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Aza-Diels-Alder *versus* 1,3-Dipolar Cycloadditions of Methyl Glyoxylate Oxime with Cyclopentadiene

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Abstract - The acid-catalyzed [3+2] and [4+2] cycloadditions between methyl glyoxylate oxime (**1**) and cyclopentadiene were investigated using various Lewis and/or Bronsted acids at different temperatures in dichloromethane as solvent. Besides the expected new adducts, (±)-methyl [(3-*exo*)-2-hydroxy-2-azabicyclo[2.2.1]hept-5-ene]-3-carboxylate (**2**) and (±)-methyl [(3-*endo*)-2-hydroxy-2-azabicyclo[2.2.1]hept-5-ene]-3-carboxylate (**3**) a third adduct, (±)-methyl (1*R*,4*R*,5*R*)-(2-ox-3-azabicyclo[3.3.0]oct-7-ene)-4-carboxylate (**4**), whose formation can be explained by a concerted 1,3-dipolar cycloaddition, was obtained. Yields and product ratios were found to be more dependent on the catalyst than on the temperature; these results and the stereochemistry of the adducts, confirmed by spectroscopic data (^{1}H and ^{13}C NMR) and by X-ray crystallography, were used to analyze and propose a mechanistic explanation for both [$\pi 4_s+\pi 2_s$] cycloadditions.

[*] *Keywords: aza-Diels-Alder reaction, 1,3-dipolar cycloaddition, glyoxylate oxime, isoxazolidines, 2-hydroxy-2-azabicyclo[2.2.1]heptenes*
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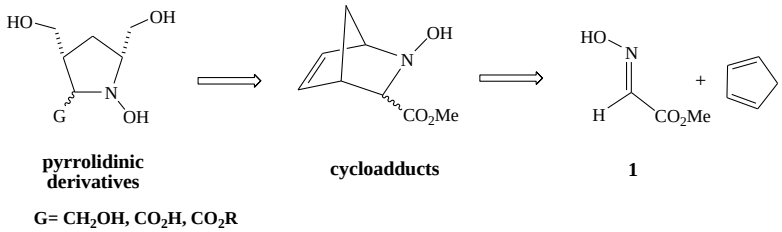
Introduction

The great versatility of cycloadditions, their high stereochemical control and the fair predictability of their regiochemistry allied to the rapid accumulation of polyfunctionality in a relatively small molecular framework, have contributed to the popularity of these reactions.[1] Within the diverse transformations comprising cycloadditions, aza-Diels-Alder reactions of imine derivatives and dienes leading to six-membered aza-heterocycles, monocyclic and bicyclic molecules, have attracted much interest, especially those employing cyclopentadiene as starting material.[2,3] The imines, used as aza-dienophiles, generally require activation by an electron-withdrawing group and a Lewis acid (LA) and/or Bronsted acid (BA) to participate in these [4+2] cycloaddition reactions.[3] It has been shown that the electronic nature of the substituents at the diene/dienophile pair may strongly influence the reaction pathways and determine either a concerted mechanism (synchronous or asynchronous) or a stepwise one[4]. In addition, experimentalists have always employed catalysts to change the kinetics of this class of reactions. In particular, a wide range of homogeneous and heterogeneous Lewis acids have been used to improve the rate and *exo/endo* selectivities of these cycloadditions.[2,3]

Reports on cycloadditions between iminodienophiles of glyoxylates and cyclopentadiene showed these reactions to be highly accelerated by the addition of a LA, due to the formation of an iminium cation complex that rapidly undergoes cycloaddition under mild conditions. The products obtained, 2-azabicyclo[2.2.1]hept-5-enes,[3] can be used as precursors of a large variety of compounds of chemical, biological and pharmaceutical interest, such as proline mimetic structures.[5] *N*-hydroxylimines (oximes) bearing electron-withdrawing groups, on both carbon and oxygen, have been used upon occasion as imino dienophiles.[6] Fleury and coworkers investigated cycloadditions of *O*-protected oxime derivatives (XYC=NOR) with cyclopentadiene to afford the corresponding adducts with low to moderate yields.[6a-c]. Nonetheless, aza-Diels-Alder reactions using non-*O*-functionalized oximes have never been reported in literature, resulting in an unknown behavior of the hydroxyl group bound to the nitrogen atom. The resulting *N*-hydroxyl-2-azabicycloalkenes would be an important and versatile group of synthons useful in the preparation of new pyrrolidinic derivatives.[5]

It is well known that LA often increase not only the rate of the Diels-Alder reactions but also their selectivity. Thus, we decided to investigate, in this work, the influence of several LA and their advantages/disadvantages relatively to BA in the aza-Diels-Alder reaction between

cyclopentadiene and methyl glyoxylate oxime (**1**) to afford the corresponding *exo*/*endo* adducts (Scheme 1).



Scheme 1. Retrosynthetic analysis of pyrrolidinic derivatives from cycloadductos of glyoxylate oxime **1** and cyclopentadiene

Results and discussion

Methyl glyoxylate oxime (**1**)[8a] was obtained by treatment of methyl 2-hydroxy-2-methoxyacetate (methyl hemiacetal of methyl glyoxylate)[7] with equimolar amounts of hydroxylamine hydrochloride, triethylamine and a catalytic amount of DMAP, in dry CH_2Cl_2 at room temperature.[8] The *E*-configuration of oxime **1** has been unambiguously assigned by X-ray crystallography (Figure 1).

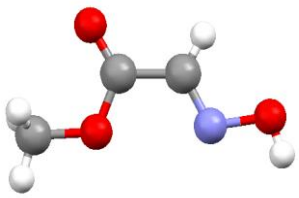
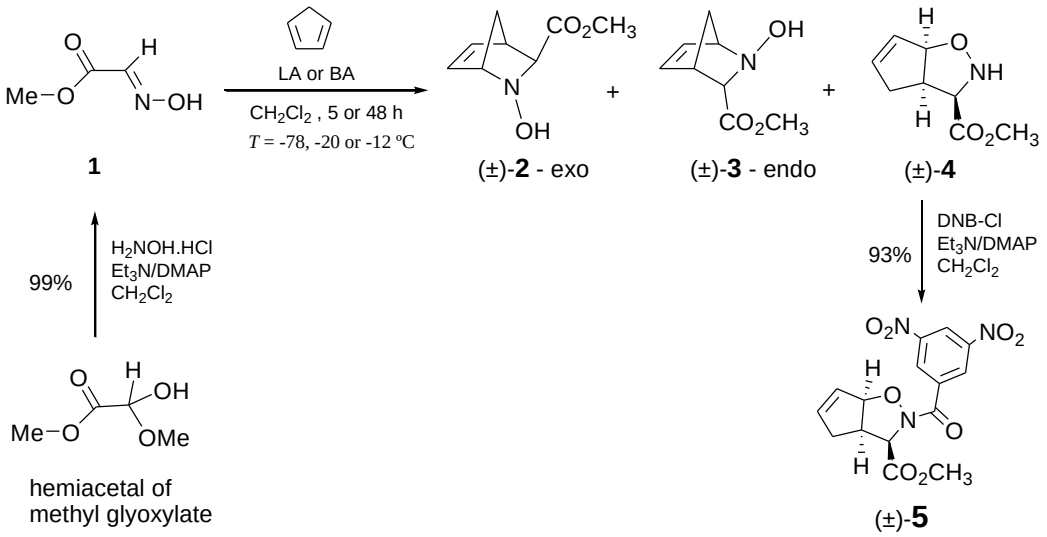


Figure 1. X-ray crystallographic structure of oxime **1**

Treatment of oxime **1** with freshly distilled cyclopentadiene (2 eq.) and acid (TFA, $BF_3.Et_2O$, $AlCl_3$, ZnI_2 or $HClO_4$) in CH_2Cl_2 under an argon atmosphere at different temperatures (-78ºC, -20ºC and -12 ºC) yielded the corresponding cycloadducts **2** and **3 (**aza-Diels-Alder reaction). A third adduct (**4)** was also obtained, probably *via* a 1,3-dipolar cycloaddition (Scheme 2).



Scheme 2. Products of cycloaddition between oxime **1** and CPD and 3,5-dinitrobenzoyl derivative of adduct **4**.

The products were isolated from the reaction mixture by chromatographic purification and identified by analytical and spectroscopic techniques.[9] Thus, the *endo*-configuration of cycloadduct **3** has been confirmed by X-ray crystallography (Figure 2).

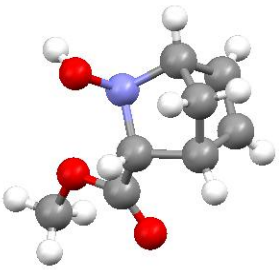


Figure 2. X-ray crystallographic structure of *endo* adduct **3**

The structure and stereochemistry of cycloadduct **4** were established not only in terms of its spectral data, but also based on the spectral data and X-ray diffraction studies of the corresponding 3,5-dinitrobenzoate derivative (±)-**5** (Figure 3). Furthermore, the ratio of adducts obtained, for each reaction, was also confirmed by GC (Table 1).

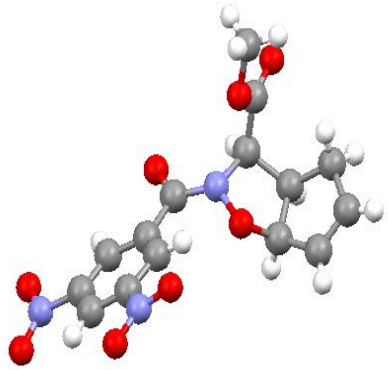


Figure 3. X-ray crystallographic structure of compound **5**

Checking the literature for 1,3-dipolar cycloadditions,[10] there are some reports on oximes undergoing 1,3-dipolar cycloadditions *via* the nitrone tautomer with alkenes (dipolarophiles) to afford isoxazolidines.[10i-k] The presence of a nitrogen atom within the isoxazolidine ring makes this heterocyclic moiety especially attractive for the synthesis of a number of alkaloids, and other nitrogen-containing natural products, and many products of potential interest.[10]

Concerning the effect of temperature on product ratio and yield, when Lewis acids were used as catalysts, little or no change was observed when the temperature was raised from -78 ºC to -12 ºC. With TFA, a significant modification in both, ratio of **2**/**4** and product yield occurred. When the reaction was performed at -20 ºC during 48 hours, and/or using excess of acid (2 eq.), a decrease in the yield was verified (all these experiments resulted in the formation of a large amount of a polymer, which may indicate some degradation of the products). However, in the cases where Lewis acids were used, the ratios of **2**/**3**/**4** remained unaltered, whereas the use of TFA and $HClO_4$ lead to a significant change in the ratio of **2**/**4**. Moreover, when these Bronsted acids were employed, the ratios of adducts (mainly **2**/**4**) depended on the experimental conditions, in a way that is not yet fully understood and is under further investigation.

In order to confirm whether adduct **4** resulted from Meisenheimer rearrangement[11] of **2** or **3** or was formed *via* an independent pathway, these adducts (**2** and **3**) were subjected to the same reaction conditions of the cycloaddition (except CPD) during 5 hours. No trace of **4** was detected in the reaction mixture, thus confirming the independent pathway hypothesis.

Generally, most oximes will undergo the normal Beckmann rearrangement in the presence of certain acids, including Lewis acids, or under neutral conditions to yield an amide or a mixture of amides, and a wide variety of examples are listed in reviews.[12] When we performed the referred

cycloaddition reactions, we were not able to isolate (or detect) any amide or nitrile or their adduct derivatives. This may be due to the *syn* geometry of the hydrogen atom (*E*-oxime) which does not allow the occurrence of the referred rearrangement; on the other hand, oxime isomerization is not probable at low temperatures.

Table 1. Cycloaddition reactions of cyclopentadiene (2 eq.) with oxime **1.** Yield (%) and ratio (%) of adducts obtained at different temperatures using different acids (1 eq.) in CH_2Cl_2

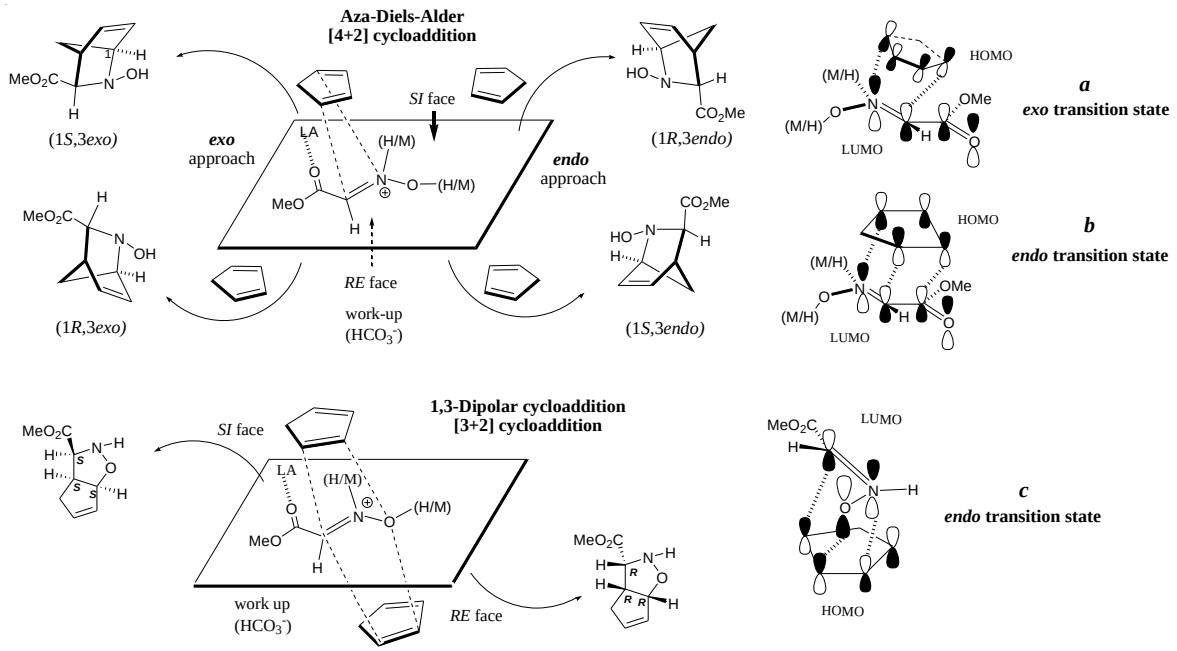
Entry	*T* (ºC)	Reaction time (h)	Acid	Yield (%)[a]	**2 / 3 / 4** Ratio (%)[b,c]
1	- 78	5	-	-	-/-/traces
2			TFA	26	32/15/53
3			BF_3	44	6/14/80
4			$AlCl_3$	32	0/42/58
5			ZnI_2	11	27/19/54
6	- 12	5	TFA	65	25/13/62
7			BF_3	48	5/18/77
8			$AlCl_3$	29	0/38/62
9			ZnI_2	12	26/21/53
10			$HClO_4$	60	28/21/51
11	-20	48	TFA	46	18/14/68
12			BF_3	24	5/18/77
13			$AlCl_3$	10	0/40/60
14			ZnI_2	9	26/22/52
15			$HClO_4$	52	40/18/42

[a] Isolated yield after aqueous work-up and trituration with methanol and filtration through of celite/silica .

[b]Adducts ratio was determinated by yield of pure, isolated compounds (flash chromatography), with recovery of oxime **1**.

[c]Adducts ratio was also determinated by GC (see supplementary data).

In an attempt to explain the stereochemical outcome of the 1,3-dipolar and aza-Diels-Alder reactions, we present in **Scheme 3** three models for the approach of diene/dienoplile and diene/1,3-dipole.



Scheme 3. The three possibilities of cycloaddition between oxime **1** and CPD. *a*- oxime **1** acts as a dienophile and CPD as diene, affording *exo* adduct; *b*- oxime **1** acts as a dienophile and CPD as diene, affording *endo* adduct; *c*- in this case, oxime **1** is the "four-electron component" and CPD acts as dipolarophile in the [3+2] cycloaddition reaction. After work up, deprotonation of the nitrogen atom takes place. Although in this scheme the catalyst (H or M = BF_3, $AlCl_3$ and ZnI_2) is arbitrarily coordinated to the nitrogen atom but there is the possibility of coordination to the oxygen atom.

The results described above are in general accord with the frontier molecular orbitals theory (FMO) of nitrone cycloadditions. 1,3-Dipolar cycloadditions, like the aza-Diels-Alder reaction, proceed through *exo* or *endo* transition states. [10g,h] The dominant primary interaction for the acid-activated cycloaddition of nitrone and cyclopentadiene involves the LUMO (dipole)-HOMO (dipolarophile) interaction.

The examination of the *endo* transition state of 1,3-dipolar cycloadditions reveals that the secondary orbital interactions between the methylene group of the diene and the ester group of the oxime (nitrone) are more important than the stereochemical interactions. Furthermore, in the close vicinity of the C=N bond of the nitrone derivative, the oxygen group ($O_{sp3/sp2p}$) exerts a larger steric hindrance than the (C_{sp2})-ester group, which favours this approach over its *exo* counterpart, thereby accounting for the formation of only racemic oxazabicycle **4**. The fact that

yield of **4** increases in the presence of acids in the order $BF_3 > AlCl_3 > ZnI_2 > TFA > HClO_4$ (see Table1), suggests two additional factors favouring the *endo* approach: i) the formation of an oxygen-metal complex and/or nitrogen-metal complex [=N(H)O-LA] which increase the orbital coefficient of nitrogen in the LUMO, increasing the secondary orbital interaction; ii) the probable formation of an ester-metal complex increases the orbital coefficient of carbon (of the C=N group) in the LUMO, increasing the primary orbital interaction.

In what concerns the aza-Diels-Alder reaction, it is more difficult to suggest a hypothesis but some plausible considerations may be taken into account to offer a rationale for the observed results:

* When Bronsted acids (TFA, $HClO_4$) and ZnI_2 (bulkier Lewis acid) were used as catalysts, the proportion of the *exo*-adduct was slightly superior than that of the *endo* one; This observation suggests that in the close vicinity of the C=N bond of the nitrone derivative, the oxygen group (O_{sp3}: OH and O-Zn complex) exerts a larger steric hindrance than the (C_{sp2})-ester group. Consequently, in order to minimize stereochemical interaction in the transition state between the methylene group of the diene and the oxygen of the nitrone (O-N=C), the *exo* approach diene-dienophile must occur in more extension than the *endo* approach.

* When BF_3 was used as Lewis acid, the *endo/exo* ratio of the adducts increased and with $AlCl_3$ only *endo*-adduct was obtained. These facts suggest that formation of the nitrone-metal complex and ester-metal complex increases the orbital coefficients of nitrone in the LUMO, increasing the primary and secondary orbital interactions, respectively.

The configuration of the nitrogen atom in the final adduct is irrelevant, since it exists as a tertiary oxyamine, after workup, capable of undergoing inversion of the lone pair of electrons to achieve the most stable configuration.

Conclusions

In conclusion, we have shown that glyoxylate oximes can act either as dienophiles or as 1,3-dipoles when reacting with 1,3-dienes, giving rise to the corresponding cycloadducts by independent concerted mechanisms. Both reactions occur by acid-mediated catalysis. According to the results obtained, the 1,3-dipolar cycloaddition seems to be kinetically more favourable. Further developments of the asymmetric cycloadditions between glyoxylate oximes and 1,3-dienes are in progress in our laboratory.

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9. (a) Crystallographic data for the structures in this paper, have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC6891 (compound **1**), CCDC689192 (compound **3**) and CCDC689200 (compound **5**); (b) Analysis data of compounds: **(±)-Methyl (1*R*,4*R*,5*R*)-(2-ox-3-azabicyclo[3.3.0]oct-7-ene)-4-carboxylate** (**4**): ^{1}H NMR (300 MHz, $CDCl_3$): 6.10-6.07 (m, 1H, 8-H), 5.62 (dt, J_d = 8.1 Hz, J_t = 2.2 Hz, 1H, 7-H), 5.43 (d, J = 6.6 Hz, 1H, 1-H), 5.38 (br s, 1 H, exch. D_2O, NH), 4.00 (dd, J_1 = 12.4 Hz, J_2 = 8.4 Hz, 1H, 4-H), 3.78 (s, 3H, OMe), 3.38 (ddt, J_t = 8.4 Hz, J_{d1} = 6.6 Hz, J_{d2} = 2.2 Hz, 1H, 5-H), 2.49 (dd, J = 18.2 Hz, J = 8.1 Hz, 1H, 6_{syn}-H), 2.09 (dquint, J_d = 18.2 Hz, J_{quint} = 2.2 Hz, 1H, 6_{anti}-H); ^{13}C NMR (75 MHz, $CDCl_3$): 169.8 (COO), 137.7 (C8), 127.9 (C7), 91.9 (C1), 67.2 (C4), 52.0 (MeO), 45.9 (C5), 34.5 (C6); ESI-MS: calculated for $[C_8H_{11}NO_3 + H]^+$ (M + H^+) 170.18, found 170.47. Anal. calcd. for $C_8H_{11}NO_3$: C 56.80, H 6.55, N 8.28; found: C 56.75, H 6.59, N 8.25. **(±)-Methyl [(3-*exo*)-2-hydroxy-2-azabicyclo[2.2.1]hept-5-ene]-3-carboxylate** (**2**): ^{1}H NMR (300 MHz, $CDCl_3$): 6.66 (br s, 1H, exch. D_2O, OH), 6.68-6.64 (m, 1H, 5-H), 6.34 (dd, J = 5.7 Hz, J = 2.1 Hz, 1 H, 6-H), 4.29 (br s, 1H, 1-H), 3.76 (s, 3H, OMe), 3.16 (br s, 1H, 4-H), 2.89 (d, J = 2.1 Hz, 1H, 3_{endo}-H), 1.82 (d, J = 9.3 Hz, 1 H, 7_{syn}-H), 1.50 (dd, J = 9.3 Hz, J = 1.5 Hz, 1 H, 7_{anti}-H). ^{13}C NMR (75 MHz, $CDCl_3$): 172.9 (COO), 138.1 (C6), 133.1 (C5), 70.4 (C3), 69.5 (C4), 52.2 (C1), 47.6 ($O\underline{C}H_3$) 45.2 (C7); ESI-MS: calculated for $[C_8H_{11}NO_3 + H]^+$ (M + H^+) 170.18, found 170.53. Anal. calcd. for $C_8H_{11}NO_3$: C 56.80, H 6.55, N 8.28; found: C 56.76, H 6.60, N 8.26. **(±)-Methyl [(3-*endo*)-2-hydroxy-2-azabicyclo[2.2.1]hept-5-ene]-3-carboxylate** (**3**): M.p. 102-105 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): 8.13 (br s, 1H, exch. D_2O, OH), 6.24 (br s, 2H, 5-H + 6-H), 4.11 (br s, 1H, 1-H), 3.76 (d, J = 3.6 Hz, 1H, 3_{exo}-H), 3.66 (s, 3H, OMe), 3.33 (br s, 1 H, 4-H), 2.22 (d, J = 8.7 Hz, 1H, 7_{syn}-H), 1.74 (d, J = 8.7 Hz, 1H, 7_{anti}-H). ^{13}C NMR (75 MHz, $CDCl_3$): 172.1 (COO), 139.5 (C5), 134.3 (C6), 72.9 (C1), 71.2 (C3), 51.9 ($O\underline{C}H_3$), 46.3 (C7), 45.3 (C4); ESI-MS: calculated for $[C_8H_{11}NO_3 + H]^+$ (M + H^+) 170.18, found 170.67. Anal. calcd. for $C_8H_{11}NO_3$: C 56.80, H 6.55, N 8.28; found: C 56.77, H 6.57, N 8.26. **(±)-Methyl (1*R*,4*R*,5*R*)-[2-(3,5-**

dinitrobenzoyl)-2-ox-3-azabicyclo[3.3.0]oct-7-ene]-4-carboxylate (**5**): M.p. 60-62 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): 9.16 (t, J_{meta} = 2.1 Hz, 1H, 4'-H), 9.07 (d, J_{meta} = 2.1 Hz, 2H, 2'-H + 6'-H), 6.21-6.17 (m, 1 H, 8-H), 5.84 (dt, J_d = 7.8 Hz, J_t = 2.2 Hz, 1H, 7-H), 5.28 (dd, J = 6.7 Hz, J =1.8 Hz, 1H, 1-H), 5.22 (d, J = 9.9 Hz, 1H, 4-H), 3.84 (s, 3H, OMe), 3.77-3.66 (m, 1H, 5-H), 2.67 (ddt, J_t = 18.0 Hz, J_{d1} = 8.7 Hz, J_{d2} = 2.2 Hz, 1H, 6_{syn}-H), 2.44 (ddt, J = 18.0 Hz, J = 2.4 Hz, J = 2.2 Hz, 1H, 6_{anti}-H). Anal. calcd. for $C_{15}H_{13}N_3O_8$: C 49.59, H 3.61, N 11.57; found: C 49.53, H 3.70, N 11.52. **Methyl glyoxylate oxime** (**1**): see supplementary data and reference 8a.

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