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SUPPORTING INFORMATION

Title: A Straightforward Synthesis of Isoxazoline-Based Carbocyclic Nucleosides from 1,3-Cyclohexadiene through Nitrosocarbonyl Chemistry

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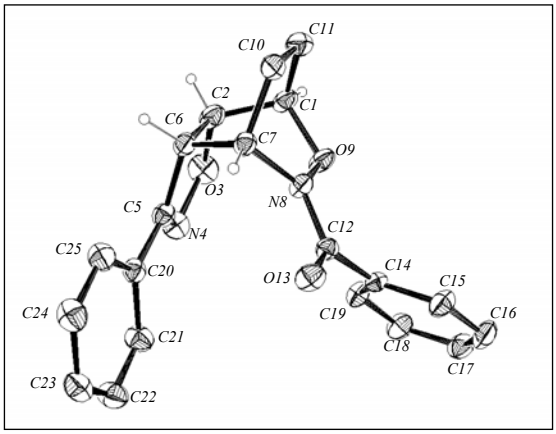
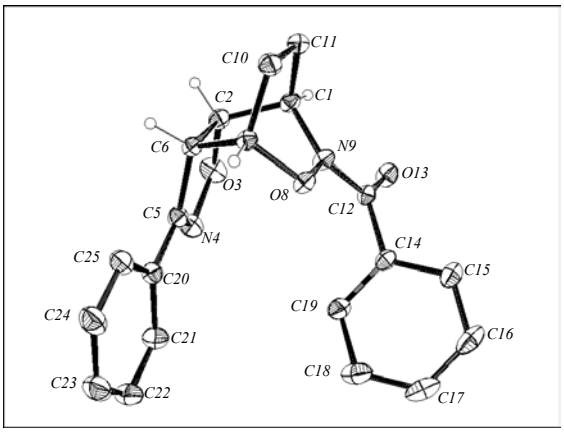


7c



7d

Table 1. Crystallographic data of cycloadducts **7c** and **7d**.

	7c	**7d**
Crystal size, mm	0.70 x 0.42 x 0.35	0.95 x 0.90 x 0.70
Temperature, K	293	293
Crystal system	Monoclinic	Monoclinic
Space group	Cc	$P2_1$ / *a*
a, Å	9.454(1)	8.213(1)
b, Å	20.653(3)	13.048(5)
c, Å	9.1836(7)	15.656(4)
β	110.086(9)	104.05(2)
V, Å^3	1684.0(4)	1627.6(8)
Z	4	4
D_{calcd}, gcm^{-3}	1.319	1.365
Absorption coeff., μ, cm^{-1}	0.898	0.929
F(000)	704	704
Range (°) for data coll.	$2.0 \le \theta \le 31.9$	$2.0 \le \theta \le 34.9$
Index range	$-14 \le h \le 13, -19 \le k \le 30, -8 \le l \le 13$	$-13 \le h \le 12, 0 \le k \le 21, 0 \le l \le 25$
No. of reflections measd.	7164	7144
No. of unique reflections	3770	7090
Absorption factors T	0.918, 0.997	0.928, 0.997
No.of obs reflect $I \ge 2\sigma(I)$.	2504	4390
No. of variables	298	298
Weights	0.0439, 0.06	0.0523, 0.06
Goodness–of–fit (all data)	1.041	1.053
R_1 (refl. $I \ge 2\sigma(I)$.)	0.0376	0.0460
wR_2 (all data)	0.0877	0.119
$(\Delta\rho)$max,min, *e*Å^{-3}	–0.11, 0.10	–0.16, 0.22

Table 2. Bond Lengths (Å), Angles and Torsion Angles (deg) with Esd's in Parentheses for compounds **7c,d**.

Bond Lengths (Å)	**7c**	**7d**	Bond Lengths (Å)	**7c**	**7d**
C1—C2	1.506(4)	1.525(2)	C7—N8	1.461(2)	
C1—O9	1.444(2)		C7—O8		1.451(1)
C1—N9		1.458(1)	C7—C10	1.520(3)	1.516(1)
C1—C11	1.501(4)	1.526(1)	N8—O9	1.422(2)	
C2—O3	1.452(3)	1.449(1)	O8—N9		1.429(1)
C2—C6	1.535(3)	1.535(1)	N8—C12	1.347(2)	
O3—N4	1.416(3)	1.411(1)	N9—C12		1.341(1)
N4—C5	1.275(3)	1.278(1)	C10—C11	1.538(4)	1.542(2)
C5—C6	1.504(3)	1.507(1)	C12—O13	1.223(2)	1.228(1)
C5—C20	1.465(3)	1.469(1)	C12—C14	1.493(2)	1.498(1)
C6—C7	1.524(3)	1.529(1)			
Bond Angles (°)					
C2—C1—O9	109.0(2)		C6—C7—C10	110.2(2)	110.85(8)
C2—C1—N9		107.50(8)	N8—C7—C10	108.0(1)	
C2—C1—C11	111.1(2)	109.01(8)	O8—C7—C10		109.75(8)
O9—C1—C11	109.5(2)		C7—N8—O9	114.7(1)	
N9—C1—C11		108.72(8)	C7—N8—C12	127.1(2)	
C1—C2—O3	110.5(2)	109.78(8)	O9—N8—C12	117.7(1)	
C1—C2—C6	109.4(2)	108.86(8)	C7—O8—N9		108.99(7)
O3—C2—C6	105.2(2)	105.62(8)	C1—N9—O8		114.86(7)
C2—O3—N4	109.9(2)	109.48(8)	C1—N9—C12		127.31(8)
O3—N4—C5	109.6(2)	110.02(9)	O8—N9—C12		117.76(8)
N4—C5—C6	114.5(2)	114.15(9)	C1—O9—N8	109.2(1)	
N4—C5—C20	120.9(2)	120.73(10)	C7—C10—C11	108.5(2)	108.80(9)
C6—C5—C20	124.5(2)	125.10(8)	C1—C11—C10	108.8(2)	108.54(9)
C2—C6—C5	100.8(2)	100.53(8)	N8—C12—O13	120.3(2)	
C2—C6—C7	108.0(2)	108.48(8)	N9—C12—O13		120.74(9)
C5—C6—C7	113.7(2)	114.10(8)	N8—C12—C14	117.6(2)	
C6—C7—N8	107.1(2)		N9—C12—C14		116.98(8)
C6—C7—O8		108.71(7)	O13—C12—C14	122.1(2)	122.28(9)
Torsion Angles (°)					
N9—C1—C2—O3		–62.5(1)	C12—N8—O9—C1	174.3(2)	
N9—C1—C2—C6		52.7(1)	C12—N9—O9—C7		–172.19(8)
O9—C1—C2—O3	–56.4(2)		O13—C12—N8—C7	–8.2(3)	
O9—C1—C2—C6	59.0(2)		O13—C12—N8—C1		11.2(1)
C11—C1—C2—O3	–177.1(2)	179.8(8)	C14—C12—N8—C7	173.7(2)	
C11—C1—C2—C6	–61.7(2)	–65.0(1)	C14—C12—N9—C1		–168.39(9)
C11—C1—N9—O8		55.5(1)	O13—C12—N8—O9	179.9(2)	
C11—C1—O9—N8	60.2(2)		O13—C12—N9—O8		–171.96(8)
C10—C11—C\—C2	58.8(3)	59.8(1)	C14—C12—N8—O9	1.9(2)	
C10—C11—C1—N9		–57.1(1)	C14—C12—N9—O8		8.4(1)
C10—C11—C1—O9	–61.7(2)		C15—C14—C12—N8	125.3(2)	
N4—C5—C20—C21	18.8(3)	12.4(2)	C15—C14—C12—N9		–123.3(1)
N4—C5—C20—C25	–165.9(2)	–166.6(1)	C19—C14—C12—N8	–58.3(3)	
C6—C5—C20—C21	–157.4(2)	–165.8(1)	C19—C14—C12—N9		61.6(1)
C6—C5—C20—C25	19,9(2)	15.1(2)	C15—C14—C12—O13	–52.7(3)	57.1(1)
C7—N8—O9—C1	1.4(2)		C19—C14—C12—O13	123.7(2)	–118.1(1)
C7—O8—N9—C1		5.9819			

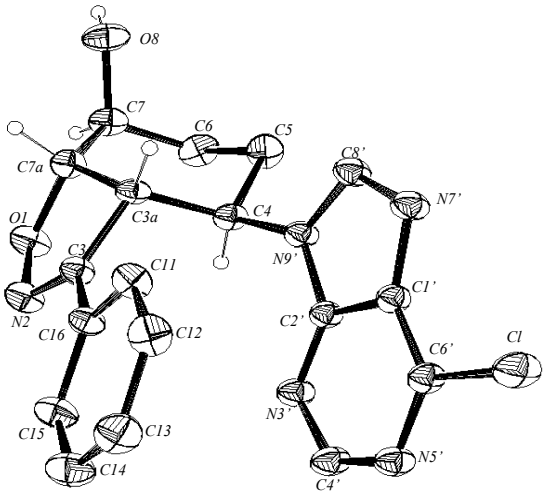


Table 3. Crystallographic data of product **12a**.

	12a
Crystal size, mm	0.63 x 0.56 x 0.14
Temperature, K	293
Crystal system	Monoclinic
Space group	$P2_1 / c$
a, Å	7.104(1)
b, Å	21.874(2)
c, Å	11.567(3)
β	107.48(1)
V, Å^3	1714.5(5)
Z	4
D_{calcd}, gcm^{-3}	1.429
Absorption coeff., μ, cm^{-1}	2.43
F(000)	768
Range (°) for data coll.	$2.0 \leq \theta \leq 30.02$
Index range	$-9 \leq h \leq 9, 0 \leq k \leq 30, 0 \leq l \leq 16$
No. of reflections measd	4988
No. of unique reflections	4914
Absorption factors T	0.955, 0.998
No.of obs reflect $I \geq 2\sigma(I)$.	3033
No. of variables	299
Weights	0.0562, 0.00
Goodness−of−fit	1.008
R_1 (refl. $I \geq 2\sigma(I)$.)	0.0443
wR_2 (all data)	0.1160
$(\Delta\rho)$max,min, *e*Å^{-3}	−0.24, 0.21

Table 4. Bond Lengths (Å), Angles and Torsion Angles (deg) with Esd's in Parentheses, in compound **12a**.

Bond Lengths			
O1—N2	1.414(2)	C7a—O1	1.455(2)
N2—C3	1.281(2)	C1'—C2'	1.403(2)
C3—C3a	1.519(2)	C1'—C6'	1.376(2)
C3—C10	1.471(2)	C1'—N7'	1.374(2)
C3a—C4	1.544(3)	C2'—N3'	1.328(2)
C3a—C7a	1.521(2)	C2'—N9'	1.369(2)
C4—C5	1.524(2)	N3'—C4'	1.327(2)
C4—N9'	1.469(2)	C4'—N5'	1.349(2)
C5—C6	1.525(3)	N5'—C6'	1.322(2)
C6—C7	1.505(3)	C6'—Cl	1.724(2)
C7—C7a	1.518(2)	N7'—C8'	1.303(2)
C7—O8	1.418(3)	C8'—N9'	1.372(2)
Bond Angles			
N2—O1—C7a	107.1(1)	C2'—C1'—C6'	114.9(1)
O1—N2—C3	109.0(1)	C2'—C1'—N7'	110.7(1)
N2—C3—C3a	112.3(1)	C1'—C2'—N3'	125.8(1)
C3—C3a—C7a	98.2(1)	C1'—C2'—N9'	105.4(1)
C4—C3a—C7a	112.7(1)	C2'—N3'—C4'	112.4(1)
C3a—C4—C5	110.8(1)	N3'—C4'—N5'	128.3(2)
C4—C5—C6	108.0(1)	C4'—N5'—C6'	116.5(1)
C5—C6—C7	111.8(2)	N5'—C6'—C1'	122.1(1)
C6—C7—C7a	113.1(2)	N5'—C6'—Cl	118.3(1)
C6—C7—O8	111.7(2)	C1'—C6'—Cl	119.5(1)
C7a—C7—O8	107.1(1)	C1'—N7'—C8'	103.8(1)
C3a—C7a—O1	102.5(1)	N7'—C8'—N9'	114.7(1)
C3a—C7a—C7	119.4(1)	C2'—N9'—C8'	105.4(1)
Torsion Angles			
N2—O1—C7a—C3a	30.7(2)	C7—C3a—C7a—O1	–33.3(2)
N2 —O1—C7a—C7	157.7(1)	C3—C3a—C7a—O1	–30.7(1)
O1—N2—C3—C3a	–5.2(2)	C3—C3a—C7a—C7	–150.1(2)
O1—N2—C3—C10	179.8(1)	C3a—C4—N9'—C2'	94.8(2)
C3a—C3—C10—C11	20.1(3)	C5—C4—N9'—C2'	–140.8(2)
N2—C3—C10—C11	–165.7(2)	C3a—C4—N9'—C8'	–75.7(2)
C3a—C3—C10—C15	–157.6(2)	C5—C4—N9'—C8'	48.6(2)
N2—C3—C10—C15	16.6(3)	C3a—C7a—C7—O8	–89.9(2)
C4—C3a—C7a—O1	86.0(2)	C3a—C7a—C7—C6	33.7(2)

Conformational analyses of crystal structures

The ORTEP[1] views of compounds **7c**, **7d** and **12a** with the atomic numbering are shown in Figures 1 and 2 of the text, respectively, were the crystal and collection data and the structure refinement are given in the insets Tables. The bond lengths, angles and the torsion angles are given in Table 3 for compounds **7c** and **7d** and in Table 4 for compound **12a**, both reported in the experimental section.

In the isoxazoline rings the angles at N4 of compounds **7c** and **7d** and N2 in **12a** are consistent with sp^2 hybridization of N4 and N2, respectively, whereby the 2*pz* lone pair takes part in π-bonding within a part of the heterocyclic rings; indeed the bond distances N4—C5 are 1.275(3) Å, 1.278(1) Å in **7c** and **7d** and N2—C3 1.281(2) Å in **12a**, indicating a double bond character. This bond and the approximate coplanarity of the isoxazoline and the phenyl are consistent with some conjugation between them; the interplanar angles are 19.99(9)° in **7c**, 14.36(7)° in **7d** and 13.70(9)° in **12a**. In compound **7c** and **7d** the sum of the angles at N8 359.5(2)° and at N9 359.93(8)° is consistent with sp^2 hybridization of N8 and N9, respectively, whereby the 2*pz* lone pair takes no part in π-bonding within the hexatomic ring, but with the C=O group; the bond distances N8—C12 1.347(2) Å in **7c** and N9—C12 1.341(1) Å in **7d** show a partial double bond character.

The angles at the nitrogen atoms O3—N4—C5 109.6(2)°, O9—N8—C7 114.7(1) differ by 5.1° in compound **7c**, and O3—N4—C5 110.02(9)°, O8—N9—C1 114.86(7)° differ by 4.84°, in compound **7d**, owing to the different types of nitrogen. The larger angle O9—N8—C7 and O8—N9—C1 in compounds **7c** and **7d**, respectively, is caused by the delocalization of the lone pair towards the C=O group. This observation explains the near coplanarity of the moiety C1 O9 N8 C7 and C1 N9 O8 C7 with the carbonylic group, divergence, 5.43(8)° and 10.96(4)°, respectively in **7c** and **7d**. The interplanar angle between the phenyl and the carbonilic group are 123.98(8) and 120.47(6), respectively in compounds **7c** and **7d**. In the isoxazoline ring bond lengths and angles compare well with the values given in the paper quoted in references.[2]

Bond lengths and angles in the phenyl rings of compounds **7c**, **7d** and **12a** are reasonable, on weighted average[3] 1.377(3) Å, 119.9(2)° ; 1.385(2) Å, 119.9(2)° and 1.386(3) Å, 120.0(3)° respectively.

In the compound **7c** the isoxazoline ring is slightly puckered with the deviations from the least-squares plane –0.008(2) to 0.009(2) Å; the puckering parameters of the isoxazoline calculated according to Cremer and Pople[4] are: Q = 0.016(2), φ = 41.9(1)° corresponding therefore to an envelope *E* conformation (ideal conformation φ = 36°). In the compound **7d** the isoxazoline ring shows atomic deviations from least-squares plane –0.0193(8), to 0.0325(9) Å, consistent with an

intermediate *E/T* conformation with the puckering parameters Q = 0.043(1), φ = 9.2(9)° (ideal values: *E,* φ = 0° and *T* φ = 18°). In the compound **12a** the deviations of atoms from the least-squares plane of isoxazoline ring, –0.178(2) to 0.241(2) Å, are consistent with an intermediate *E/T* conformation, with the puckering parameters Q = 0.320(2), φ = 152.3(3) (ideal values φ = 144° for *E* and φ = 162° for *T)*.

The six-membered condensed rings in compound **7c**, C1 O9 N8 C7 C6 C2, C1 O9 N8 C7 C10 C11 and C1 C2 C6 C7 C10 C11 exhibit boat conformations with puckering parameters respectively, Q = 0.811(1), φ = 2.0(1)°, θ = 90.1(1)°, Q = 0.799(4), φ = 1.37(2)°, θ = 90.7(2)° and Q = 0.821(3). φ = 2.0(2)°, θ = 90.9(2)°.

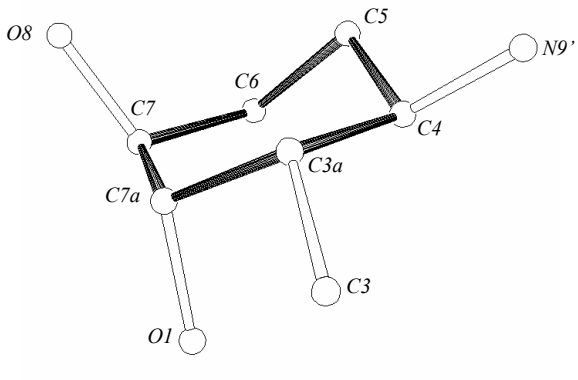
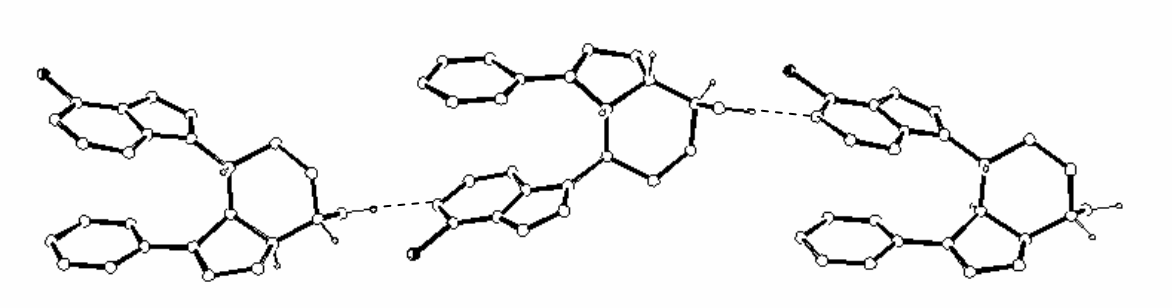


Figure 1. Conformation of the six-membered ring in compound **12a**.

In compound **7d** the puckering analysis for the atoms C1 N9 O8 C7 C6 C2, C1 N9 O8 C7 C10 C11 and C1 C2 C6 C7 C10 C11 gives: Q = 0.813(1), φ = 4.36(7)°, θ = 91.08(7)°; Q = 0.796(1), φ =4.01(7)°, θ = 89.10(7)° and Q = 0.838(1), φ = 3.72(7)°, θ = 88,82(7)°, respectively, consistent with a boat conformation.

In the cyclohexane ring of compound **12a** the deviations from the least-squares plane show a chair distorted in the direction of a half-boat with the puckering parameters Q = 0.538(2), φ = 59.4(5)°, θ = 24.8(2)° (ideal values for chair φ = 60°, θ = 0° and for half-boat φ = 60°, θ = 45°) (Figure 3). This chair distortion is attributable to the isoxazoline ring condensed in C3a—C7a with the cyclohexane. In the 1,2-oxazine tetrahydro rings of compounds **7c** and **7d** the N-O distances 1.422(2) Å and 1.429(1) Å, respectively, are comparable with the values 1.434(3) Å and 1.433(2) Å found in compounds (1*R,*2*S,*5*R*)-5-Methyl-2-[1-methyl-1-(2-naphthyl)ethyl]-cyclohexyl-(1*R*,4*S*)-2-oxa-3-azabicyclo[2.2.2.]oct-5-ene-3-carboxylate and tert-Butyl (1*S**,4*R**,5*R**)-5-(6-chloro-3-pyridyl)-2-oxa-3-azabicyclo[2.2.2]octane-3-carboxylate,[5] where the N atom is bonded to the C=O group. On the contrary in compound (*R*)-3-(4-Bromophenyl)-8,8-dimethyl-2-oxa-3-aza-

bicyclo[2.2.2]octan-6-one, the N-O bond, 1.466(8) Å,[6] is longer because the N atom is bonded to a phenyl group without delocalization. In the purine moiety of compound **12a** the N7'—C8' distance 1.303(2) Å, corresponds to a double bond whereas the remaining four distances in the five-membered ring correspond to shortened single bonds. The internal angles at the nitrogen atoms C1'—N7'—C8' 103.8(1)° and C2'—N9'—C8' 105.4(1)° differ by 1.60°; this is due to the lone–pair on N7'. In the six-membered moiety of purine the bond distances are intermediate between single and double bond, thus suggesting a π-delocalization over the purine system. In compound **12a** an intermolecular hydrogen bonding links the hydroxyl HO8 (*x, y, z)* and the N5' atom of the molecule $-x+2$, $y+1/2$, $-z+1/2$ (HO8…N5' 2.14(4) Å, O8…N5' 3.095 Å, O8—HO8…N5' 164.2°), as well as the N5' (*x, y, z*) atom links the hydroxyl of the molecule $-x+2$, $y-1/2$, $-z+1/2$, so giving molecular chains along *b* axis as shown in Figure 2.



C A B

Figure 2. Molecular chain of **12a** due to hydrogen bonds, developing along *b*.

A = (x, y, z); B = (-x+2, y+½, -z+½); C = (-x+2, y-½, -z+½)

The compound **7c** exhibit the chiral centers at C1, C2, C6, C7 and their configurations specified by the sequence rule[7] are described as *S,R,S,R*. For the centrosymmetric compound **7d**, of course, the configurations are *R,S,S,S* or *S,R,R,R* because of the simmetry centre.

In compound **12a** the chiral atoms C3a, C4, C7 and C7a have the following configurations *R,R,S,S* or *S,S,R,R* because of the centric space group.

The molecular packing of compounds **7c** and **7d** is determined only by van der Waal's contacts. In **12a** it is determined by the quoted intermolecular hydrogen bond and the van der Waal's contacts.

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