Tetrahedron 64 (2008) 7312–7317

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

From 1,3-cyclohexadiene through nitrosocarbonyl chemistry, the synthesis of pyrimidine isoxazoline-carbocyclic nucleosides

Paolo Quadrelli *, Mariella Mella, Giulio Assanelli, Andrea Piccanello

Dipartimento di Chimica Organica, Università degli Studi di Pavia, Viale Taramelli 10, 27100 Pavia, Italy

ARTICLE INFO

Article history:
Received 29 February 2008
Received in revised form 28 April 2008
Accepted 15 May 2008
Available online 18 May 2008

ABSTRACT

N-Benzoyl-2-oxa-3-azabicyclo[2.2.2]oct-5-ene undergoes cycloaddition with benzonitrile oxide affording a mixture of *syn* and *anti* regioisomeric cycloadducts. The *anti* cycloadducts were easily elaborated to stereodefined isoxazoline-carbocyclic aminols that served as synthons for the linear construction of pyrimidine nucleosides, while the *syn* cycloadducts do not enter the same synthetic route.

1. Introduction

The development of new modified nucleosides as antiviral agents has remained a very active field of research.[1] Despite the fact that carbocyclic nucleosides have been extensively studied, few examples are reported in the literature of six-membered carbocyclic analogues.[2] The major reasons, which highlight the importance of six-membered carbocyclic nucleosides are the resistance to hydrolysis[3] and their (bio)isosteric nature with the furanose ring.[3,4] In particular, the conformational behaviour of cyclohexene derivatives proved to be relevant in determining the antiviral activity, being similar to that of a saturated five-membered ring.[5] The presence of two sp^2-hybridized carbon atoms in the cyclohexene ring limits the number of accessible conformations with respect to a cyclohexane and conformational analyses[6] as well as the application of the bioisosteric concept between a furanose ring and a cyclohexene ring in the nucleoside field led to the discovery of new potent antiviral agents.[4] Traditionally, cyclohexenyl nucleosides are prepared through Mitsunobu reaction on cyclohexenyl alcohols[3a,7] or through palladium-catalyzed reactions from cyclohexenyl acetates.[8] Few examples have been reported on syntheses starting from cyclohexenyl aminols.[9]

When a second carbocyclic or heterocyclic ring is fused to the main carbocyclic moiety of a nucleoside derivative, the conformational flexibility is somewhat decreased. A few examples are reported in the literature in the case of cyclopentane-nucleoside derivatives fused with three-[10] and four-carbocyclic[11] rings as well as five-membered heterocyclic rings such as a pyrazole[12] or isoxazolines.[13] Nucleosides lacking a methylene group in the side chain belong to the so-called nor-variety and display, in some cases, a reduced cytotoxicity.[14]

Recently, we have developed the synthesis of some representative bicyclic cyclohexenyl nucleosides with a fused isoxazoline ring **5** by the linear construction of the desired purine bases on the regioisomeric aminols **4** (Scheme 1) obtained through elaboration of the Hetero Diels–Alder (HDA) cycloadducts **2** of cyclohexadiene **1** with the nitrosocarbonyl intermediates (RCONO).[15] These fleeting intermediates are generated traditionally by periodate oxidation of hydroxamic acids[16] or by oxidation of nitrile oxides with *N*-methylmorpholine *N*-oxide (NMO),[17] and are promptly trapped with dienes to afford HDA cycloadducts in high yields. The HDA cyclohexadiene cycloadducts **2** have proved to be reactive dipolarophiles towards nitrile oxides, affording rather unselectively the *syn* and *anti* regioisomeric 1,3-dipolar cycloadducts. The *anti* derivatives of type **3** are converted quantitatively by detachment of the acyl moiety and reductive cleavage of the N–O bond into the stereodefined *anti* aminols **4**.[18] Starting from these, by the linear construction of the heterobases, we have detailed the first synthesis of a class of racemic purine-carbocyclic nucleosides **5** containing a fused isoxazolinic ring and lacking a methylene group in the side chain in the carbocyclic unit.[13a]

We complete the work here by reporting the syntheses of pyrimidine-type nucleosides starting from the *anti* aminols of type **4**.[15] We also demonstrate that the *syn* 1,3-dipolar cycloadducts cannot be synthetically used in the same type of chemistry since their structures evolve differently from the parent *anti* cycloadducts.

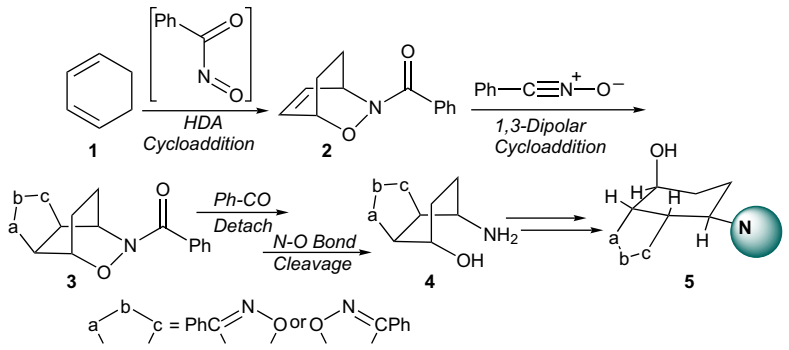
2. Results

2.1. Conversion of the *anti* aminols into pyrimidine nucleosides

From *N*-benzoyl-2-oxa-3-azabicyclo[2.2.2]oct-5-ene **2**, the *anti* regioisomeric 1,3-dipolar cycloadducts **3a**,**b** have been obtained

* Corresponding author.
E-mail address: paolo.quadrelli@unipv.it (P. Quadrelli).

0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.05.061



Scheme 1. In the 1,3-dipolar cycloadducts, the moieties deriving from the nitrile oxides have been abbreviated as 'a–b–c', to concisely depict the two possible regioisomers as previously reported.[13a]

through the addition of excess BNO (1.5 equiv) in fair yields and separated from the *syn* cycloadducts **6a**,**b** by column chromatography (Scheme 2).[15]

The reaction yields indicate the lack of any noteworthy regiochemical or stereochemical selectivity in the cycloaddition[19] of BNO to *N*-benzoyl 2-oxa-3-azabicyclo[2.2.2]oct-5-ene **2**. This is attributed to the comparable electron withdrawing ability of the alkoxy and acylamino allylic substituents, which have similar σ_I substituent constants[20] and the quite small pyramidalization of the hetero-disubstituted bicyclo[2.2.2]oct-5-ene **2**.[21]

The *anti* cycloadducts **3a**,**b** were almost quantitatively converted to the aminols through the detachment of the benzoyl groups by alkaline hydrolysis at rt to afford the corresponding cyclic hydroxylamines **7a**,**b**, which were reduced by catalytic hydrogenation into the desired aminols **4a**,**b** (Scheme 3). The stereoisomeric aminols **4a**,**b** were converted into the uracil and thymine nucleosides[22] through the linear construction of these heterocycles.[23] The synthetic route to uracil and thymine nucleosides involves the steps illustrated in Scheme 4 and started with the preparation of the appropriate isocyanate **8U**,**T**.

The 3-methoxy-2-propenoyl isocyanate **8U** was easily obtained starting from the commercially available methyl 3-methoxy-2-propenoate through basic hydrolysis to the acid,[23] conversion to the acid chloride with thionyl chloride[24] and coupling with silver cyanate in benzene.[23] 3-Methoxy-2-methyl-2-propenoyl isocyanate **8T** was similarly obtained from the corresponding methyl 3-methoxy-2-methyl-2-propenoate. The latter is available from methyl methacrylate according to a convenient reported protocol.[25]

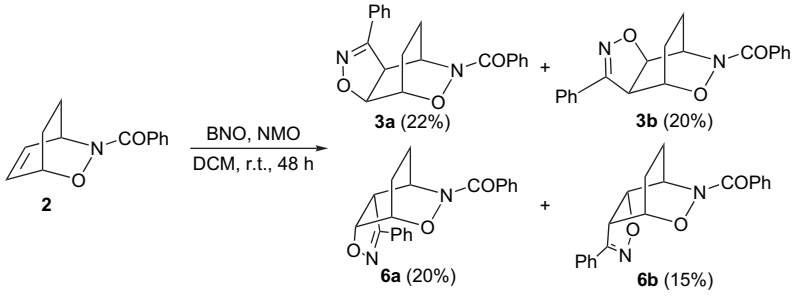
The addition reactions of the aminols **4a**,**b** to isocyanates **8U**,**T** were conducted according to the procedure reported in the literature[23] by performing the reactions at −20 °C in DMF solutions for 12 h. After chromatographic purification, the urea adducts **9a**,**b**(**U**,**T**) were obtained in fair yields (50–60%). Their structures rely upon the analytical and spectroscopic data. Table 1 reports the yields, the physical constants and the significative spectroscopic data. Neat distinctive bands corresponding to the OH and the two NH groups were evident in the IR spectra. The NMR spectra showed the signals of the methoxy propenoyl and methoxy methyl-propenoyl chains as well as those of the carbocyclic moiety in the usual ranges.

Cyclization of the ureas **9** took place smoothly upon heating in 2 M H_2SO_4 solution for 3 h at reflux. The uracil nucleosides **10Ua**,**b** and the thymine analogues **10Ta**,**b** were isolated from these solutions after pH adjustment to 7 and extraction with dichloromethane. The yields of the cyclization steps were satisfactory (85–94%) and the structures of the nucleosides **10** rely upon their analytical and spectroscopic data. The IR spectra of nucleosides **10a**,**b** showed neat and distinct OH and NH bands, which are reported in Table 1. The ^{1}H NMR spectra in DMSO of the uracil nucleosides **10Ua**,**b** showed the characteristic coupled alkenyl protons of the uracil unit as broad singlets at δ 5.52 and 7.66 for **10Ua** and as doublets at δ 5.69 and 7.85 (J=8 Hz) for **10Ub** while the thymine nucleosides **10Ta**,**b** display the vinyl proton and the methyl of the thymine unit as singlets at δ 7.53, 7.54 and 1.75, 1.81, respectively.

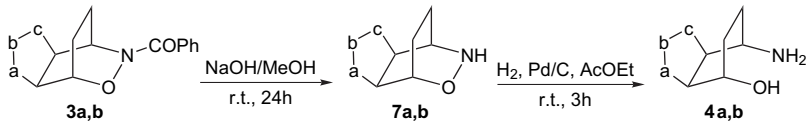
The isoxazolinic protons all occur at different chemical shifts with different multiplicities owing to the regiochemistry and the conformational changes imposed by the isoxazoline-cyclohexane moiety. In compound **10Ua** the H4 and H5 isoxazoline protons are doublets (J=5 Hz) found at δ 4.35 and 5.32, respectively, while in the regioisomeric **10Ub** they are shifted apart, the H4 upfield at δ 3.36 (m) and the H5 downfield at δ 6.26 (d, J=3 Hz). In the thymine derivative **10Ta**, the H4 and H5 isoxazoline protons are found at δ 4.12 as a broad singlet and δ 5.31 (d, J=4 Hz), respectively, while in the regioisomeric **10Tb** the H4 is found at δ 2.55 (m) and the H5 at δ 6.27 (d, J=4 Hz).

2.2. Reactivity of the *syn* cycloadducts

We have also considered the possibility of using the *syn* 1,3-dipolar cycloadducts **6a**,**b** for the preparation of the stereoisomeric *syn* isoxazoline-carbocyclic nucleosides. The reactivity of



Scheme 2.



Scheme 3.

cycloadducts **6a**,**b**, and in particular their transformation into *syn* aminols to be used in nucleoside syntheses, has been studied (Scheme 5).

We submitted the two cycloadducts **6a**,**b** to the classical initial step, i.e., the alkaline hydrolysis performed at rt by adding a slight excess of NaOH to a methanol solution of the two compounds. Surprisingly, both the cycloadducts **6a**,**b** did not react under these conditions, even after long reaction times, and compounds were recovered unchanged. Hence, the same reactions were performed upon heating the basic solutions. In the reaction of cycloadduct **6a**, a new product was formed after 3 days at reflux. Evaporation of methanol, adjustment of the pH to neutrality and extraction of the water phase with dichloromethane (DCM) afforded the organic phase, which was dried and concentrated to leave a residue, which was submitted to chromatographic purification yielding the isomeric product **11a** in a 54% yield. The structure of **11a** relies upon its analytical and spectroscopic data.

In the IR spectrum of product **11a**, a neat band at 3210 cm^{-1} suggests the presence of an OH group while the strong and sharp band at 1638 cm^{-1} reports the presence of an amide-like C=O group. The ^1H NMR spectrum in $CDCl_3$ showed a complex group of signals between δ 7.3 and 7.9 integrating for 10H, attributable to two phenyl groups, while a deshielded singlet at δ 8.99 is consistent with the acidic proton of an OH group. More significant are the two signals at δ 5.68 (d, J=10 Hz) and 5.85 (m) indicating the presence of a cis alkene double bond. In the ^{13}C NMR spectrum in $CDCl_3$, the alkene double bond carbons showed signals at δ 121.2 and 126.9. The isoxazoline protons are found at the expected values, the H5 at δ 5.24 (dd, J=8, 3 Hz) and the H4 at δ 4.34 (m); the relative carbons are found at δ 79.1 and 49.4. A signal at δ 4.75 (m) corresponds to the CH–N proton while the methylene occurs at δ 2.62 (m). ^1H,^1H-COSY and HSQC experiments corroborated the signal assignments and their couplings agree with the reported structure **11a**, which derives from the base promoted elimination of the *N*-alkyl hydroxamate anion as shown in Scheme 6.

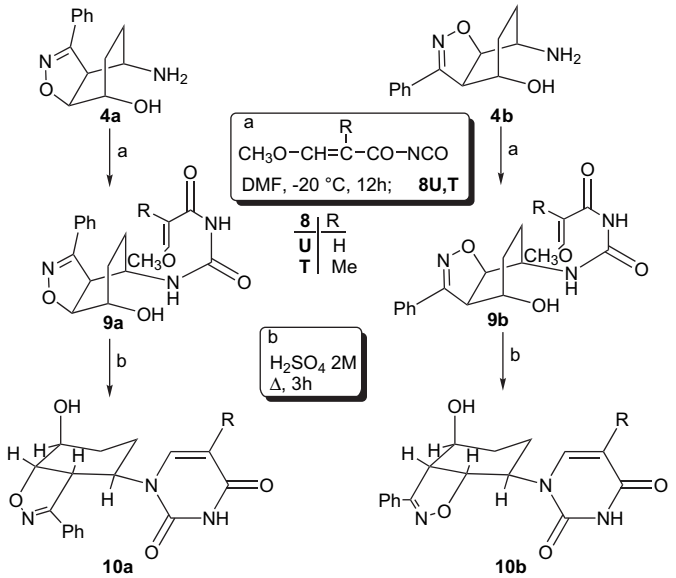
Table 1
Yields, physical constants and significative spectroscopic data of the ureas **9** and nucleosides **10**

Compounds	Yield [%]	Mp [°C][a]	IR [cm^{-1}]	
			ν_{OH}	ν_{NH}
9Ua	50	190–193	3521	3330, 3295
9Ta	60	208–210	3526	3315, 3283
9Ub	57	168–171	3311	3242, 3089
9Tb	58	212–215	3430	3254, 3120
10Ua	85	250–253 (dec)	3331	3173
10Ta	94	276–280 (dec)	3351	3199
10Ub	87	242–245 (dec)	3421	3179
10Tb	90	258–262 (dec)	3402	3163

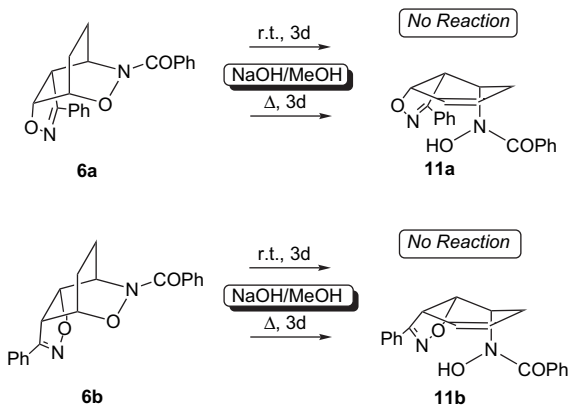
[a] From EtOH/^{i}Pr$_2$O.

The alkaline hydrolysis of cycloadduct **6b** took the same time under reflux (3 days) and gave a product, which was isolated from the reaction mixture after the usual work-up and chromatographic purification. Scheme 5 reports the structure, which relies upon its analytical and spectroscopic data. Compound **11b** (51%) is the regioisomer of compound **11a** and showed in the IR spectrum a neat band at 3273 cm^{-1} due to the presence of an OH group while the band at 1597 cm^{-1} indicates the presence of a conjugated C=O group. The ^1H NMR spectrum in DMSO showed the group of signals between δ 7.3 and 7.8 integrating for 10H and corresponding to the two phenyl groups of the molecule while a deshielded singlet at δ 9.86 is consistent for the *N*-alkyl hydroxamate OH proton. Two multiplets at δ 5.61 and 5.92 account for the presence of an alkene double bond, whose carbons are found at δ 121.7 and 128.0. The isoxazoline protons are found at the expected values, the H5 at δ 5.01 (m) and the H4 at δ 4.60 (m) while the relative carbons at δ 81.2 and 52.4, respectively. The signal at δ 4.95 (d, J=8 Hz) corresponds to the CH–N proton and the methylene is found between δ 2.1 and 2.7 (m). The reported structure **11b** derives from the base promoted ring opening shown in Scheme 6.

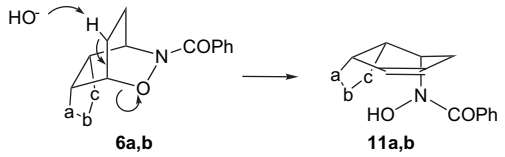
The acidities of hydroxamic acids and their *N*-alkyl derivatives are in the range of phenols and the anions are moderately good leaving groups thus accounting for the feasibility of the ring opening.[26] The usual cleavage of the *N*-benzoyl group requires an attack, which is strongly hindered by the presence in the *syn*



Scheme 4. Conditions: (a) DMF, −20 °C, 12 h. (b) Δ, 3 h.



Scheme 5.



Scheme 6.

cycloadducts **6a**,**b** of the isoxazoline ring facing the reaction site. The attack of the base to the amide carbonyl from the *exo* face (shown in Fig. 1 by the arrows) looks feasible but the formation of the tetrahedral intermediate is, however, severely hindered because the ensuing pyramidalization of the amide carbonyl pushes its phenyl and oxygen substituents towards the facing isoxazoline ring.

Thus, the crowding around the amide group reduces its reactivity. A related case is the reactivity decrease in ester hydrolysis due to increased hindrance of α-carbon substituents and evidenced by the Taft E_s parameters.[27]

3. Conclusions

We have again demonstrated that the *anti* cycloadducts **3a**,**b** are suitable starting materials for isoxazoline-cyclohexane nucleoside synthesis. Detachment of the benzoyl group and reductive cleavage of the N–O bond provide the stereodefined aminols **4a**,**b**, which are used for the linear construction of uracil and thymine nucleosides **10a**,**b**(**U**,**T**) according to the well-established synthetic protocols[13] and samples of these new compounds were submitted for antiviral tests. Many possible useful variations can be suggested besides the change of the heterobases. These are the merits of the approach where the nature of the heterocyclic ring can be easily varied through suitable 1,3-dipolar cycloaddition reactions. The good dipolarophilic activity of the initial HDA nitrosocarbonyl cycloadduct **2** lends itself to the proper structural variation depending upon the biological response.

The *syn* cycloadducts **6a**,**b** did not enter the same synthetic route since the first step, the alkaline hydrolysis, does not occur at rt. Harsher conditions are required to transform the cycloadducts into new structures, which differ substantially from those required for the nucleosidic synthesis developed here.

4. Experimental section

4.1. General

All melting points are uncorrected. Elemental analyses were done on a C. Erba 1106 elemental analyzer. IR spectra (Nujol mulls) were recorded on an FT-IR Perkin–Elmer RX-1. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE 300 in the specified deuterated solvents. Chemical shifts are expressed in parts per million from internal tetramethylsilane (δ). Column chromatography and TLC: silica gel 60 (0.063–0.200 mm) (Merck); eluant cyclohexane/ethyl acetate from 9:1 to 5:5. The identification of samples from different experiments was secured by mixed mps and superimposable IR spectra.

4.2. Materials

Benzhydroximoyl chloride, the precursor of BNO,[28] was obtained by treatment of benzaldoxime with sodium hypochlorite.[29] Methyl 3-methoxy-2-propenoate and silver cyanate were obtained from ACROS ORGANICS. Methyl methacrylate was from SIGMA–ALDRICH.

*4.2.1. Cycloaddition of BNO to N-benzoyl-2-oxa-3-azabicyclo[2.2.2]oct-5-ene **2***

BNO was generated in situ by dehydrohalogenation of benzhydroximoyl chloride with triethylamine.[28] To a stirred solution of the dipolarophile **2** (25 mmol) in anhydrous DCM (100 mL) and triethylamine (5 mL, 1.1 equiv), a solution of benzhydroximoyl chloride (5 g, 32 mmol) in the same solvent (20 mL) was added under stirring at 0 °C over a 0.5 h period. After keeping the reaction mixture for 2 days at rt, the organic phase was washed twice with water and dried over Na_2SO_4. The filtrate was evaporated under reduced pressure leaving a residue, which was separated by column chromatography to give the stereoisomeric cycloadducts **3a**,**b** and **6a**,**b**, which were found to be identical to the authentic samples previously prepared.[15]

4.3. Syntheses of the isocyanate adducts 9a,b(U,T)

4.3.1. General method

To solutions of aminols **4a**,**b** (3.50 mmol) in anhydrous DMF (10 mL) at −20 °C, solutions of isocyanates **8U**,**T** (3.85 mmol) in anhydrous benzene were added dropwise with stirring in a nitrogen atmosphere and in the presence of MS 4 Å. After stirring over night at rt, the solutions were filtered and solvent removed under reduced pressure. The residues were submitted to column chromatography to isolate compounds **9a**,**b**(**U**,**T**). Table 1 reports the physical constants (solvent of crystallization) and the yields of the isocyanate adducts **9a**,**b**(**U**,**T**).

Compound **9Ua**: 0.63 g (50%), mp 190–193 °C, colourless crystals from ethanol/diisopropyl ether. ^{1}H NMR (300 MHz, DMSO, 25 °C): δ=1.42 (m, 1H, CH_2–CH_2), 1.68 (m, 3H, CH_2–CH_2), 3.67 (s, 3H, OMe), 3.72 (m, 1H, H4 isox.), 3.82 (t, *J*=8.5 Hz, 1H, CH–N), 3.96 (t, *J*=3 Hz,

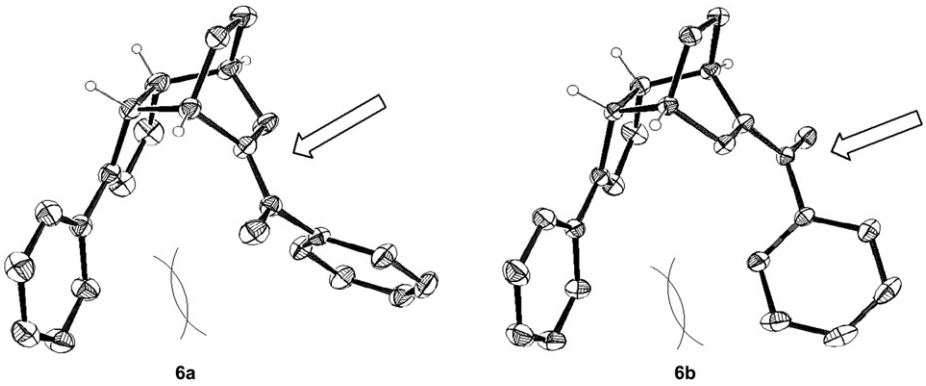


Figure 1. X-ray structures[15a] of cycloadducts **6a**,**b** show feasible directions of the base attack (arrows) to the amide carbonyl while crowding (crossed parentheses) opposes to the formation of the tetrahedral intermediate.

1H, OH), 4.31 (dd, *J*=7, 3 Hz, 1H, CH–O), 5.22 (d, *J*=4 Hz, 1H, H5 isox.), 5.42 (d, *J*=12 Hz, 1H, =CH–CO), 7.36 (m, 3H, arom.), 7.59 (d, *J*=12 Hz, 1H, =CH–OMe), 7.70 (m, 2H, arom.), 8.72 (d, *J*=9 Hz, 1H, CH–NH), 9.78 (s, 1H, CO–NH–CO) ppm. ^{13}C NMR (75 MHz, DMSO, 25 °C): *δ*=24.2, 27.3, 47.5, 48.3, 57.9, 65.9, 85.1, 97.8, 127.3, 128.2, 129.0, 129.9, 152.7, 162.6, 162.7, 167.2 ppm. IR: *ν*=3521 (OH), 3330, 3295 (NH), 1693 (C=N), 1671 (C=O), 1618 (C=C) cm^{-1}. $C_{18}H_{21}O_5N_3$ (359.37): C 60.16, H 5.89, N 11.69; found: C 60.2, H 5.9, N 11.5.

Compound **9Ta**: 0.78 g (60%), mp 208–210 °C, colourless crystals from ethanol/diisopropyl ether. ^{1}H NMR (300 MHz, DMSO, 25 °C): *δ*=1.42 (m, 1H, CH_2–CH_2), 1.61 (s, 3H, Me), 1.69 (m, 3H, CH_2–CH_2), 3.79 (m, 5H, H4 isox., CH–N and OMe), 3.97 (s, 1H, CH–O), 4.31 (m, 1H, H5 isox.), 5.21 (s, 1H, OH), 7.31 (m, 3H arom.), 7.38 (m, 1H, =CH–OMe), 7.70 (m, 2H, arom.), 8.84 (d, *J*=9 Hz, 1H, CH–NH), 9.39 (s, 1H, CO–NH–CO) ppm. ^{13}C NMR (75 MHz, DMSO, 25 °C): *δ*=8.8, 24.2, 27.3, 47.6, 48.3, 61.0, 62.9, 85.1, 106.8, 127.3, 128.2, 129.1, 129.8, 152.8, 157.8, 162.7, 169.3 ppm. IR: *ν*=3526 (OH), 3315, 3283 (NH), 1686 (C=N), 1672, 1656 (C=O), 1623 (C=C) cm^{-1}. $C_{19}H_{23}O_5N_3$ (373.40): C 61.11, H 6.21, N 11.25; found: C 61.0, H 6.1, N 11.4.

Compound **9Ub**: 0.72 g (57%), mp 168–171 °C, colourless crystals from ethanol/diisopropyl ether. ^{1}H NMR (300 MHz, DMSO, 25 °C): *δ*=1.49 (m, 2H, CH_2–CH_2), 1.73 (m, 2H, CH_2–CH_2), 3.56 (m, 1H+1H, CH–OH and H4 isox.), 3.69 (s, 3H, OMe), 4.11 (m, 1H, CH–N), 4.50 (m, 1H, H5 isox.), 5.21 (br s, 1H, OH), 5.56 (d, *J*=12 Hz, 1H, =CH–C=O), 7.44 (m, 3H, arom.), 7.63 (d, *J*=12 Hz, 1H, =CH–OMe), 7.80 (m, 2H, arom.), 9.00 (d, *J*=8 Hz, 1H, NH), 10.2 (s, 1H, NH) ppm. ^{13}C NMR (75 MHz, DMSO, 25 °C): *δ*=23.4, 27.3, 44.2, 51.5, 58.0, 67.3, 83.0, 97.8, 127.6, 128.4, 129.3, 130.0, 153.3, 162.4, 162.9, 167.8 ppm. IR: *ν*=3311 (OH), 3242, 3089 (NH), 1680 (C=N and C=O), 1625 (C=C) cm^{-1}. $C_{18}H_{21}O_5N_3$ (359.37): C 60.16, H 5.89, N 11.69; found: C 60.3, H 5.9, N 11.6.

Compound **9Tb**: 0.76 g (58%), mp 212–215 °C, colourless crystals from ethanol/diisopropyl ether. ^{1}H NMR (300 MHz, DMSO, 25 °C): *δ*=1.51 (m, 2H, CH_2–CH_2), 1.64 (d, *J*=1 Hz, 3H, Me), 1.72 (m, 2H, CH_2–CH_2), 3.56 (m, 1H+1H, CH–OH and H4 isox.), 3.81 (s, 3H, OMe), 4.12 (m, 1H, CH–N), 4.49 (dd, *J*=7, 4 Hz, 1H, H5 isox.), 5.22 (d, *J*=4 Hz, 1H, OH), 7.44 (m, 3H, arom.), 7.51 (d, *J*=1 Hz, 1H, =H–OMe), 7.80 (m, 2H, arom.), 9.13 (d, *J*=8 Hz, 1H, NH), 9.86 (s, 1H, NH) ppm. ^{13}C NMR (75 MHz, DMSO, 25 °C): *δ*=8.8, 23.4, 27.3, 44.1, 51.4, 61.1, 67.4, 83.1, 106.9, 127.6, 128.5, 129.3, 130.0, 153.4, 158.3, 162.4, 169.8 ppm. IR: *ν*=3430 (OH), 3254, 3120 (NH), 1664 (C=N, C=O and C=C) cm^{-1}. $C_{19}H_{23}O_5N_3$ (373.40): C 61.11, H 6.21, N 11.25; found: C 61.1, H 6.2, N 11.2.

4.4. Construction of the uracil and thymine nucleosides 10a,b(U,T)

4.4.1. General method

Adducts **9a**,**b**(**U**,**T**) (1.2 mmol) are suspended in 2 M H_2SO_4 (50 mL) solutions and heated at reflux for 3 h. After cooling, the pH is adjusted to 7 with $NaHCO_3$ and the water phase extracted with dichloromethane. Evaporation of the dried organic phase afforded the uracil or thymine nucleosides, which were purified by crystallization.

Compound **10Ua**: 0.33 g (85%), mp 250–253 °C (dec), colourless crystals from diisopropyl ether/ethanol. ^{1}H NMR (300 MHz, DMSO, 25 °C): *δ*=1.42 (m, 1H, CH_2–CH_2), 1.80 (m, 2H, CH_2–CH_2), 2.08 (m, 1H, CH_2–CH_2), 4.12 (s, 1H, OH), 4.23 (b, 1H+1H, CH–OH and CH–N), 4.35 (d, *J*=5 Hz, 1H, H4 isox.), 5.32 (d, *J*=5 Hz, 1H, H5 isox.), 5.52 (br s, 1H, =CH–C=O), 7.33 (m, 3H, arom.), 7.44 (m, 2H, arom.), 7.66 (br s, 1H, =CH–N), 10.85 (s, 1H, NH) ppm. ^{13}C NMR (75 MHz, DMSO, 25 °C): *δ*=22.0, 28.5, 41.3, 45.7, 61.6, 85.6, 101.8, 126.4, 126.9, 128.4, 128.8, 130.2, 142.3, 150.4, 162.6, 163.1 ppm. IR: *ν*=3331 (OH), 3173 (NH), 1673 (C=N and C=O) cm^{-1}. $C_{17}H_{17}O_4N_3$ (327.33): C 62.37, H 5.24, N 12.84; found: C 62.3, H 5.3, N 12.8.

Compound **10Ta**: 0.39 g (94%), mp 276–280 °C (dec), colourless crystals from diisopropyl ether/ethanol. ^{1}H NMR (300 MHz, DMSO, 25 °C): *δ*=1.41 (m, 1H, CH_2–CH_2), 1.75 (m, 3H+1H, Me and CH_2–CH_2), 1.89 (m, 1H, CH_2–CH_2), 2.14 (m, 1H, CH_2–CH_2), 4.12 (br s, 1H+1H, H4 isox. and CH–N), 4.35 (d, *J*=6 Hz, 1H, CH–OH), 5.31 (d, 1H, *J*=4 Hz, H5 isox.), 7.27 (m, 3H, arom.), 7.36 (m, 2H, arom.), 7.53 (s, 1H, =CH–N), 10.77 (s, 1H, NH) ppm. ^{13}C NMR (75 MHz, DMSO, 25 °C): *δ*=11.9, 22.1, 28.6, 45.8, 61.6, 85.6, 109.5, 127.0, 128.3, 128.8, 130.1, 150.4, 163.2 ppm. IR: *ν*=3351 (OH), 3199 (NH), 1695 (C=O), 1655 (C=N) cm^{-1}. $C_{18}H_{19}O_4N_3$ (341.36): C 63.33, H 5.61, N 12.31; found: C 63.3, H 5.6, N 12.4.

Compound **10Ub**: 0.34 g (87%), mp 242–245 °C (dec), colourless crystals from diisopropyl ether/ethanol. ^{1}H NMR (300 MHz, DMSO, 25 °C): *δ*=1.94 (m, 2H, CH_2–CH_2), 2.12 (m, 2H, CH_2–CH_2), 3.36 (m, 1H, H4 isox.), 4.57 (m, 1H, CH–N), 5.43 (m, 1H, CH–OH), 5.69 (d, *J*=8 Hz, 1H, =CH–C=O), 6.26 (d, *J*=3 Hz, 1H, H5 isox.), 7.54 (m, 3H, arom.), 7.64 (m, 2H, arom.), 7.85 (d, *J*=8 Hz, 1H, =CH–N), 11.42 (s, 1H, NH) ppm. ^{13}C NMR (75 MHz, DMSO, 25 °C): *δ*=23.7, 25.9, 40.3, 55.2, 80.3, 102.0, 125.7, 127.3, 127.5, 129.2, 130.6, 136.3, 142.1, 151.0, 156.5, 162.9 ppm. IR: *ν*=3421 (OH), 3179 (NH), 1683 (C=N and C=O) cm^{-1}. $C_{17}H_{17}O_4N_3$ (327.33): C 62.37, H 5.24, N 12.84; found: C 62.4, H 5.3, N 12.7.

Compound **10Tb**: 0.37 g (90%), mp 258–262 °C (dec), colourless crystals from diisopropyl ether/ethanol. ^{1}H NMR (300 MHz, DMSO, 25 °C): *δ*=1.81 (s, 3H, Me), 1.91 (m, 2H, CH_2–CH_2), 2.07 (m, 2H, CH_2–CH_2), 2.55 (m, 1H, H4 isox.), 4.56 (m, 1H, CH–N), 5.44 (m, 1H, CH–OH), 6.27 (d, *J*=4 Hz, 1H, H5 isox.), 7.51 (m, 3H, arom.), 7.54 (s, 1H, =CH–N), 7.71 (m, 2H, arom.), 11,38 (s, 1H, NH) ppm. ^{13}C NMR (75 MHz, DMSO, 25 °C): *δ*=12.1, 23.8, 25.8, 54.8, 80.3, 109.7, 125.6, 127.4, 127.5, 129.2, 130.6, 136.4, 137.6, 151.0, 156.5, 163.6 ppm. IR: *ν*=3402 (OH), 3163 (NH), 1696 (C=O and C=N) cm^{-1}. $C_{18}H_{19}O_4N_3$ (341.36): C 63.33, H 5.61, N 12.31; found: C 63.4, H 5.6, N 12.4.

4.5. Alkaline hydrolysis of the *N*-benzoyl adducts 6a,b

4.5.1. General method

To a stirred solution of **6a**,**b** (0.48 g, 1.43 mmol) in methanol (30 mL), an excess of NaOH (2 equiv) was added and the mixture heated under gentle reflux. After 3 days, the filtered solution was concentrated under reduced pressure, taken up with DCM and the organic phase washed three times with water, and finally dried over Na_2SO_4. Evaporation of the solvent afforded a residue, which was submitted to chromatographic separation.

Compound **11a**: 258 mg (54%), mp 204–205 °C, colourless crystals from ethanol. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): *δ*=2.62 (m, 2H, CH_2), 4.34 (m, 1H, H4 isox.), 4.75 (m, 1H, CH–N), 5.24 (dd, *J*=8, 3 Hz, 1H, H5 isox.), 5.68 (d, *J*=10 Hz, 1H, =CH–CH), 5.85 (m, 1H, =CH–CH_2), 7.47 (m, 6H, arom.), 7.74 (m, 4H, arom.), 8.99 (s, 1H, OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): *δ*=23.8 (CH_2), 49.4 (CH), 79.0 (CH–N), 79.1 (CH), 121.2 (=CH), 126.8 (C), 126.9 (=CH), 127.0 (CH), 128.2 (CH), 128.7 (C), 128.8 (CH), 130.3 (CH), 131.6 (C), 132.1 (CH), 159.7 (C=N), 166.7 (C=O) ppm. IR: *ν*=3210 (OH), 1638 (C=O and C=N) cm^{-1}. $C_{20}H_{18}O_3N_2$ (334.36): C 71.84, H 5.43, N 8.38; found: C 71.7, H 5.5, N 8.4.

Compound **11b**: 244 mg (51%), mp 203–204 °C, colourless crystals from ethanol. ^{1}H NMR (300 MHz, DMSO, 25 °C): *δ*=2.14 and 2.67 (m, 1H+1H, CH_2), 4.60 (m, 1H, H4 isox.), 4.95 (d, *J*=8 Hz, 1H, CH–N), 5.01 (m, 1H, H5 isox.), 5.61 (m, 1H, =CH–CH), 5.92 (m, 1H, =CH–CH_2), 7.47 (m, 6H, arom.), 7.71 (m, 2H, arom.), 7.78 (m, 2H, arom.), 9.86 (s, 1H, OH) ppm. ^{13}C NMR (75 MHz, DMSO, 25 °C): *δ*=21.9 (CH_2), 49.2 (CH–N), 52.4 (CH), 81.2 (CH), 121.7 (=CH), 126.8 (CH), 127.7 (CH), 128.0 (=CH), 128.3 (C), 128.4 (CH), 129.0 (CH), 130.1 (C), 130.3 (C), 134.9 (C), 159.3 (C=N), 169.4 (C=O) ppm. IR: *ν*=3273 (OH), 1597 (C=O and C=N) cm^{-1}. $C_{20}H_{18}O_3N_2$ (334.36): C 71.84, H 5.43, N 8.38; found: C 71.7, H 5.5, N 8.4.

Acknowledgements

Financial support by University of Pavia (Fondo d'Ateneo per la Ricerca, FAR) and Ministero dell'Università e Ricerca (MiUR, PRIN 2005) is gratefully acknowledged.

References and notes

1. (a) Hnang, W.; Miller, M. J.; De Clercq, E.; Balzarini, J. *Org. Biomol. Chem.* **2007**, *5*, 1164–1166; (b) Piperno, A.; Chiacchio, M. A.; Iannazzo, D.; Romeo, R. *Curr. Med. Chem.* **2006**, *13*, 3675–3695; (c) McGuigan, C.; Hassan-Abdallah, A.; Srinivasan, S.; Wang, Y.; Siddiqui, A.; Daluge, S. M.; Gudmundsson, K. S.; Zhou, H.; McLean, E. W.; Peckham, J. P.; Burnette, T. C.; Marr, H.; Hazen, R.; Condreay, L. D.; Johnson, L.; Balzarini, J. *J. Med. Chem.* **2006**, *49*, 7215–7226; (d) Jiang, M. X.-W.; Jin, B.; Gage, J. L.; Priour, A.; Savela, G.; Miller, M. J. *J. Org. Chem.* **2006**, *71*, 4164–4169; (e) Jeong, L. S.; Lee, J. A. *Antiviral Chem. Chemotherapy* **2004**, *15*, 235–250; (f) Merino, P. *Curr. Med. Chem. Anti-Infective Agents* **2002**, *1*, 389–411; (g) Martin, J. N.; Jones, R. C. F. *Synthetic Applications of 1,3-Dipolar Cycloaddition: Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; John Wiley and Sons: Hoboken, NJ, 2003; pp 1–81; (h) Mizuno, Y. *The Organic Chemistry of Nucleic Acids*; Kadansha: Tokyo, 1986; (i) Ueda, T. *Chemistry of Nucleosides and Nucleotides*; Townsend, Ed.; Plenum: New York, NY, 1988; Vol. 1, Chapter 1; (j) Srivasta, P. C.; Robins, R. K.; Meyer, R. B., Jr. *Chemistry of Nucleosides and Nucleotides*; Townsend, Ed.; Plenum: New York, NY, 1988; Vol. 1, Chapter 2; (k) Revenkar, G. R.; Robins, R. K. *Chemistry of Nucleosides and Nucleotides*; Townsend, Ed.; Plenum: New York, NY, 1988; Vol. 2, Chapter 4.
2. Wang, J.; Froeyen, M.; Herdewijn, P. *Adv. Antiviral Drug Design* **2004**, *4*, 119–145.
3. (a) Barral, K.; Halfon, P.; Pepe, G.; Camplo, M. *Tetrahedron Lett.* **2002**, *43*, 81–84; (b) Nair, V.; Buenger, G. S. *J. Org. Chem.* **1990**, *55*, 3695–3697.
4. (a) Herdewijn, P.; De Clercq, E. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1591–1597; (b) Wang, J.; Froeyen, M.; Hendrix, C.; Andrei, G.; Snoeck, R.; De Clercq, E.; Herdewijn, P. *J. Med. Chem.* **2000**, *43*, 736–745.
5. See Ref. 4b.
6. Cremer, D.; Szabo, K. J. *Conformational Behaviour of Six-membered Rings*; VCH: New York, NY, 1995; pp 59–135.
7. (a) Barral, K.; Courcambeck, J.; Pépe, G.; Balzarini, J.; Neyts, J.; De Clercq, E.; Camplo, M. *J. Med. Chem.* **2005**, *48*, 450–456; (b) Wang, J.; Morral, J.; Hendrix, C.; Herdewijn, P. *J. Org. Chem.* **2001**, *66*, 8478–8482; (c) Pérez-Pérez, M. J.; Rozenski, J.; Busson, R.; Herdewijn, P. *J. Org. Chem.* **1995**, *60*, 1531–1537.
8. (a) Rosenquist, Å.; Kvarnström, I.; Classon, B.; Samuelsson, B. *J. Org. Chem.* **1996**, *61*, 6282–6288; (b) Konkel, M. J.; Vince, R. *Tetrahedron* **1996**, *52*, 799–808; (c) Konkel, M. J.; Vince, R. *Tetrahedron* **1996**, *52*, 8969–8978; (d) Ramesh, K.; Wolfe, M. S.; Lee, Y.; Van der Velde, D. R.; Borchardt, T. *J. Org. Chem.* **1992**, *57*, 5861–5868; (e) Konkel, M. J.; Vince, R. *Nucleosides Nucleotides* **1995**, *14*, 2061–2077; (f) Arango, J. H.; Geer, A.; Rodriguez, P. E.; Young, P. E.; Scheiner, P. *Nucleosides Nucleotides* **1993**, *12*, 773–784.
9. Katagiri, N.; Ito, Y.; Shiraishi, T.; Maruyama, T.; Sato, Y.; Kaneko, C. *Nucleosides Nucleotides* **1996**, *15*, 631–647.
10. (a) Joshi, B. V.; Moon, H. R.; Fettinger, J. C.; Marquez, V. E.; Jacobson, K. A. *J. Org. Chem.* **2005**, *70*, 439–447; (b) Chun, B. K.; Olgen, S.; Hong, J. H.; Newton, M. G.; Chu, C. K. *J. Org. Chem.* **2000**, *65*, 685–693; (c) Marquez, V. E.; Russ, P.; Alonso, R.; Siddiqui, M. A.; Hernandez, S.; George, C.; Nicklaus, M. C.; Dai, F.; Ford, H., Jr. *Helv. Chim. Acta* **1999**, *82*, 2119–2129; (d) Hong, J. H.; Chun, B. K.; Chu, C. K. *Tetraheron Lett.* **1998**, *39*, 225–228.
11. Alibes, R.; Alvarez-Larena, A.; de March, P.; Figueredo, M.; Font, J.; Parella, T.; Rustullet, A. *Org. Lett.* **2006**, *8*, 491–494.
12. Garcia, M. D.; Caamaño, O.; Fernandez, F.; Garcia-Mera, X.; Perez-Castro, I. *Synthesis* **2006**, 3967–3972.
13. (a) Quadrelli, P.; Scrocchi, R.; Caramella, P.; Rescifina, A.; Piperno, A. *Tetrahedron* **2004**, *60*, 3643–3651; (b) Quadrelli, P.; Vazquez Martinez, N.; Bovio, B.; Mella, M.; Piccanello, A.; Caramella, P. *Tetrahedron* **2006**, *62*, 7370–7379.
14. (a) Kitade, Y.; Kojima, H.; Zulfiqur, F.; Kim, H. S.; Wataya, Y. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3963–3965; (b) Ramesh, N. G.; Klunder, A. J. H.; Zwanenburg, B. *J. Org. Chem.* **1999**, *64*, 3635–3641; (c) Wu, J.; Schneller, S. W.; Seley, K. L.; De Clerq, E. *Heterocycles* **1998**, *47*, 757–763; (d) Siddiqui, S. M.; Raissian, M.; Schneller, E.; Ikeda, S.; Snoeck, R.; Andrei, G.; Balzarini, J.; De Clerq, E. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 663–666; (e) Da Silva, A. D.; Coimbra, E. S.; Fourrey, J. L.; Machado, A. S.; Robert-Gero, M. *Tetrahedron Lett.* **1993**, *34*, 6745–6748; (f) Koga, M.; Schneller, S. W. *Tetrahedron Lett.* **1990**, *31*, 5861–5864.
15. (a) Quadrelli, P.; Mella, M.; Carosso, S.; Bovio, B.; Caramella, P. *Eur. J. Org. Chem.* **2007**, 6003–6015; (b) Quadrelli, P.; Piccanello, A.; Mella, M.; Corsaro, A.; Pistarà, V. *Tetrahedron* **2008**, *64*, 3541–3547.
16. (a) Kirby, G. W. *Chem. Soc. Rev.* **1977**, *6*, 1–24; (b) Vogt, P. F.; Miller, M. J. *Tetrahedron* **1998**, *54*, 1317–1348; (c) Boger, L.; Weinreb, S. M. *Hetero Diels–Alder Methodology in Organic Synthesis*; Academic: San Diego, CA, 1987.
17. (a) Quadrelli, P.; Gamba Invernizzi, A.; Caramella, P. *Tetrahedron Lett.* **1996**, *37*, 1909–1996; (b) Quadrelli, P.; Mella, M.; Gamba Invernizzi, A.; Caramella, P. *Tetrahedron* **1999**, *55*, 10497–10510.
18. (a) Quadrelli, P.; Mella, M.; Paganoni, P.; Caramella, P. *Eur. J. Org. Chem.* **2000**, 2613–2620; (b) Quadrelli, P.; Fassardi, V.; Cardarelli, A.; Caramella, P. *Eur. J. Org. Chem.* **2002**, 2058–2065.
19. Caramella, P.; Grünanger, P. *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley and Sons: New York, NY, 1984; Vol. 1, pp 291–392.
20. Exner, O. *Correlation Analysis in Chemistry*; Chapman, N. B., Shorter, J., Eds.; Plenum: London, 1978, Chapter 10.
21. (a) Mehta, G.; Chandrasekhar, J. *Chem. Rev.* **1999**, *99*, 1437–1467; (b) Rondan, N. G.; Paddon-Row, M. N.; Caramella, P.; Houk, K. N. *J. Am. Chem. Soc.* **1981**, *103*, 2436–2438; (c) Houk, K. N.; Rondan, N. G.; Brown, F. K.; Jorgensen, W. L.; Madura, J. D.; Spellmeyer, D. C. *J. Am. Chem. Soc.* **1983**, *105*, 5980–5988; (d) Spanget-Larsen, J.; Gleiter, R. *Tetrahedron* **1983**, *39*, 3345–3350; (e) Seebach, D.; Maetzke, T.; Petter, W.; Klötzer, B.; Plattner, D. A. *J. Am. Chem. Soc.* **1991**, *113*, 1781–1786.
22. (a) Muray, B.; Rifè, J.; Branchedall, V.; Ortuno, R. M. *J. Org. Chem.* **2002**, *67*, 4520–4525; (b) Estrada, E.; Uriarte, E.; Montero, A.; Teijeira, M.; Santana, L.; De Clerq, E. *J. Med. Chem.* **2000**, *43*, 1975–1985; (c) Wyatt, P. G.; Auslow, A. S.; Coomber, B. A.; Cousins, R. P. C.; Evans, D. N.; Gilbert, V. S.; Humber, D. C.; Paternoster, I. L.; Sallis, S. L.; Topolczay, D. J.; Weingarten, G. G. *Nucleosides Nucleotides* **1995**, *14*, 2039–2049; (d) Beres, J.; Sagi, Gy.; Tömösközi, I.; Gruber, L.; Gulacsi, E.; Ötrös, L. *Tetrahedron Lett.* **1988**, *29*, 2681–2684.
23. (a) Crimmins, M. T. *Tetrahedron* **1998**, *54*, 9229–9272; (b) Borthwick, A. D.; Biggadike, K. *Tetrahedron* **1992**, *48*, 571–623; (c) Santana, L.; Teijeira, M.; Uriarte, E. *J. Heterocycl. Chem.* **1999**, *36*, 293–295; (d) Fulmer Shealy, Y.; Allen O'Dell, C. *J. Heterocycl. Chem.* **1976**, *13*, 1015–1020; (e) Moon, H. R.; Kim, H. O.; Chun, M. W.; Jeong, L. S. *J. Org. Chem.* **1999**, *64*, 4733–4741; (f) Fulmer Shealy, Y.; Allen O'Dell, C.; Thorpe, M. C. *J. Heterocycl. Chem.* **1981**, *18*, 383–389; (g) Hrouoski, L. J. J.; Szarek, W. H. *Can. J. Chem.* **1988**, *66*, 61–70.
24. Weiguny, J.; Schöfer, H. J. *Liebigs Ann. Chem.* **1994**, 225–233.
25. (a) Shaw, G.; Warrener, R. N. *J. Chem. Soc.* **1958**, 153–156 and *J. Chem. Soc.* **1958**, 157–161; (b) Bieber, P. *Bull. Soc. Chim. Fr.* **1954**, 56–58 and *Bull. Soc. Chim. Fr.* **1954**, 199–203; (c) Csuk, R.; von Scholz, Y. *Tetrahedron* **1995**, *51*, 7193–7206; (d) Effenberger, F.; Hartmann, W. *Chem. Ber.* **1969**, *102*, 3260–3267.
26. (a) Bauer, L.; Exner, O. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 376–384; (b) Ventura, O. N.; Rama, J. B.; Turi, L.; Dannenberg, J. J. *J. Am. Chem. Soc.* **1993**, *115*, 5754–5761; (c) Bordwell, F. G.; Fried, H. E.; Hughes, D. L.; Lynch, T.-Y.; Satish, A. V.; Whang, Y. E. *J. Org. Chem.* **1990**, *55*, 3330–3336.
27. Taft, R. W., Jr. *Steric Effects in Organic Chemistry*; Newman, M. S., Ed.; Wiley: New York, NY, 1956; Chapter 13, p 556.
28. Grundmann, C.; Grünanger, P. *The Nitrile Oxides*; Springer: Heidelberg, 1971.
29. Corsico Coda, A.; Tacconi, G. *Gazz. Chim. Ital.* **1984**, *114*, 131–132.