_2$); 7.39 (d, 1H, J = 7 Hz, N-CH); 7.58 (m, 4H, arom.); 7.88 (d, 1H, $J$ = 8 Hz, arom.); 8.00 (m, 1H, arom.); 8.13 (m, 2H, arom.); 8.66 (s, 1H, arom). $^{13}$C NMR (DMSO) $\delta$: 22.8; 25.1; 26.0; 47.2; 63.4; 82.7; 94.7; 124.3; 124.8; 125.6; 125.7; 126.4; 126.6; 126.8; 126.9; 127.7; 128.5; 128.6; 130.5; 130.6; 140.0; 154.4; 163.8; 165.3. Anal. Calcd for $C_{24}H_{22}O_3N_4$ (414.45) C, 69.55; H, 5.35; N, 13.52. Found: C, 69.51; H, 5.31; N, 13.52.

**Competition Experiments.** Equimolecular amounts (20 equiv) of 3-methyl-2-buten-1-ol and the corresponding acetate and methyl ether were allowed to react with 1 equiv of either benzonitrile oxide or mesitonitrile oxide in the presence of 1.2 equiv of NMO in anhydrous DCM as solvent. After the workup previously described, the reaction mixtures were submitted to chromatographic separation for the isolation and quantification of the ene obtained from the yields given in Table 1 (see Table 2).

**Biological Tests.** Primary screen (dose response): determination of a 90% inhibitory concentration (IC90). The initial screen is conducted against *Mycobacterium tuberculosis* H37Rv (ATCC 27294) in BACTEC 12B medium using the microplate Alamar Blue assay (MABA). Compounds are tested in ten 2-fold dilutions, typically from 100 to 0.19 $\mu$g/mL. The IC90 is defined as the concentration effecting a reduction in fluorescence of 90% relative to controls. This value is determined from the dose−response curve using a curve-fitting


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**Table 2**

| Ar-CONO | alkene couples | ratios from data of Table1 |
|---|---|---|
| **8P** | **9d**/**e** 0.86 | **9d**/**e** 0.77 |
| | **9d**/**f** 1.00 | **9d**/**e** 0.87 |
| **8M** | **9d**/**e** 0.77 | **9d**/**e** 0.67 |
| | **9d**/**f** 0.85 | **9d**/**e** 0.75 |

program. Any IC90 value of ≥10 μg/mL is considered "Active" for antitubercular activity. For further information, see: http://www.taacf.org.

**X-ray Crystallography.** A summary of crystal data, data collection, and structure refinement of compounds **11Md** and **21A** is given in Table S2 of the Supporting Information. The structures are solved by direct methods. Non-hydrogen atoms were refined anisotropically, and hydrogen atoms, located from the difference Fourier synthesis, were refined isotropically.[40]

CCDC 905532 for compound **11Md** and CCDC 905533 for compound **21A** contain the supplementary data. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallography Data Centre 12, Union Road, Cambridge CB2 IEZ, U.K., Fax: +44−1223/336033; E-mail: deposit@ccdc.cam.ac.uk].[41]

## ■ ASSOCIATED CONTENT

### Supporting Information

NMR spectra of new compounds, X-ray crystallographic data, and crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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