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Acid-catalyzed aza-Diels–Alder versus 1,3-dipolar cycloadditions of methyl glyoxylate oxime with cyclopentadiene

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ABSTRACT

The acid-catalyzed 1,4- and 1,3-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-oxa-3-azabicyclo[3.3.0]oct-7-ene)-4-carboxylate (**4**), whose formation can be explained by a 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 cycloadditions.

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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 co-workers 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 the literature, resulting in an unknown behaviour 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 LAs 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 LAs and their advantages/disadvantages relatively to BAs in the aza-Diels–Alder reaction between cyclopentadiene and methyl glyoxylate oxime (**1**) to afford the corresponding *exo*/*endo* adducts (Scheme 1).

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

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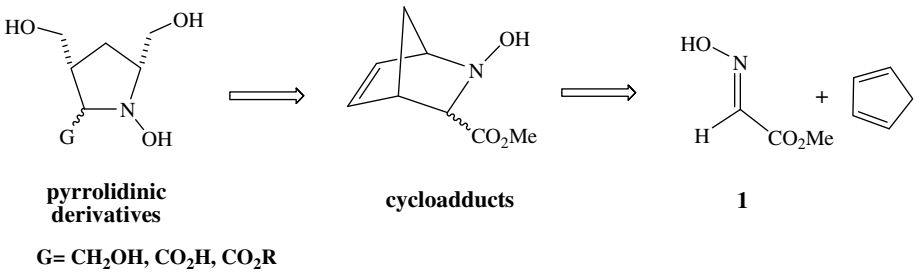


Scheme 1. Retrosynthetic analysis of pyrrolidinic derivatives from cycloadducts of glyoxylate oxime **1** and cyclopentadiene.

dry CH_2Cl_2 at room temperature.[8] The *E*-configuration of oxime **1** has been unambiguously assigned by X-ray crystallography (Fig. 1).

Treatment of oxime **1** with freshly distilled cyclopentadiene (2 equiv) and acid (TFA, $BF_3{\cdot}Et_2O$, $AlCl_3$, ZnI_2 or $HClO_4$) in CH_2Cl_2 under an argon atmosphere at different temperatures (−78 °C, −20 °C and −12 °C) yielded a mixture of the *exo* and *endo* formally [4+2] aza-Diels–Alder cycloadducts **2** and **3,** together with the formally [3+2] cycloadduct **4** (Scheme 2).

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 (Fig. 2).

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** (Fig. 3). Furthermore, the ratio of adducts obtained, for each reaction, was also confirmed by GC (Table 1).

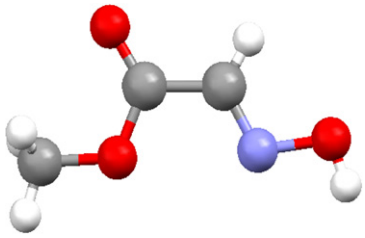


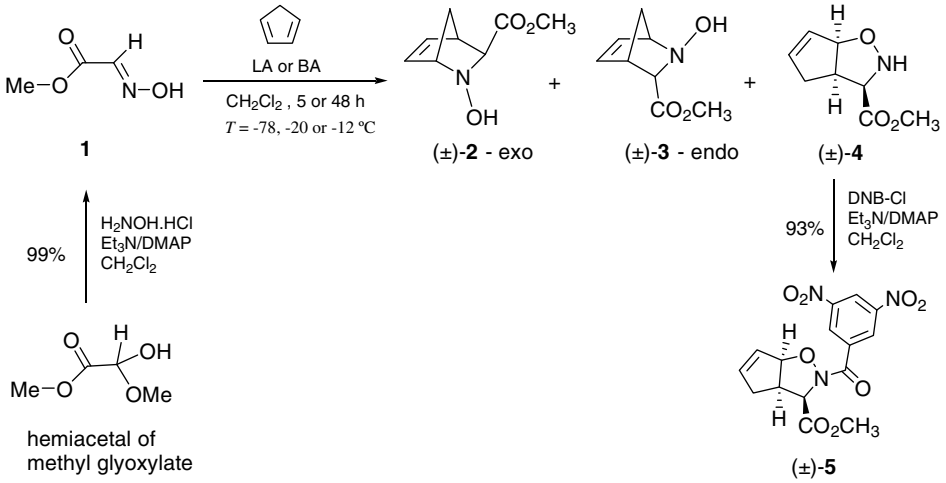
Figure 1. X-ray crystallographic structure of oxime **1**.

On 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.[10h–j] Nonetheless, 1,3-polar cycloadditions using non-O-functionalized oximes have never been reported in literature, resulting in an unknown behaviour of the hydroxyl group bound to the nitrogen atom. The presence of a nitrogen atom within the resulting 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 °C to −12 °C. However, with TFA, a significant modification in both ratio of **2**/**4** and product yield occurred. When the reaction was performed at −20 °C during 48 h, and/or using excess of acid (2 equiv), 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). The dependence of the ratios of adducts (mainly **2**/**4**), when using Bronsted acids, on the experimental conditions 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 Cp) during 5 h. No trace of **4** was detected in the reaction mixture, thus confirming the independent pathway hypothesis.

Generally, most oximes 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



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

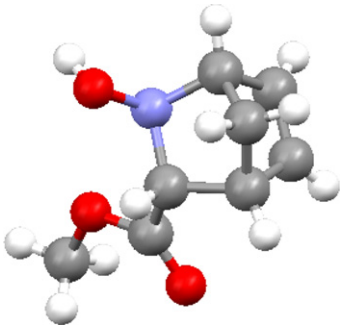


Figure 2. X-ray crystallographic structure of *endo* adduct **3**.

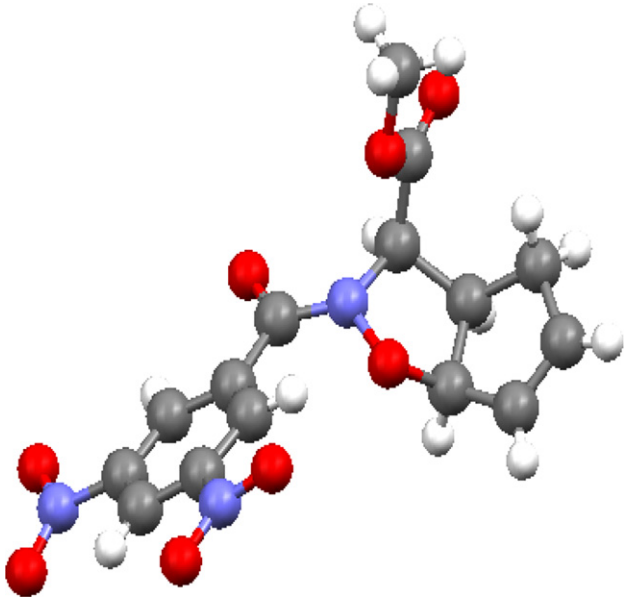


Figure 3. X-ray crystallographic structure of compound **5**.

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.

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.

Although in this scheme the catalyst (H or M = BF_3, $AlCl_3$ and ZnI_2) is arbitrarily coordinated to the nitrogen atom, there is the possibility of coordination to the oxygen atom. Besides the cycloadducts **2**/**3**/**4**, no more isomers have been obtained.

For the interpretation of the experimental results, at least in a qualitative way, some quantum chemical calculations have been carried out.

Calculations were carried out with DFT (density functional theory) employing B3LYP functional. B3LYP combines the three-coefficient dependent hybrid functional for the exchange energy proposed by Becke (B3) with the correlation functional proposed by Lee, Yang and Parr (LYP).[13] 6-31G(d) Pople's basis set were used for all elements except iodine, for which the *effective core potential* LANL2DZ was used.[14] All calculations were carried out with GAUSSIAN03 program.[15]

Table 1
Cycloaddition reactions of cyclopentadiene (2 equiv) with oxime **1**

Entry	*T* (°C)	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

Yield (%) and ratio (%) of adducts obtained at different temperatures using different acids (1 equiv) in CH_2Cl_2.

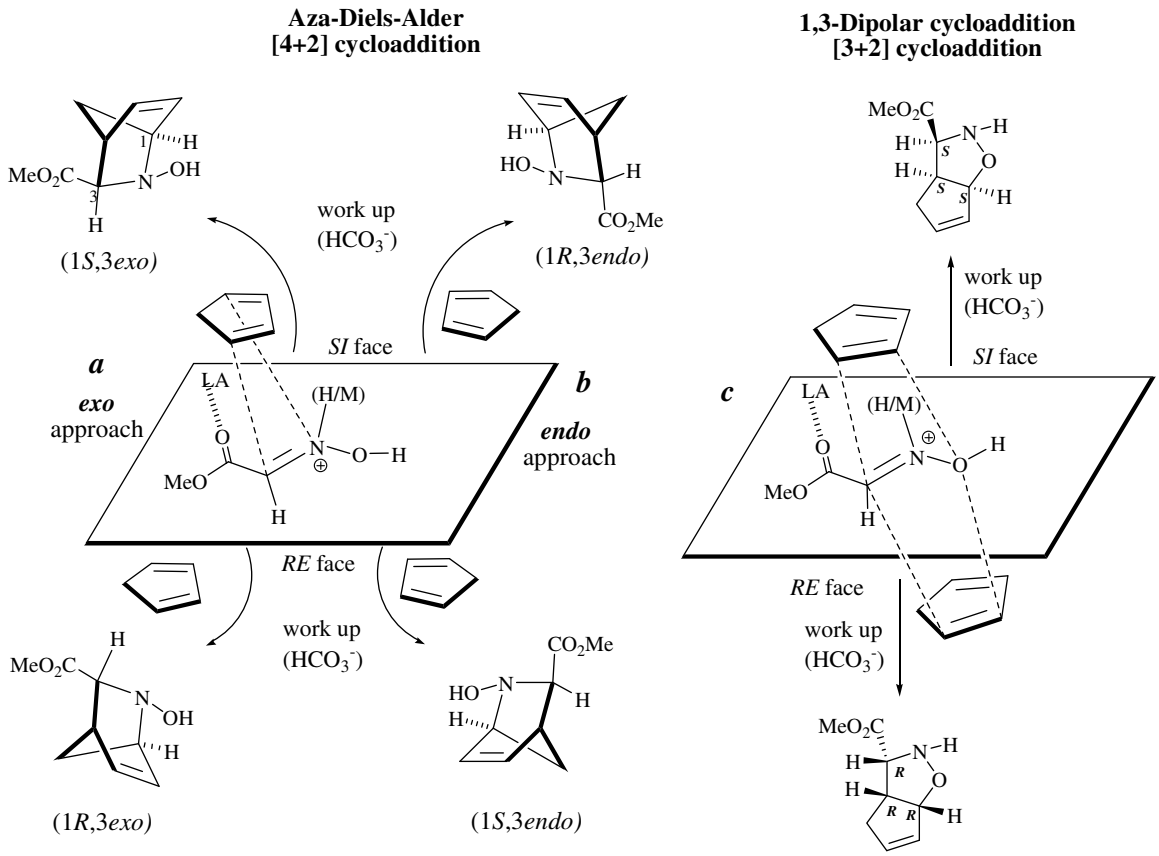
[a] Isolated yield after aqueous work-up, trituration with methanol and filtration through a pad of Celite/silica.

[b] Adduct ratios determined by yield of pure, isolated compounds (flash chromatography), with recovery of oxime **1**.

[c] Adduct ratios determined by GC (see Supplementary data).

Recent studies devoted to Diels–Alder and 1,3-dipolar cycloaddition reactions have shown that the global indexes defined in the context of DFT theory are a powerful tool to understand the behaviour of polar cycloadditions[16] or highly asynchronous concerted cycloadditions.[3b] The difference of global electrophilicity between the reagent pair, $\Delta\omega$, can be used to predict the polar character of the process and thereby the feasibility of the cycloaddition. The global electrophilicity index, ω, has been defined by Parr et al.[17] by the following simple expression: $\omega = (\mu^2/2\eta)$, in terms of the electronic chemical potential, μ, and the chemical hardness, η. Both quantities may be approached in terms of the one electron energies of the frontier molecular orbital HOMO and LUMO, ε_H and ε_L, as $\mu \approx (\varepsilon_H + \varepsilon_L)/2$ and $\eta \approx (\varepsilon_L + \varepsilon_H)$, respectively.[18] Table 2 shows the calculated parameters for the reactants **1** and Cp, and for the intermolecular complexes involved in the cycloadditions catalyzed by BA and LA; several interesting conclusions can be drawn from this table. First, it is worth noting that protonation (corresponding to BA) or coordination (corresponding to LA) to the carbonyl oxygen or oxime nitrogen atoms of **1** gives rise to complexes of similar electron energies. Therefore, these complexes can be in equilibrium, opening the reactive channels for the formation of the formally [4+2] and [3+2] cycloadducts. The low electrophilicity of **1** (1.77 eV), which leads to a value of only 0.94 eV for $\Delta\omega$, is the reason for the high temperature required to perform the uncatalyzed reaction. In contrast, protonation of **1** or formation of LA complexes increases considerably the electrophilicity of this reactant, which increases $\Delta\omega$ values and, therefore, favours the polar character of the process and the feasibility of the cycloaddition. The increment in electrophilicity is much more noticeable for BA than for LA, which is in general agreement with the higher yield obtained with BA.

Regarding the LAs, $AlCl_3$ and ZnI_2 are able to form an intermolecular complex in which the metal is coordinated simultaneously to the carbonyl oxygen and the oxime nitrogen atom; this may be due to their large size. However, there is a clear difference between these two LAs: only in the case of ZnI_2, this dicoordinated complex is clearly more favourable than the other two possible monocoordinated complexes. This fact makes it possible that ZnI_2 activates electrophilically the α and β positions of **1,** simultaneously. This behaviour is in agreement with the ratio of the 1,3-cycloaddition



Scheme 3. Cycloaddition of oxime **1** and Cp. (a) oxime **1** acts as a dienophile and Cp as diene, affording *exo* adduct; (b) oxime **1** acts as a dienophile and Cp as diene, affording *endo* adduct; (c) oxime **1** is the 'four-electron component' and Cp acts as polarophile in the [4+2] cycloaddition reaction. During work-up, deprotonation of the nitrogen atom takes place.

Table 2
Computed parameters for **1**, Cp, protonated **1** and intermolecular complexes formed between **1** and LA: electron energy (a.u.), HOMO and LUMO energies (a.u.), electronic chemical potential (a.u.), chemical hardness (a.u.) and electrophilicity (eV)

	E	ε_{HOMO}	ε_{LUMO}	μ	η	ω
1	−397.68341	−0.27938	−0.05897	−0.1692	0.2204	1.77
Cp	−194.10106	−0.21153	−0.00987	−0.1107	0.2017	0.83
1–H^+(N)	−398.01179	−0.48789	−0.30242	−0.3952	0.1855	11.46
1–H^+(O)	−398.00985	−0.47199	−0.28373	−0.3779	0.1883	10.32
1–BF_3(N)	−722.25781	−0.30706	−0.09736	−0.2022	0.2097	2.65
1–BF_3(O)	−722.25220	−0.30535	−0.09879	−0.2021	0.2066	2.69
1–$AlCl_3$(N)	−2020.96315	−0.30491	−0.13038	−0.2176	0.1745	3.69
1–$AlCl_3$(O)	−2020.96756	−0.28674	−0.12511	−0.2059	0.1616	3.57
1–$AlCl_3$(NO)[a]	−2020.96557	−0.27980	−0.13705	−0.2084	0.1428	4.13
1–ZnI_2(N)	−2199.69821	−0.24201	−0.13127	−0.1866	0.1107	4.28
1–ZnI_2(O)	−2199.68703	−0.24171	−0.11373	−0.1777	0.1280	3.36
1–ZnI_2(NO)[a]	−2199.70691	−0.23129	−0.13284	−0.1821	0.0985	4.58

[a] Metal is coordinated simultaneously to the carbonyl oxygen and the oxime nitrogen atom.

to the aza-Diels–Alder products observed experimentally, as only with ZnI_2 as catalyst, a ratio of approximately 1:1 is obtained for all the temperatures. For BF_3, this ratio is the highest (3–4:1), so 1,3-polar cycloaddition is clearly favoured. Therefore, it seems that a more favourable coordination with the oxime's nitrogen atom favours this cycloaddition. Concerning this ratio of adducts, $AlCl_3$ (where the coordination with the carbonyl oxygen atom is the most favourable) occupies an intermediate position between the LAs.

The analysis of the *endo*/*exo* selectivity would require a deeper computational study, which implies that all the transition states must be optimized for all the possible catalyzed reactions. However, some conclusions can be inferred from the geometries of the intermolecular complexes. So, while the bulky $AlCl_3$ catalyst affords total *endo* selectivity due to the hindrance of the *exo* approach, the smaller BF_3 allows obtaining some amount of *exo* cycloadduct. On the other hand, the ZnI_2 complex yields a reverse *exo* selectivity as a consequence of the double coordination (N,O) that disfavours the *endo* approach of Cp to the N=C bond. Nevertheless, the energies and geometries of the transition states should be known in order to better explain the observed selectivities.

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 highly asynchronous 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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Supplementary data

This material contains the synthetic methods and characterization data of all compounds (^{1}H NMR, ^{13}C NMR, DEPT, COSY and HMQC spectra, chromatographic data and X-ray data). Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.07.110.

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9. (a) Crystallographic data for the structures in this Letter, have been deposited at the Cambridge Crystallographic Data Centre as Supplementary Publication Numbers CCDC 689191 (compound **1**), CCDC 689192 (compound **3**) and CCDC689200 (compound **5**); (b) Analysis data of compounds: *(±)-Methyl (1R,4R,5R)-(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, 1H, 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 (OCH_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**): Mp 102–105 °C; ^{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, 1H, 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 (OCH_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 (1R,4R,5R)-[2-(3,5-dinitrobenzoyl)-2-ox-3-azabicyclo[3.3.0]oct-7-ene]-4-carboxylate* (**5**): Mp 60–62 °C; ^{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, 1H, 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 Ref. 8a.
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