JOC Article

Synthesis, Structure, and *E*−*Z* Isomerization of *β*-(Hetero)aryl-α-nitro-α,*β*-enals

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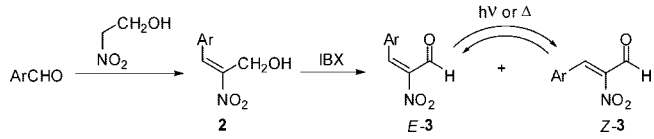
Received December 21, 2007



The first general methodology for the gram-scale preparation of previously overlooked *β*-(hetero)aryl-α-nitro-α,*β*-enals (**3**) is reported. Condensation of (hetero)aromatic aldehydes with 2-nitroethanol gave the *E*-isomers of uncommon *β*-(hetero)aryl-α-hydroxymethyl-α,*β*-unsatured-nitroalkenes (**2**), as determined by NOE and X-ray studies. α-Nitro-α,*β*-enals **3** were subsequently obtained by hypervalent iodine oxidation of **2** as *E*−*Z*-mixtures in solid form. They showed varied stability and solvent-dependent thermal-promoted and photopromoted *E*−*Z* interconversion. Starting with furfural, experimental conditions were developed to prepare the corresponding nitroenal **3a** enriched in either the *E* or the *Z* isomer: *E*-**3a**/*Z*-**3a** ≈ 90/10 and 20/80, respectively. In contrast with other structurally related compounds, nitroenals **3** have their (hetero)aryl-vinyl unit and their formyl and nitro groups all in a planar arrangement, both in solid form and in solution; accordingly, they are colored compounds with predicted high dipole moments. As deduced from solution-NMR and X-ray data, the C═C and the C═O double bonds in **3** are exclusively *s-cis*-oriented; this disposition corresponds in fact to the DFT-computed most stable conformer.

Introduction

β-(Hetero)aryl-α-nitro-α,*β*-enals (ArCH═C(NO$_2$)CHO, **3**) densely combine a (hetero)aromatic ring, a C═C double bond, a nitro group and a formyl group to form an extended *π* system, where three functionalities of demonstrated utility in synthesis, namely, a (hetero)arylvinyl unit, an α,*β*-unsaturated nitroalkene, and an α,*β*-enal, intimately coexist sharing a common double bond. Attractive as this combination of structural and functional features could be, *β*-(hetero)aryl-α-nitro-α,*β*-enals have nevertheless been essentially overlooked and their properties and synthetic potential unexplored. In fact, at the outset of our study, only three *β*-furyl-analogues (**3a**, **3i**, and **3j**)[1] and an azulene derivative (**3k**)[2] had been prepared, and a *β*-aryl-α-nitro-α,*β*-enal **3*l*** had been named in a patent[3] (see below); also, there were no precedents for the use of *β*-(hetero)aryl-α-nitro-α,*β*-enals (**3**) in synthesis.

Before our work in the area, procedures to prepare *β*-(hetero)aryl-α-nitro-α,*β*-enals **3** were limited to those reported for **3a** and **3i**−**k**. Preparation of **3a, 3i**, and **3j** involved N_2O_4-promoted nitration of the corresponding *β*-furyl-α,*β*-enal precursors: 3-(2-furyl)propenal (**7a**) for both **3a** and **3i**, and 3-(5-methyl-2-furyl)propenal (**7i**) for **3j**. Nitration of **7a** took place at the formyl α-position to give **3a** in 17% yield,[1a] and concurrently, to some extent, in the furane ring, thus also giving dinitrocompound **3i.**[1b] Blockade of the furyl-ring most-activated C5 position with a methyl group, as in **7i**, allowed the nitration to be more selective, rendering **3j** in 53% yield.[1c] In turn, **3k** was prepared in 36% yield by condensation of guaiazulene (5-

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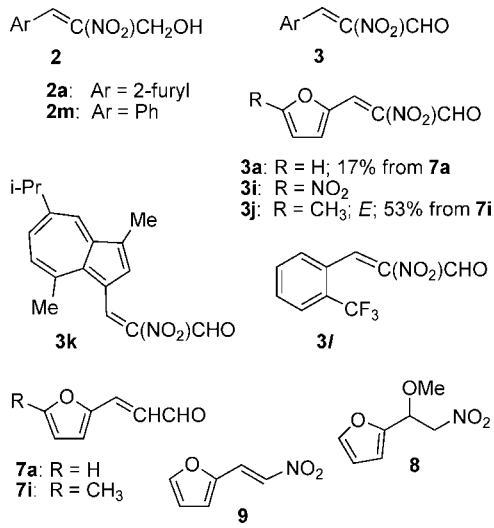
(1) (a) Sitkin, A. I.; Klimenko, V. I.; Fridman, A. L. *Zh. Org. Khim.* **1975**, *11*, 2452. (b) Klimenko, V. I.; Sitkin, A. I.; Fridman, A. L. *Vses. Nauchn. Konf. Khim. Tekhnol. Furanovykh Soedin.*, [*Tezisy Dokl.*], *3rd, Riga, USSR* **1978**, 116. (c) Sitkin, A. I.; Klimenko, V. I.; Fridman, A. L. *Khim. Geterotsikl. Soedin.* **1977**, 1604.

(2) Kirby, E. C.; Reid, D. H. *J. Chem. Soc.* **1961**, 3579.

(3) Goldmann, S. Bechem, M. Ger. Offen. DE 4222770 A1, 1994. Neither details nor references regarding preparation, properties, and use of **3*l***, are explicitly given.

10.1021/jo702731b CCC: $40.75 © 2008 American Chemical Society
Published on Web 04/23/2008

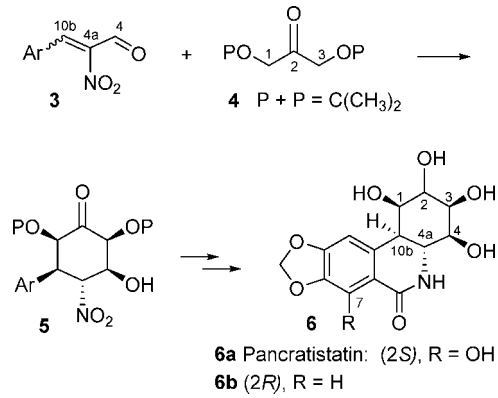


isopropyl-3,8-dimethylazulene) with nitromalondialdehyde in the presence of perchloric acid.[2]

Looking for general, safer (N_2O_4,[4] $HClO_4$, and nitromalondialdehyde[5] free), more selective, and higher yielding syntheses of enals **3**, we judged 3-(hetero)aryl-2-nitroprop-2-en-1-ols **2** to be suitable precursors (see structures above). The hydroxyl group in **2**, being allylic, should be easily oxidized under mild conditions, thus minimizing chances for side reactions and presumably facilitating the isolation of the resulting nitroenals **3**.

Unexpectedly, we also found compounds **2** to be rare, with only two examples described in the literature: **2a** (Ar = 2-furyl) in an article in 1958,[6] and **2m** (Ar = Ph) in a patent in 1982[7a] (see structure above). Compound **2a** was obtained as a byproduct when 2-(1-methoxy-2-nitroethyl)furan (**8**), contaminated with 2-(2-nitrovinyl)furan (**9**), was heated with 33% HCHO−MeOH. This result was suggestive of the preparation of intermediates **2** by hydroxymethylation of nitrovinylarenes, e.g., **2a** from **9**, through a Morita−Baylis−Hillman (MBH) reaction. However, in spite of the fact that the MBH reaction had been widely studied[8] we found no single report of its application to nitrovinylarenes. After we had prepared compounds **2** (and nitroenals **3** there from) by condensation of aldehydes with nitroethanol (vide infra) and while proceeding to patent-protection,[9] it was demonstrated that the synthesis of **2** by α-hydroxymethylation of conjugated nitroalkenes via the Morita−Baylis−Hillman reaction was indeed feasible.[10]

SCHEME 1. First Reported Use of β-(Hetero)aryl-α-nitro-α,β-enals (3) in Synthesis: Total Synthesis of *rac*-7-Deoxy-2-*epi*-Pancratistatin Tetraacetate (*rac*-6b)[a]



[a] See refs 9 and 12.

Our interest in α-nitroenals **3** originated from the need to efficiently prepare aminocyclitol units. In particular, we judged **3** potential annulation partners of protected dihydroxyacetone **4** for the one-step formation of nitrocyclitols **5**, on their way to the antitumoral natural product pancratistatin (**6a**) and their analogues (Scheme 1).[11] The implementation of this annulation, and its successful application to a short, one-batch, 0.8 g scale synthesis of *rac*-7-deoxy-2-*epi*-pancratistatin tetraacetate (*rac*-**6b**) clearly established, for the first time, that β-(hetero)aryl-α-nitro-α,β-enals **3** are useful building blocks in organic synthesis.[12] Further study of the properties and the value of this type of compounds by the scientific community requires them to be readily available. We herein satisfy such a requisite by disclosing procedures for the gram-scale preparation of **3** from commercially available (hetero)aromatic aldehydes. These procedures additionally supply the rare and interesting 2-nitroprop-2-en-1-ols **2**. We also report on the particular structural characteristics of **2** and **3**, as deduced from NMR, X-ray, and UV data and supported by theoretical calculations, as well as on the stability and *E*/*Z* interconversion of nitroenals **3**.

Results and Discussion

Synthesis of β-(Hetero)aryl-α-nitro-α,β-enals (3). Having selected 2-nitropropenols **2** as precursors of nitroenals **3**, we decided to explore, in light of the literature precedents depicted above, the preparation of **2** by condensation of 2-nitroethanol with commercially available (hetero)aromatic aldehydes.[7b] We first looked for conditions where the addition of 2-nitroethanol to the aldehyde could concurrently take place with the dehydration of the diol so formed, to directly render the desired 2-nitropropenols **2**. In our hands, use of aluminiumphosphate oxynitrides (ALPON)[13] did not induce any transformation of 5-methoxypiperonal when heated with 2-nitroethanol (1equiv)

(4) Nitrogen tetroxide (or dinitrogen tetroxide, N_2O_4) is a powerful, highly toxic, and corrosive oxidizer: http://encyclopedia.airliquide.com/sds/en/090_AL_EN.pdf.

(5) (a) Nitromalonaldehyde itself is unstable; its sodium salt, widely used as a synthetic equivalent, is, in crude form, impact-sensitive and thermally unstable, and should be handled as a potentially explosive material: Fanta, P. E.; Stein, R. A. *Chem. Rev.* **1960**, *60*, 261. (b) For a new synthetic equivalent of nitromalonaldehyde, see: Nishiwaki, N.; Ogihara, T.; Takami, T.; Tamura, M.; Ariga, M. *J. Org. Chem.* **2004**, *69*, 8382.

(6) Saikachi, H.; Hoshida, H. *Yakugaku Zasshi* **1958**, *78*, 917–20; CAN 52: 113630, AN 1958:113630.

(7) (a) Eian, G. L.; Trend, J. E. EP Patent 46083, 1982. (b) In ref 7a, nitrocinnamylalcohol (2-nitro-3-phenylprop-2-en-1-ol, **2m**) was prepared from benzaldehyde and 2-nitroethanol; neither isomer configuration nor yields are given for **2m**.

(8) For reviews, see: (a) Basavaiah, D. Rao, A. J. Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811. (b) Ciganek, E. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1997; Vol. 51, p 201.

(9) Alonso Alonso, R.; Ozores Viturro, L.; Cagide Fagin, F.; Ortiz Lara, J. C. ES 2245603 A1; priority date June, 25th, 2004; WO 2006003227.

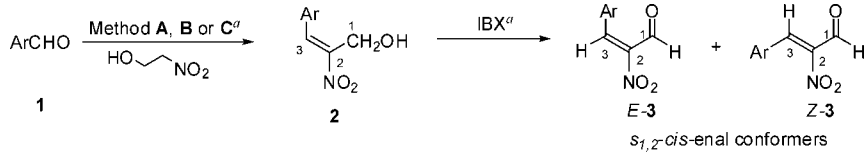
(10) (a) Rastogi, N.; Namboothiri, I. N. N.; Cojocaru, M. *Tetrahedron Lett.* **2004**, *45*, 4745. (b) Mohan, R.; Rastogi, N.; Namboothiri, I. N. N.; Mobin, S. M.; Panda, D. *Bioorg. Med. Chem.* **2006**, *14*, 8073.

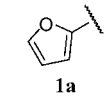
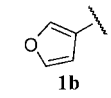
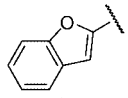
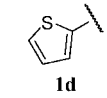
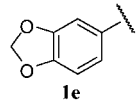
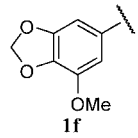
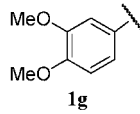
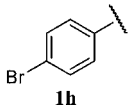
(11) Pancratistatins comprise a family of antitumoral natural products; for the most recent reviews, see: (a) Chapleur, Y.; Chretien, F.; Ahmed, S. I.; Khaldi, M. *Curr. Org. Synth.* **2006**, *3*, 341. (b) Rinner, U.; Hudlicky, T. *Synlett* **2005**, 365. See also: (c) Wilson, R. M.; Danishefsky, S. J. *Chem. Soc. Rev.* **2007**, *36*, 1207. For the pharmacological potential and biological mode of action of pancratistatins, see: (d) Pandey, S.; Kekre, N.; Naderi, J.; McNulty, J. *Artif. Cells Blood Substit. Immobil. Biotechnol.* **2005**, *33*, 279. (e) McLachlan, A.; Kekre, N.; McNulty, J.; Pandey, S. *Apoptosis* **2005**, *10*, 619. (f) Kekre, N.; Griffin, C.; McNulty, J.; Pandey, S. *Cancer Chemother. Pharmacol.* **2005**, *56*, 29.

(12) Ortiz, J. C.; Ozores, L.; Cagide-Fagin, F.; Alonso, R. *Chem. Commun.* **2006**, 4239.

(13) Climent, M. J.; Corma, A.; Guil-Lopez, R.; Iborra, S.; Primo, J. *Catal. Lett.* **1999**, *59*, 33.

TABLE 1. Two-Step Synthesis of *β*-(Hetero)aryl-α-nitro-α,*β*-enals (3) from (Hetero)aromatic Aldehydes (1) through 2-Nitroprop-2-en-1-ol Intermediates 2[a]



Entry	Ar 1	Method[a] g,[b] h,[c] 2 %[d]	3 %,[d] E/Z	*E*-3 H: δ,[e] m,[f] $J_{H,H'}$,[g]	*Z*-3 H: δ,[e] m,[f] $J_{H,H'}$,[g]
1	 **1a**	**A** 0.50 g, 3 h, **2a** 55% **B** 5.86 g, 9 h, **2a** 94%	**3a** 82%, 2/1	**H3:** 8.37, d, 2.6_{H1} **H1:** 10.40, d, 2.6_{H3}	**H3**: 7.53, s **H1**: 9.83, s
2	 **1b**	**A** 0.15 g, 0.6 h, **2b** 26% **B** 1.08 g, 9 h, **2b** 91%	**3b** 96%, 1.8/1	**H3**: 8.31, d, 2.4_{H1} **H1**: 10.33, d, 2.4_{H3}	**H3**: 7.50, s **H1**: 9.76, s
3	 **1c**	**B** 0.20 g, 9 h, **2c** 63%	**3c** 95%, ≈1/1	**H3**: 8.36, d, 1.5_{H1} **H1**:10.47, d, 1.5_{H3}	**H3**: 8.51, s **H1**: 9.69, s
4	 **1d**	**B** 0.48 g, 3 h, **2d** 19%	**3d** 80%, 6/1	**H3**: 8.73, d, 2.5_{H1} **H1**: 10.40, d, 2.5_{H3}	**H3**: 7.9-8.1[h] **H1**: 10.07, s
5	 **1e**	**A** 3 g, 1 h, **2e** 43% (57%) **C** 1 g, **2e** 52%	**3e** 99%,[i] ≈1/1	**H3**: 8.33, d, 2.4_{H1} **H1**: 10.24, d, 2.4_{H3}	**H3**: 7.23, s **H1**: 9.50, s
6[j]	 **1f**	**A**[j] 3.5 g, 0.5 h, **2f** 18% (84%)	**3f** 92%,[i] ≈1/1	**H3**: 8.30, d, 2.4_{H1} **H1**: 10.24, d, 2.4_{H3}	**H3**: 7.20, s **H1**: 9.49, s
7	 **1g**	**A** 6.6 g, 3 h, **2g** 23% (67%) **C** 1.1 g, **2g** 52%[k]	**3g** 97%, ≈1/1	**H3**: 8.38, d, 2.5_{H1} **H1**: 10.28, d, 2.5_{H3}	**H3**: 7.29, s **H1**: 9.53, s
8	 **1h**	**A** 0.3 g, 11 h, **2h** 15% (40%) **C** 1.23 g, **2h** 34%	**3h** 94%, 1/2.3	**H3**: 8.31, d, 2.2_{H1} **H1**: 10.16, d, 2.2_{H3}	**H3**: 7.30, s **H1**: 9.53, s

[a] For detailed procedures, see the Experimental Section. [b] Amount of **1** in grams. [c] Reaction time in h. [d] Isolated yields. [e] Chemical displacement for proton **H** in ppm. [f] Multiplicity. [g] **H**−H′ coupling constant in Hz. [h] Hidden by the signals of major *E*-**3d**. [I] The yield was essentially quantitative; minor amounts of the starting aldehyde **1** and/or some derivatives of the oxidation reagents were sometimes detected. [j] Method C did not work because of the insolubility of **1f** in the reaction mixture. [k] *Z*-**2g** was also obtained (11%).

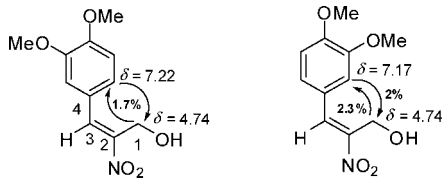
in toluene at 75 °C for 12 h. Higher temperatures caused decomposition. Alternatively, heating 0.5 g of furfural (**1a**) with 3 equiv each of 2-nitroethanol and $AcONH_4$, in acetic acid (1.25 M in **1a**) at 75 °C, gave **2a** in 55% yield after chromatography (Table 1, entry 1, method A).

A stepwise process, where the Henry reaction was first performed by adding furfural to a solution of 2-nitroethanol in 20% aqueous potassium hydroxide at –15 °C and the dehydration was subsequently carried out with 18% hydrochloric acid, gave improved results (94% of **2a**, 5–10 g scale, no chromatography, Table 1, entry 1, method B).[14]

Method B was also suitable for the condensation of 2-nitroethanol with furan-3-carbaldehyde (**1b**) and benzo[*b*]furan-2-carbaldehyde (**1c**), to yield the corresponding 2-nitropropenols **2b** and **2c** in 91% and 63% yields, respectively (entries 2 and 3). It was less effective for thiophen-2-carbaldehyde (**1d**) (19%, entry 4) and ineffective for the substituted benzaldehydes **1e**−**h**. For these, method A was followed. Better overall yields were obtained when the reactions were worked up before complete conversion of the starting aldehydes, which were then separated from the desired 2-nitropropenols **2e**−**h** by chromatography (15–43% yields for **2e**−**h**, 40–84% when recovered aldehyde is taken into account, gram scale, entries 5–8). Attempts to increase yields by extending reaction times led to decomposition of **2** with formation of a black gum. Addition of free-radical inhibitors (2,6-di-*tert*-butyl-4-methylphenol, TEMPO and benzoquinone) to the reaction mixture had no significant beneficial effect. Although method **A** allowed us to prepare gram quantities of **2e**−**h**, we finally found that the addition of an aqueous solution of NaOH (10.5 M) to a cooled solution of the starting aldehyde and 2-nitroethanol in methanol, followed by treatment

(14) For details, see the Experimental Section and/or the Supporting Information.

SCHEME 2. Selected NOEs ($CDCl_3$, 400 MHz) for *E*-2g



with 25% aqueous HCl (method C), was more efficient and experimentally more convenient (Table 1).

With 2-nitropropenols **2** in hand, we next studied their conversion into nitroenals **3**. Attempted oxidation of the allylic hydroxyl group in **2a** with MnO_2 did not take place [**2a** was unaltered on treatment with activated MnO_2 (6 equiv, Fluka 63548) in refluxing CH_2Cl_2 for 2 h]. Although the reaction proceeded with Cr(VI) oxidants, we isolated **3a** in low yields [e.g., 18% with PCC (4 equiv), 0.1 g scale, 0.06 M in CH_2Cl_2, Sieves 3 Å (0.5 g), 1 h at rt]. Better results were obtained with either Dess−Martin periodinane [DMP (1 equiv), ^{t}BuOH (1 equiv), 1.7 g scale, 0.1 M in CH_3CN, 1 h at rt] or with 2-iodoxybenzoic acid [IBX (1 equiv), 1.38 g scale, 6–10 h, refluxing suspension in AcOEt],[15] which gave nitroenal **3a** as a yellow solid in 78% and 82% yield, respectively, after chromatography (Table 1, entry 1). Oxidation of **2b**−**h** proceeded as for **2a** to give the desired nitroenals **3b**−**h** in good yields (Table 1, entries 2–8).

Stability and Characterization of 2-Nitropropenols 2. 2-Nitroprop-2-en-1-ols ($ArCHC(NO_2)CH_2OH$, **2**) were obtained as single geometric isomers in the form of yellow or orange stable solids. The configuration of the double bond proved to be *E*, as deduced from NOE studies on **2g**, which showed enhancements of the methylene signal (δ 4.74) on saturation of the aromatic protons at δ 7.17 and 7.22, and vice versa (Scheme 2).[16]

Similarly, the X-rays of **2a** and **2d** (yellow crystals from EtOAc)[17,18] showed a trans-arrangement of the nitro group with the furyl- and the thienyl-ring, respectively (Table 2, entries 1 and 2).[19] They also showed the entire π system to be almost planar with C=C−N−O dihedral absolute values of about 4° and 10° for **2a** and **2d**, respectively. The nitro group is a bit twisted with one of its oxygen atoms tilted toward the hydroxyl group. For **2d**, the −N(O)O···HO distance of about 2.86 Å suggests an intramolecular stabilizing interaction between the nitro and the hydroxyl groups in the crystal.

DFT [B3LYP/6-31G(d), gas phase] calculations[20] also showed the *E*-isomers of **2a** and **2d** (*E*-**2a** and *E*-**2d**) to be more stable than their corresponding *Z*-isomers (*Z*-**2a** and *Z*-**2d**), by at least 2.5 and 1.9 kcal/mol, respectively (Table 3). For *E*-**2a**, the s_{3-4}-*cis* conformer is predicted to be more stable than the s_{3-4}-*trans* by 1.1 kcal/mol. This is in line with the X-ray of *E*-**2a** (Table 2, entry 1), where only the s_{3-4}-*cis* conformer is found. *E*-**2d** follows a similar trend: the s_{3-4}-*cis* conformer found in the crystal (Table 2, entry 2) is also more stable than the s_{3-4}-*trans* in the gas phase, in this case by just 0.3 kcal/mol (Table 3).

Stability and Characterization of β-(Hetero)aryl-α-nitro-α,β-enals 3. Nitroenals **3** were obtained as colored (yellow to orange or red) solids of varied stability. Furylnitroenals **3a** and **3b** showed the highest stability: they could be chromatographed on silica gel and stored with no appreciable decomposition for at least one month at room temperature and for more than six months at

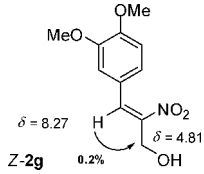
TABLE 2. Crystallographic Structures for 2a,[a] 2d,[b] 3d,[a,c] and *Z*-10[d]

Entry	Compound	Crystallographic structure[e]
1[a]	**2a**	
2[a,b]	**2d**	
3[a,c]	*E*-**3d**	
4[a,c]	*Z*-**3d**	
5[d]	*Z*-**10**	

[a] This work, see refs 14 and 17. [b] See also ref 18. [c] *E*-**3d**:*Z*-**3d** = 8:2 in the crystal. [d] From ref 17b. [e] See ref 19.

(15) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Tojo, G.; Fernández, M. In *Basic Reactions in Organic Synthesis, Oxidation of Alcohols to Aldehydes and Ketones*; Springer: New York, 2006; Chapter 3. (c) **Caution**! IBX and DMP are explosive under impact or heating >200 °C: Plumb, J. B.; Harper, D. J. *Chem. Eng. News* **1990**, *68* (29), 3; see also comments in ref 15b, pp 203 and 183, respectively, and references cited therein.

(16) For the particular case of **2g**, minor quantities of the *Z*-isomer were obtained when following protocol C. *Z*-**2g** showed enhancement of the methylene signal (δ 4.81) on saturation of H3 at δ 8.27:



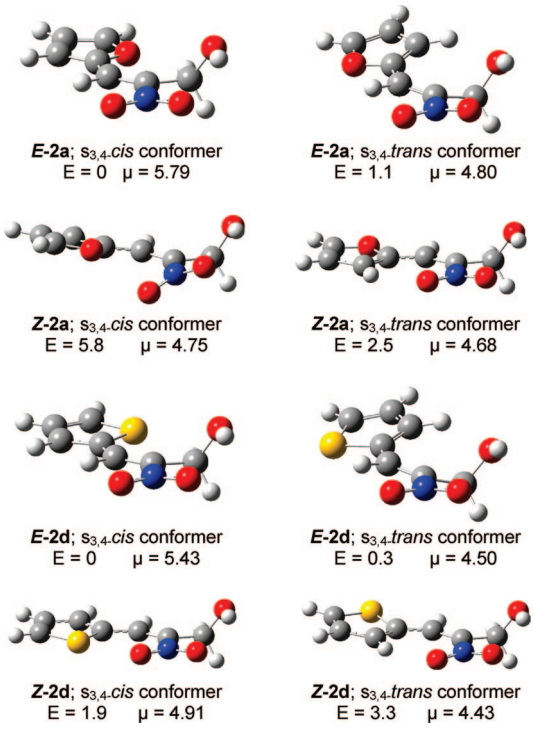
(17) (a) Crystallographic data for **2a** [EtOAc, $C_7H_7NO_4$, M = 169.14, orthorhombic, a = 4.2404(10) Å, b = 22.1197(6) Å, c = 7.9235(2) Å, V = 731.38 (3) Å^3, T = 100 (2) K, space group *Cc*, Z = 4], **2d** [EtOAc, $C_7H_7N_1O_3S_1$, M = 185.2, monoclinic, a = 11.4493(1) Å, b = 5.0645(1) Å, c = 13.6414(1) Å, V = 760.419 (17) Å^3, T = 100 (2) K, space group *P*21/*n*, Z = 4], and **3d** [$C_7H_5N_1O_3S_1$, M = 183.2, monoclinic, a = 8.4333(3) Å, b = 5.3908(2) Å, c = 16.6554(6) Å, V = 7736.10 (5) Å^3, T = 100 (2) K, space group *P*21/*n*, Z = 4], have been deposited with the Cambridge Crystallographic Data Centre as CCDC 641192, 641193, and 641194, respectively, and can be obtained free of charge at www.ccdc.cam.ac.uk/data_request/cif. (b) Panfilova, L. V.; Antipin, M. Y.; Churkin, Y. D.; Struchkov, Y. T. *Khim. Geterotsikl. Soedin.* **1979**, *9*, 1201.

(18) For crystallographic data of **2d** [CH_2Cl_2−petroleum ether = 1–3, T = 293(2) K], see also ref 10b.

(19) Crystallographic structures in Table 2 were prepared by using ORTEP-3 for Windows (Farrugia, L. J. *J. Appl. Crystallogr.* **1997**, *30*, 565.) and Mercury 1.4.2.

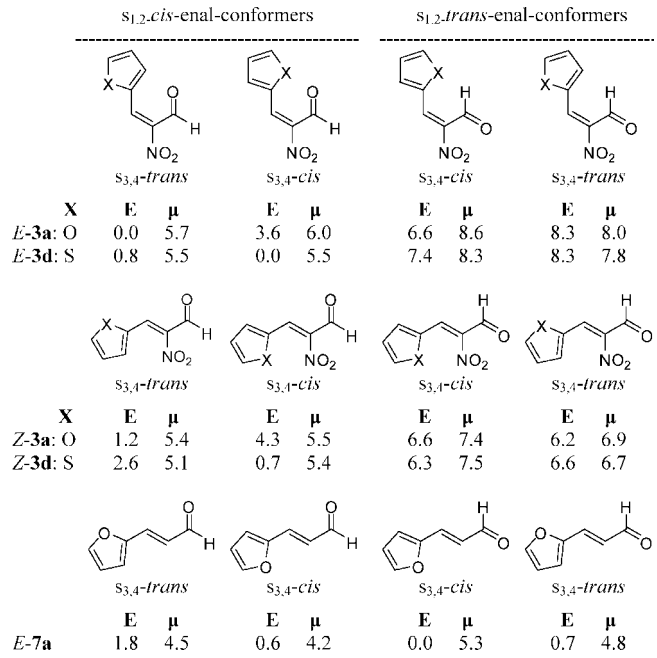
(20) See computational details in the Experimental Section.

TABLE 3. B3LYP/6-31G(d) Relative Gibbs Free Energies (*E*, kcal/mol) and Dipole Moments (*μ*, Debyes) for Hetero(aryl)nitroprop-2-en-1-ols *E*-2a, *Z*-2a, *E*-2d, and *Z*-2d[a,b,c]



[a] For details, see the Experimental Section and the Supporting Information. [b] For every $s_{3,4}$-conformer ($s_{3,4}$-*trans* and $s_{3,4}$-*cis*) of 2-nitropropenols *E*-**2a**, *Z*-**2a**, *E*-**2d**, and *Z*-**2d**, only the most stable conformer around O−C1 and C1−C2 bonds is represented (GaussView). [c] For a more complete set of conformers, see the Supporting Information.

TABLE 4. B3LYP/6-31G(d) Relative Gibbs Free Energies (*E*, kcal/mol) and Dipole Moments (*μ*, Debyes)[a] for Nitroenals 3a and 3d and Enal 7a[b]



	X	E	μ	E	μ	E	μ	E	μ
E-**3a**:	O	0.0	5.7	3.6	6.0	6.6	8.6	8.3	8.0
E-**3d**:	S	0.8	5.5	0.0	5.5	7.4	8.3	8.3	7.8

	X	E	μ	E	μ	E	μ	E	μ
Z-**3a**:	O	1.2	5.4	4.3	5.5	6.6	7.4	6.2	6.9
Z-**3d**:	S	2.6	5.1	0.7	5.4	6.3	7.5	6.6	6.7

	E	μ	E	μ	E	μ	E	μ
E-**7a**	1.8	4.5	0.6	4.2	0.0	5.3	0.7	4.8

[a] For details, see the Experimental Section and the Supporting Information. [b] A total of four conformers were found in every case (*E*-**3a**, *E*-**3d**, *Z*-**3a**, *Z*-**3d**, and *E*-**7a**) around C1−C2 ($s_{1,2}$-*cis*-enal and $s_{1,2}$-*trans*-enal conformers) and C3−C4 ($s_{3,4}$-*trans* and $s_{3,4}$-*cis* conformers) bonds.

–20 °C. A quick silica gel chromatography was also feasible for the purification of **3c** and **3d.** However, *β*-aryl α-nitro-α,*β*-enals **3e**−**h** decomposed on attempted chromatography. Accordingly, they were isolated from the reaction mixture of **2e**−**h** with IBX by cooling in the appropriate media, filtration, and solvent evaporation; in some cases they were additionally purified by precipitation.[14]

Nitroenals **3** were isolated as *E*−*Z* mixtures, as clearly seen in their ^{1}H NMR spectra that showed a characteristic set of signals for every geometric isomer. In particular, proton H3 appeared as a doublet at *δ* 8.3–8.7 coupled with H1 with $J_{H3-H1} \approx 1.5$–2.6 Hz for one isomer, and as a singlet at *δ* 7.2–8.5 for the other isomer (Table 1, columns 5 and 6, respectively). The coupled lower field signals of H3 were attributed to the s_{1-2}-*cis*-enal conformers of nitroenals *E*-**3** (represented at the top of Table 1),[21] where H3 would be deshielded by the vicinal cis-disposed nitro group and its resonance split by H1 because of the relative spatial W-arrangement of both protons. On the other hand, the singlets observed for H3 at higher fields were expected for, and consequently attributed to, the s_{1-2}-*cis*-enal conformers of *Z*-**3**.

Further support for this assignation came from B3LYP/6-31G(d) studies, which showed that the two C3−C4 conformers (the s_{3-4}-*trans* and the s_{3-4}-*cis*) found for the s_{1-2}-*cis*-enal *E*-**3a** were both considerably more stable than their corresponding s_{1-2}-*trans*-enal analogues (Table 4). The s_{1-2}-*cis*-enal conformers were also more stable for *Z*-**3a** and for both geometric isomers of **3d**, *E*-**3d**, and *Z*-**3d** as well (Table 4).

Additionally, an X-ray study showed that in fact **3d** exists in the solid state as the s_{1-2}-*cis*-enal conformer for both geometric isomers ***E*-3d** and ***Z*-3d** (Table 2, entries 3 and 4). The X-ray also showed that their whole molecular structures in the crystal are essentially planar with CCNO dihedral absolute values of 6° and 8° for the *E*- and the *Z*-isomers, respectively. This also looks to be the case in solution, at least in chloroform, where the UV spectra of a **3d** sample (*E*/*Z* = 81/19) showed its long-wave absorption band, λ_{max}, at 388 nm ($\varepsilon_{\lambda_{max}} = 13797$ cm^{-1} mol^{-1}, Table 5, entry 1). Its good agreement with the value (380 nm) calculated by adding the tabulated bathochromic shift for a formyl group (30 nm)[22] to the experimental λ_{max} of (*E*)-2-(2-nitrovinyl)thiophene (**11**, 350 nm, entry 6)[23] looks to appropriately reflect additive effects of the nitro and the formyl groups, i.e., a planar arrangement of both groups with the 2-vinylthiophene unit in **3d**.

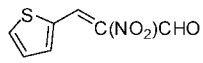
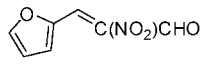
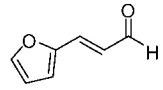
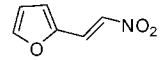
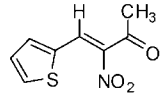
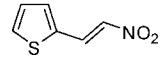
The UV of nitroenal **3a** (*E*/*Z* = 95:5) was similar to that of the thienyl analogue **3d**. Its long-wave absorption band λ_{max} at 384 nm ($\varepsilon_{\lambda_{max}} = 20623$ cm^{-1} mol^{-1}, $CHCl_3$, Table 5, entry 2) again matched the expected values for a fully planar conjugated system: 378 or 376 nm, calculated by adding the tabulated bathochromic shifts for a formyl (30 nm) or a nitro group (60 nm) to the experimental λ_{max} values for either the (*E*)-2-(2-

(21) Through this work, the C1−C2 conformers of nitroenals **3** having the C1═O and the C2═C3 bonds *cis*- and *trans*-disposed are preferably termed $s_{1,2}$-*cis*-enals and $s_{1,2}$-*trans*-enals, respectively, even when the substituents of higher priority (the O atom of the carbonyl group at C1, and the nitro group at C2) are $s_{1,2}$-*trans*-disposed in the first case and $s_{1,2}$-*cis*-disposed in the second one.

(22) Pretsch, E.; Bühlmann, P.; Affolter, C.; Herrera A.; Martínez, R. *Structure Determination of Organic Compounds*; Springer: New York, 2002; p 385.

(23) Berestovitskaya, V. M.; Aboskalova, N. I.; Ishmaeva, E. A.; Bakhareva, S. V.; Berkova, G. A.; Vereshchagina, Ya. A.; Fel'gendler, A. V.; Fattakhova, G. R. *Russ. J. Gen. Chem.* **2001**, *71*, 1942.

TABLE 5. Experimental UV Data for 3d,[a] 3a,[a] 7a,[b] 9,[c] Z-10,[c] and 11[c]

Entry	Compound	λ_{max}[d] ($\varepsilon_{\lambda max}$)[e] Solvent
1[a]	 **3d** *E*/Z = 81:19	388 (13797) $CHCl_3$
2[a]	 **3a** *E*/Z = 95:5	384 (20623) $CHCl_3$
3[b]	 **7a**	316 (25700) CH_2Cl_2
4[c]	 **9**	348 (17000) EtOH
5[c]	 *Z*-**10**	325 (15200) CH_3CN
6[c]	 **11**	350 (17400) EtOH

[a] This work. [b] Reference 24. [c] Reference 23. [d] λ_{max} in nm. [e] $\epsilon_{\lambda_{max}}$ in cm^{-1} mol^{-1}.

nitrovinyl)furan (**9**, λ_{max} = 348 nm) or the (*E*)-3-(furan-2-yl)acrylaldehyde (**7a**, λ_{max} = 316 nm, CH_2Cl_2),[24] respectively.

The X-ray of Z-**3d** shows an antiparallel stacking of its molecules along the direction normal to the [1,0,0] plane (Table 2, entry 4), what probably reflects the high polarity of compounds **3**, where the planar π-system would be strongly polarized by the combined action of two strong electron-withdrawing substituents located at one end, and an electron-rich heteroaromatic system at the other end. Calculated dipole moments for nitroenals **3a** and **3d** (~5.7 and 5.5 D, respectively, Table 4), which are higher than that for simpler enals, e.g., 2-(2-furyl)propenal (**7a**, 4.2–5.3 D), and nitroolefines, e.g. 2-(2-furyl)-nitroethylene (**9**, 4.7 D), are in line with this expectation.

Notably, the preferred s_{1-2}-*cis*-enal conformation and the fully planar geometry shown by β-(hetero)aryl-α-nitro-α,β-enals **3**, as discussed above, do not directly apply to similar compounds, even if structurally very similar. In particular, nitroenone *Z*-**10** (Table 5, entry 5), with just a methyl group instead of the formyl-attached hydrogen of nitroenal **3d**, is neither fully planar nor has a s_{1-2}-*cis*-enal but a s_{1-2}-*trans*-enal preferred conformation. Actually, λ_{max} for nitroenone Z-**10**[23] appears at only 325 nm (CH_3CN). This wavelength value, even lower than that for (*E*)-2-(2-nitrovinyl)thiophene (**11**, Table 5, entry 6, λ_{max} = 350 nm), is reasonable for a conformation where the nitro group is not coplanar with the thiophenylbutenone-conjugated system. This is in fact the case in the solid state, as shown in the X-ray of *Z*-**10**, where the nitro group is nearly perpendicular (93.3°) to the 3-thienylpropenal planar conjugated system (Table 2, entry 5).[17b] The substitution of the formyl hydrogen atom in **3d** by a methyl group, as in *Z*-**10**, also makes the s_{1-2} conformation change: while the C=C and the C=O groups in α-nitroenal **3d** are *cis*-disposed, they prefer to be *trans* in α-nitroenone *Z*-**10**.

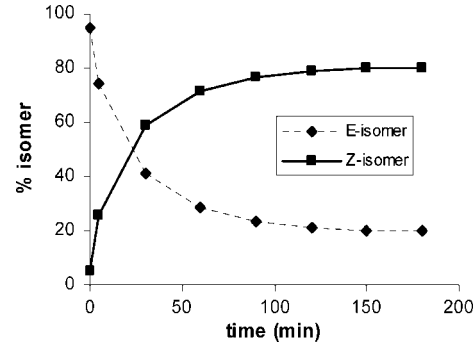


FIGURE 1. Thermal *E*−*Z* isomerization of nitroenal **3a** in DMF-d_7 at 0 °C.

***E*−*Z* interconversion of *E*- and *Z*-Enriched 3-(Furan-2-yl)-2-nitroacrylaldehyde (3a).** The formation of nitroenals **3** as *E*/*Z* mixtures (*E*/*Z* ≈ 6/1 to 1/1) by oxidation of pure *E*-isomers of their hydroxymethyl precursors **2** with IBX in refluxing ethyl acetate revealed that the double bond was undergoing isomerization under the reaction conditions. Due to the important role that the double bond geometry of nitroenals **3** could play in the outcome of their reactions (e.g., on their reported annulation with dioxanone **4**,[12] or on their potential behavior as dienophiles, Michael acceptors, etc), we decided to examine the isomerization process in more detail. For our studies, we chose the particularly stable nitroenal **3a**. Starting from a small sample of **3a** enriched in the chromatographically slightly faster *E*-isomer (*E*/*Z* = 95/5, silica gel, EtOAc/Hex = 1/4), we studied the variation of its *E*/*Z* composition with time in different solvents. ^{1}H NMR showed that *E*−*Z* isomerization was not taking place in $CDCl_3$ (ε = 4.70) at 0 °C, and that it was very slow, at higher temperatures reaching *E*/*Z* values of 93/7, 91/8, and 89/11 after successive hours at 25, 40, and 55 °C, respectively.

E−*Z* isomerization of **3a** was quicker in CH_3CN (ε = 6.02). From the initial *E*/*Z* = 95/5 mixture, ratios of 90/10 and 73/27 were observed after 1 h at 0 °C and a subsequent hour at 25 °C, respectively. The process was even quicker in DMF (ε = 36.7), where a similar isomer ratio (74/26) was reached after only 5 min at 0 °C, and a constant 20/80 *E*/*Z* plateau was reached after 150 min at the same temperature (Figure 1).

Light-promoted isomerization (300-W tungsten-filament lamp) was more effective: 1 h of irradiation at 25 °C in $CDCl_3$ was sufficient to convert the initial 95/5 into a 58/42 *E*/*Z* ratio. Again, isomerization was quicker in more polar CH_3CN: irradiation for 1 h at 25 °C changed the initial 95/5 into a 28/72 *E*/*Z* ratio (the same change needed 4 h of irradiation in $CDCl_3$ under the same conditions). A second hour of irradiation in CH_3CN at 25 °C led to **3a** with the *Z* isomer already prevailing: *E*/*Z* ratio = 15/85; essentially no change was observed on further irradiation.

On the basis of the isomerization data, in particular in the slow isomerization at low *T* in $CDCl_3$, we could prepared enriched samples of *E*-**3a** (*E*/*Z* = 90:10) by oxidation of **2a** with DMP in either $CHCl_3$ or CH_2Cl_2 as solvents at 0 °C or at rt. Workup conditions were shown to be critical; while the use of aqueous base, aqueous thiosulfate, and other reducing agents produced appreciable *E*−*Z* isomerization,[15] a quick filtration of the reaction mixture through a thin layer of $KHCO_3$ packed between two layers of silica gel in a column reproducibly afforded **3a** with a *E*/*Z* ratio of 90:10 at the 1.2 g scale.

Taking advantage of the quick photopromoted *E*−*Z* isomerization in acetonitrile, we were also able to prepare enriched

Z-**3a** at the 120 mg scale (*E*/*Z* ratio = 35/65) by direct irradiation of **3a** in CH_3CN with a tungsten lamp for 4 h, followed by solvent evaporation and flash chromatography. Similar results (*E*/*Z* ratio = 32/68) where obtained by heating the nitroenal in acetone for 5 h at 55 °C, and then evaporation of solvent at low temperature.

In summary, hitherto largely overlooked conjugated 2-nitroprop-2-en-1-ols **2** and β-(hetero)aryl-α-nitro-α,β-enals **3** can now be prepared at the gram scale from (hetero)arylaldehydes through safe procedures.[25] Condensation of (hetero)arylaldehydes with nitroethanol under different conditions renders **2** in the form of their *E*-isomers.[16] Oxidation of *E*-**2** with IBX then easily gives 2-nitroenals **3**. Nitroenals **3** were demonstrated to undergo easy isomerization, which was quicker in more polar solvents and when light-promoted. Study of this *E*−*Z* isomerization allowed the conditions to preferentially obtain nitroenal **3a** enriched in either the *Z* or the *E* isomer to be determined. The strong absorptions at high wavelengths that nitroenals **3** display in solution are compatible with them being colored and with a planar fully conjugated structure. This feature is indeed revealed in the solid state, where not only the formyl, but also the nitro group is virtually coplanar with the (hetero)aryl-vinyl group. Importantly, the enal in **3** has an $s_{1,2}$-*cis* disposition, both in solution and in the crystal. These particular features of **3** are expected to manifest themselves in the form of new properties and reactivity that can now be studied with the help of the synthetic methodology reported here. Work in this direction is being carried out in our laboratory; new results will be reported in due course.

Experimental Section

***E*-3-(Hetero)aryl-2-nitroprop-2-en-1-ols (2). General Methods (A, B, and C) for the Condensation of (Hetero)aromatic Aldehydes with 2-Nitroethanol: Method A:** A solution of the aldehyde (1 mmol), 2-nitroethanol (97%, 3 mmol), and NH_4AcO (3 mmol) in AcOH (6.5 mL) was heated at 75 °C for the specified time (0–15 h). The reaction mixture was diluted with water (65 mL) and the product was extracted with Et_2O (3 × 10 mL). **Method B:** 2-Nitroethanol (97%, 5 mL, 67.6 mmol, 0.83 equiv) was added dropwise to 20% aqueous KOH (35 mL) at –16 °C. After 20 min, the aldehyde (81.24 mmol) was added dropwise and the reaction mixture was allowed to reach 0 °C and stirred for 9 h. The reaction mixture was then transferred to an extraction funnel previously charged with a mixture of crushed ice (82 g) and 37% aqueous HCl (82 mL, previously cooled to –20 °C) and extracted with cold (−20 °C) Et_2O (6 × 100 mL). **Method C:** Aqueous NaOH (0.7 mL, 10.5 M) was added to a solution of the aldehyde (6.7 mmol) and 2-nitroethanol (9.25 mmol, 1.38 equiv) in MeOH (1.7 mL) at 0 °C. After 10 h at 0 °C and 4 h at rt, 25% aqueous HCl (13 mL) was added. After 20 min, the reaction was extracted with CH_2Cl_2.

In every method (A, B, and C), the organic extracts were collected and dried (anhydrous Na_2SO_4) and the solvents rotaevaporated. Flash chromatography (method A), washing or precipitation of the residue (hexane, Et_2O, or Et_2O/hexane), followed by filtration or percolation through silica gel (20–25% EtOAc/hexane, methods B and C) afforded 2-nitropropenols *E*-**2**.

(*E*)-3-(Furan-2-yl)-2-nitroprop-2-en-1-ol (2a, Table 1, entry 1).[26,27] Obtained by methods A [0.5 g, 55% after chromatography (20% EtOAc/hexane)] and B (10.75 g, 94%) as a yellow solid (mp 83 °C).

(*E*)-3-(Furan-3-yl)-2-nitroprop-2-en-1-ol (2b, Table 1, entry 2).[26,27] Obtained by methods A [0.09 g, 26% after chromatography (40% EtOAc/hexane)] and B (1.81 g, 91%) as a yellow solid (mp 74 °C).

(*E*)-3-(Benzofuran-2-yl)-2-nitroprop-2-en-1-ol (2c, Table 1, entry 3).[26] Obtained by method B[0.16 g, 63% after chromatography (30% EtOAc/hexane)] as a yellow solid (mp = 98 °C).

(*E*)-2-Nitro-3-(thiophen-2-yl)prop-2-en-1-ol (2d, Table 1, entry 4).[26,27] Obtained by method B [0.12 g, 14% after chromatography (10% EtOAc/hexane)] as a yellow solid (mp 97 °C).

(*E*)-3-(Benzo[*d*][1,3]dioxol-5-yl)-2-nitroprop-2-en-1-ol (2e, Table 1, entry 5).[26,27] Obtained by methods A [0.71 g, 43% after chromatography (25% EtOAc/hexane)] and C (0.77 g, 52%) as an orange solid [mp (Et_2O/hexane) 89–93 °C].

(*E*)-3-(4-Methoxybenzo[*d*][1,3]dioxol-6-yl)-2-nitroprop-2-en-1-ol (2f, Table 1, entry 6).[26] Obtained by method **A** [0.88 g, 18% after chromatography (two columns, eluted with CH_2Cl_2 and 20% EtOAc/hexane, respectively)] as a yellow solid [mp (Et_2O) 101–103 °C].

(*E*)-3-(3,4-Dimethoxyphenyl)-2-nitroprop-2-en-1-ol (2g, Table 1, entry 7).[26,27] Obtained by methods A [2.19 g, 23% after chromatography (20% EtOAc/hexane)] and C (0.832 g, 52%) as an yellow solid, [mp (Et_2O/hexane) 90–93 °C].

(*E*)-3-(4-Bromophenyl)-2-nitroprop-2-en-1-ol (2h, Table 1, entry 8).[26] Obtained by methods A [0.064 g, 15% after chromatography (20% EtOAc/hexane)] and C (0.58 g, 34%) as a pale yellow solid [mp (Et_2O) 73–75 °C].

***(E/Z)*-β-(Hetero)aryl-α-nitro-α,β-enals (3).** General procedure for the oxidation of *E*-3-(hetero)aryl-2-nitroprop-2-en-1-ols (**2**). 2-Iodoxybenzoic acid (IBX)[25] (2 mmol) was added to a solution of the corresponding 2-nitropropenol **2** (1 mmol) in EtOAc (6 mL). The suspension was refluxed for 6–8 h, then allowed to cool to rt.[28] EtOAc was then removed in the rotavapor with no heating, using a water bath at rt (the magnetic stirring bar kept in the mixture helped to prevent bumping during this operation). The residue was magnetically stirred with Et_2O while cooling with a dry ice−acetone bath (−78 °C; around 20 mL of Et_2O were used for a 200 mg reaction scale; use of Et_2O stabilized with 2,6-di-*tert*-butyl-4-methylphenol (BTH) proved to be adequate; use of Et_2O stabilized with ethanol led sometimes to nitroenal decomposition). Once the entire solid was liberated from the walls of the flask (sometimes with the help of a spatula) and was freely floating, the suspension was filtered through a sintered glass funnel (porosity grade 5). The solid was washed with additional cold (−78 °C) Et_2O. Nitroenals **3** were obtained as solids after solvent rotaevaporation with no heating, using a water bath at rt. Further purification was carried out either by crystallization−precipitation with appropriate solvents (usually Et_2O or Et_2O followed by the addition of *n*-hexane or *n*-pentane) or by flash chromatography, as indicated. Complete characterization details for nitroenals **3a**−**e** are given below; when the ^1H NMR data obtained for the *E*−*Z* mixture are separately assigned to *E*-**3** and to *Z*-**3**, integral values are normalized to one proton (1 H) for every geometric isomer.

3-(Furan-2-yl)-2-nitroacrylaldehyde (3a, Table 1, entry 1).[26,29] **3a** was prepared according to the general procedure from **2a** (1.3 g, 7.87 mmol) and IBX (4.4 g, 15.7 mmol) in EtOAc (40 mL) and purified by flash chromatography (20% EtOAc/hexane): 1.08 g, 82%, yellow solid, mp 86 °C. IR (KBr) cm^{-1} 3138, 3000, 1686, 1572, 1502, 1456, 1313, 784. ^1H NMR ($CDCl_3$, 300 MHz, *E*-**3a**/

(24) Lasseuguette, E.; Gandini, A.; Timpe, H.-J. *J. Photochem. Photobiol., A* **2005**, *174*, 222.

(25) Preparation of **3** involves final oxidation with IBX. While caution should always be exercised when dealing with this reagent, we have routinely prepared and used it in batches of as much as 25 g without a single incident. See ref 15.

(26) For spectra and/or complete characterization data see the Supporting Information.

(27) See also ref 10b.

Z-**3a** = 2/1) *E*-**3a** δ 10.40 (d, *J* = 2.6 Hz, 1H), 8.47 (d, *J* = 3.8 Hz, 1H), 8.37 (d, *J* = 2.6 Hz, 1H), 7.93 (d, *J* = 1.7 Hz, 1H), 6.78 (dd, *J* = 3.8 Hz, *J* = 1.7 Hz, 1H), *Z*-**3a** δ 9.83 (s, 1H), 7.83 (d, *J* = 1.7 Hz, 1H), 7.72 (d, *J* = 3.8 Hz, 1H), 7.53 (s, 1H), 6.74 (dd, *J* = 3.8 Hz, *J* = 1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz, *E*-**3a**/*Z*-**3a** = 2/1) δ 183.4, 182.0, 152.0, 150.5, 147.3, 146.5, 140.2, 139.2, 129.8, 128.2, 126.0, 125.2, 115.3, 114.8. LRMS (CI^+) *m*/*z* (%) 167 [100, $(M + H)^+$]. Anal. Calcd for $C_7H_5NO_4$: C, 50.31; H, 3.02; N, 8.38; O, 38.29. Found: C, 49.98; H, 2.95; N, 8.18; O, 38.89.

3-(Furan-3-yl)-2-nitroacrylaldehyde (3b, Table 1, entry 2). 3bwas prepared according to the general procedure from **2b** (0.52 g, 3.05 mmol) and IBX (1.70 g, 6.1 mmol) in EtOAc (15.3 mL) and purified by flash chromatography (20% EtOAc/hexane): 0.47 g, 96%, yellow solid, mp 53 °C. IR (KBr) 3440, 3142, 1694, 1642, 1599, 1531, 1323, 1160, 868. ^{1}H NMR ($CDCl_3$, 400 MHz, *E*-**3b**/*Z*-**3b** = 1.8/1) *E*-**3b** δ 10.33 (d, *J* = 2.4 Hz, 1H), 8.70 (m, 1H), 8.31 (d, *J* = 2.4 Hz, 1H), 7.59 (m, 1H), 7.09 (m, 1H), *Z*-**3b** δ 9.76 (s, 1H), 8.21 (m, 1H), 7.56 (m, 1H), 7.50 (s, 1H), 6.77 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, *E*-**3b**/*Z*-**3b** = 1.8/1) δ 184.2, 182.1, 153.9, 152.2, 145.6, 145.0, 143.5, 142.2, 135.4, 130.7, 118.3, 118.0, 112.9, 110.3. LRMS (CI^+) *m*/*z* (%) 168 [96, $(M + H)^+$]. Anal. Calcd for $C_7H_5NO_4$: C, 50.31; H, 3.02; N, 8.38; O, 38.29. Found: C, 50.46; H, 3.25; N, 8.14; O, 38.15.

3-(Benzofuran-2-yl)-2-nitroacrylaldehyde (3c, Table 1, entry 3). 3c was prepared according to the general procedure from **2c** (39.6 mg, 0.18 mmol) and IBX (0.10 g, 0.36 mmol) in EtOAc (0.9 mL) and purified by flash chromatography (20% EtOAc/hexane): 37.2 mg, 95%, yellow solid, mp 92 °C dec. IR (KBr) 3040, 2926, 1691, 1680, 1630, 1609, 1529, 1319, 1261, 1115, 755. ^{1}H NMR ($CDCl_3$, 250 MHz, *E*-**3c**/*Z*-**3c** ≈ 1/1) δ 10.47 (d, *J* = 1.5 Hz, 1H, CHO *E*-**3c**), 9.69 (s, 1H, CHO *Z*-**3c**), 8.51 (s, 1H), 8.36 (d, *J* = 1.5 Hz, 1H), 7.80–7.28 (m, 10H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 183.2, 181.4, 158.0, 157.2, 147.5, 146.7, 143.1, 141.9, 130.5, 130.3, 129.8, 128.0, 127.7, 125.1, 124.6, 124.4, 123.8, 123.2 (2C), 120.8, 112.2, 112.1. LRMS (CI^+) *m*/*z* (%) 218 [100, $(M + H)^+$]. HRMS (ESI^+) calcd for $C_{11}H_8NO_4$ $(M + H)^+$ 218.0448, found 218.0446. Anal. Calcd for $C_{11}H_7NO_4$: C, 60.83; H, 3.25; N, 6.45; O, 29.47. Found: C, 59.62; H, 3.37; N, 6.06; O, 30.94.

2-Nitro-3-(thiophen-2-yl)acrylaldehyde (3d, Table 1, entry 4). 3d was prepared according to the general procedure from **2d** (0.50 g, 2.70 mmol) and IBX (1.51 g, 5.39 mmol) in EtOAc (13.5 mL), purified by flash chromatography (20% EtOAc/hexane), and crystallized from $CHCl_3$: 0.40 g, 80%, yellow crystalline solid, mp 113 °C. IR (KBr) 3437, 3084, 1680, 1564, 1410, 1296, 754. ^{1}H NMR ($CDCl_3$, 250 MHz, *E*-**3d**/*Z*-**3d** = 6/1) *E*-**3d** δ 10.40 (d, *J* = 2.5 Hz, 1H), 8.73 (d, *J* = 2.5 Hz, 1H), 8.04 (dt, *J* = 1 Hz, *J* = 5 Hz, 1H), 8.00 (dd, *J* = 1 Hz, *J* = 4 Hz, 1H), 7.35 (dd, *J* = 4 Hz, *J* = 5 Hz, 1H), *Z*-**3d** δ 10.07 (s, 1H), 8.09 (dt, *J* = 1 Hz, *J* = 5 Hz, 2H), 8.1–7.9 (1H, H3, hidden by protons of the major *E* isomer), 7.91 (dd, *J* = 1 Hz, *J* = 4 Hz, 1H), 7.32 (dd, *J* = 4 Hz, *J* = 5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 62.5 MHz, *E*-**3d**/*Z*-**3d** = 6/1) *E*-**3d** δ 184.5, 145.8, 142.0, 138.9, 138.0, 133.4, 129.2, *Z*-**3d** δ 183.2, 144.9, 134.2, 128.8, three C resonances, two of them quaternary, did not appear in the spectrum due to the small proportion of the *Z*-isomer present in the *E*-*Z* mixture. LRMS(CI^+) *m*/*z* (%) 184 $[M + H]^+$. HRMS (ESI^+) calcd for $C_7H_6NO_3S^+$ $(M + H)^+$ 184.0063, found 184.0060. Anal. Calcd for $C_7H_7NO_3S$: C, 45.90; H, 2.75; N, 7.65; S, 17.50; O, 26.20. Found: C, 45.9623; H, 2.7395; N, 7.6386; S, 17.4936; O, 26.17.

3-(Benzo[*d*][1,3]dioxol-5-yl)-2-nitroacrylaldehyde (3e, Table 1, entry 5). 3e was prepared according to the general procedure from **2e** (0.27 g, 1.22 mmol) and IBX (0.69 g, 2.45 mmol), and isolated by precipitation with Et_2O/hexane: 0.27 g, 99%, red solid, [mp (Et_2O) 92–97 °C]. IR (film) ν_{max} 3534, 2990, 1503 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz, *E*-**3e**/*Z*-**3e** ≈ 1/1) *E*-**3e** δ 10.24 (d, *J* = 2.4 Hz, 1H), 8.33 (d, *J* = 2.4 Hz, 1H), 7.93 (d, *J* = 1.8 Hz, 1H), 7.55 (dd, *J* = 8.2 Hz, *J* = 1.8 Hz, 1H), 6.94 (d, *J* = 8.2 Hz, 1H), 6.13 (s, 2H), *Z*-**3e** δ 9.50 (s, 1H), 7.23 (s, 1H), 7.16 (dd, *J* = 8.2 Hz, *J* = 1.8 Hz, 1H), 7.06 (d, *J* = 1.8 Hz, 1H), 6.90 (d, *J* = 8.2 Hz, 1H), 6.09 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 183.9, 181.6, 154.0, 152.7, 148.9, 148.4, 145.8, 145.1, 142.4, 139.0, 133.6, 130.0, 123.6, 122.7, 111.9, 109.1, 109.0, 108.9, 102.6, 102.4. LRMS (CI^+) *m*/*z* (%) 222 [100, $(M + H)^+$]. HRMS (CI^+) calcd. for $C_{10}H_7NO_5$ $(M + H)^+$, 222.0402, found 222.0399).

3-(4-Methoxybenzo[*d*][1,3]dioxol-6-yl)-2-nitroacrylaldehyde (3f, Table 1, entry 6). 3f was prepared according to the general procedure from **2f** (0.87 g, 3.46 mmol) and IBX (1.94 g, 6.93 mmol) in EtOAc (11 mL) at 80 °C for 10 h and isolated as a red solid (0.80 g, 92%), mp 109–111 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, *E*-**3f**/*Z*-**3f** ≈ 1/1) *E*-**3f** δ 10.24 (d, *J* = 2.4 Hz, 1H), 8.30 (d, *J* = 2.4 Hz, 1H), 7.42 (d, *J* = 1.6 Hz, 1H), 6.79 (d, *J* = 1.6 Hz, 1H), 6.14 (s, 2H), 3.99 (s, 3H), *Z*-**3f** δ 9.49 (s, 1H), 7.59 (d, *J* = 1.5 Hz, 1H), 7.20 (s, 1H), 6.81 (d, *J* = 1.5 Hz, 1H), 6.10 (s, 2H), 3.92 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 183.9, 181.5, 149.8, 149.2, 145.8, 143.8, 143.5, 142.8, 142.1, 141.8, 140.6, 138.9, 123.6, 122.8, 115.9, 113.2, 108.0, 104.7, 103.0, 102.8, 56.71, 56.68. HRMS (ESI^+-TOF-MS) calcd. for $C_{11}H_{10}NO_6$ $(M + H)^+$ 252.0508, found 252.0503.

3-(3,4-Dimethoxyphenyl)-2-nitroacrylaldehyde (3g, Table 1, entry 7). 3g was prepared according to the general procedure from **2g** (1.44 g, 6.02 mmol) and IBX (3.37 g, 12.04 mmol) and isolated by precipitation with Et_2O or Et_2O/hexane: 1.39 g, 97%, orange solid, [mp (Et_2O) 99–103 °C]. ^{1}H NMR ($CDCl_3$, 300 MHz, *E*-**3g**/*Z*-**3g** ≈ 1/1) *E*-**3g** δ 10.28 (d, *J* = 2.5 Hz, 1H), 8.38 (d, *J* = 2.5 Hz, 1H), 8.15 (d, *J* = 1.9 Hz, 1H), 7.64 (dd, *J* = 1.9 Hz, *J* = 8.5 Hz, 1H), 6.98 (d, *J* = 8.5 Hz, 1H), 4.01 (s, 3H), 3.99 (s, 3H), *Z*-**3g** δ 9.53 (s, 1H), 7.29 (s, 1H), 7.26 (dd, *J* = 8.5 Hz, *J* = 1.9 Hz, 1H), 7.11 (d, *J* = 1.9 Hz, 1H), 6.94 (d, *J* = 8.5 Hz, 1H), 3.97 (s, 3H), 3.88 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 184.2, 181.7, 155.5, 154.1, 149.4, 148.9, 146.2, 142.2, 141.7, 139.4, 132.0, 128.0, 122.5, 121.4, 115.1, 112.3, 111.2, 110.9, 56.2, 56.1, 56.0, 55.9. LRMS (CI^+) *m*/*z* (%) 238 [100, $(M + H)^+$], 222 [14, $(M - CH_3)^+$], 208 [34, $(M - OH)^+$], 191 [40, $(M - NO_2)^+$]. HRMS (CI^+) calcd for $C_{11}H_{12}N_1O_5$ $(M + H)^+$ 238.0715, found 238.0715.

3-(4-Bromophenyl)-2-nitroacrylaldehyde (3h, Table 1, entry 8). 3h was prepared according to the general procedure from **2h** (0.100 g, 0.39 mmol) and IBX (0.22 g, 0.75 mmol) and isolated by precipitation with Et_2O/*n*-pentane: 0.088 g, 94%, pale yellow solid, [mp (Et_2O/*n*-pentane) 61–62 °C]. ^{1}H NMR ($CDCl_3$, 300 MHz, *E*-**3h**/*Z*-**3h** = 1/2.3) *E*-**3h** δ 10.16 (d, *J* = 2.2 Hz, 1H), 8.31 (d, *J* = 2.2 Hz, 1H, H3), 7.83 (d, *J* = 8.4 Hz, 2H), 7.64 (d, *J* = 8.4 Hz, 2H), *Z*-**3h** δ 9.53 (s, 1H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.39 (d, *J* = 8.5 Hz, 2H), 7.30 (s, 1H, H3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 183.2, 181.3, 146.9, 143.9, 137.5 134.4, 132.9, 132.4, 132.0, 131.6, 129.6, 128.6, 127.7, 127.4. LRMS (EI) *m*/*z* (%) 256 [80, $(M + H)^+$]. HRMS $(CI)^+$ calcd for $C_9H_6BrNO_3$ $(M + H)^+$ 254.9475, found 254.9478.

Computational Details. All calculations were performed using the Gaussian 03 software package.[30] Geometries and energies were optimized at the B3LYP level and the 6–31G(d) basis set. Frequency calculations, performed to confirm the nature of the stationary points, showed no imaginary frequencies for every minima. All geometries were optimized without constraints; all reported energies are Gibbs free energies at 298 K and 1 atm.

Acknowledgment. This work was supported by the Spanish Ministries of Science and Technology (Project BQU2002-01176) and Education and Science (Project CTQ2005-02338) in collaboration with ERDF, the Xunta de Galicia (through Project PGIDIT05BTF20901PR). P. M-B., F. C.-F., J. C.O., K. K., L. O.-V., and M. F.-G. acknowledge support from the Xunta de Galicia in the form of contracts. L.F.R. acknowledges

(28) At this stage, a simplified workup protocol, which simply involved addition of *n*-hexane (6.5 mL), cooling to 0° C, filtration, and solvent rotaevaporation at rt, was alternatively used in a number of cases.

(29) See also ref 1.

the University of Santiago for a fellowship. We are also grateful to the Supercomputing Centre of Galicia (CESGA) for computing facilities and computational time.

Supporting Information Available: *E*−*Z* isomerization studies for **3a**, selective preparation of *E*- and *Z*-enriched nitroenal **3a**, UV data for **3a** and **3d**, analytical and spectroscopic data for **2a**−**h**, relative DFT Gibbs free energies for conformers of **2a**, **2d**, **3a**, and **3d**, ^{1}H NMR, ^{13}C NMR, and DEPT spectra for **2a**−**h** and **3a**−**h**, and CIF files for nitropropenols **2a** and **2d** and for nitroenal **3d**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO702731B

(30) Frisch, M. J.; et al. *Gaussian 03*, revision C.O1; Gaussian, Inc.: Wallingford, CT, 2004. See the Supporting Information for the full citation.