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Azodioxy-carbonyl compounds by oxidation of cyclic imines with *m*-CPBA

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ABSTRACT

This article reports a simple and efficient synthesis of *C*-nitroso compounds (azodioxy esters or ketones and oximes) through a double oxidation of cyclic imines (4,5-dihydrooxazoles and 3,4-dihydro-2*H*-pyrroles) with *m*-CPBA. *C*-Nitroso derivatives seem to be potential donors of nitric oxide, one of the most powerful biological messenger.

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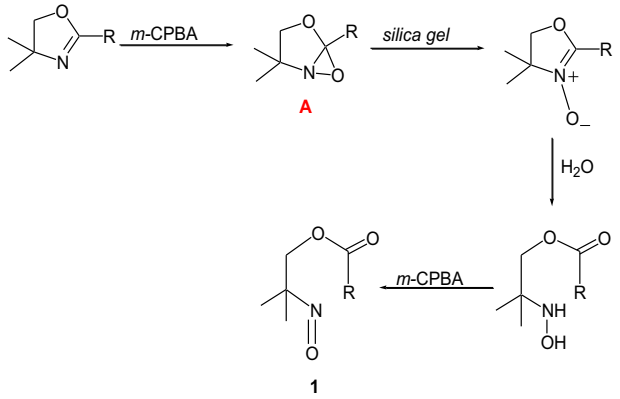
1. Introduction

C-Nitroso compounds (RN=O; R=alkyl or aryl group) are an interesting family of molecules that have an important role in organic chemistry and biochemistry. Recently, it was reported that appropriately substituted *C*-nitroso compounds act solely as donors of neutral nitric oxide (NO) through a first-order homolytic C–N bond scission.[1] The nitric oxide, considered a very pollutant gas for decades, also co-responsible of the atmospheric ozone layer depletion, was lately identified as one of the most powerful endogenous signalling molecule. This messenger is produced in living organisms for controlling many of their biological functions.[2–8]

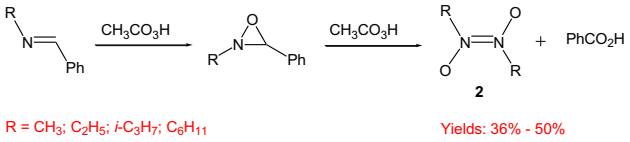
Methods for the preparation of *C*-nitroso compounds have been recently reviewed.[9] Lee and Keana[10] showed that oxazoline oxidation with 3-chloroperoxybenzoic acid (*m*-CPBA) gave the condensed oxaziridine (**A**) (Scheme 1), which upon further manipulation converted into the nitroso ester **1** as the final product.

According to Taylor et al.[11] oxaziridines, prepared by oxidation of an imine (1.0 mmol) with peracetic acid (1.0 mmol), were oxidized with a second mole of peroxy acid giving nitrosoalkane dimers **2** (Scheme 2).

Analogously, Emmons[12] observed that oxaziridines reacted smoothly with 1 equiv of peracetic acid affording good yields of nitrosoalkanes that rapidly dimerized (Scheme 3).



Scheme 1. *C*-nitroso compounds through oxazoline oxidation.



Scheme 2. Azodioxy compounds from imines.

The stability of nitrosoalkane dimers has been commented on previously by Gowenlock.[13]

Recently, we synthesized several chiral and achiral oxaziridines that have been successively used in the [3+2] cycloaddition

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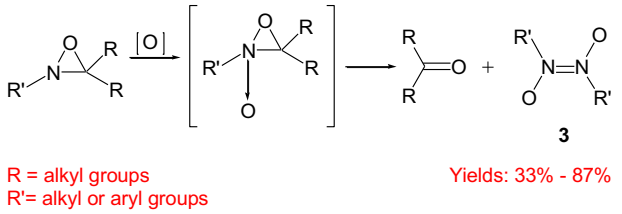
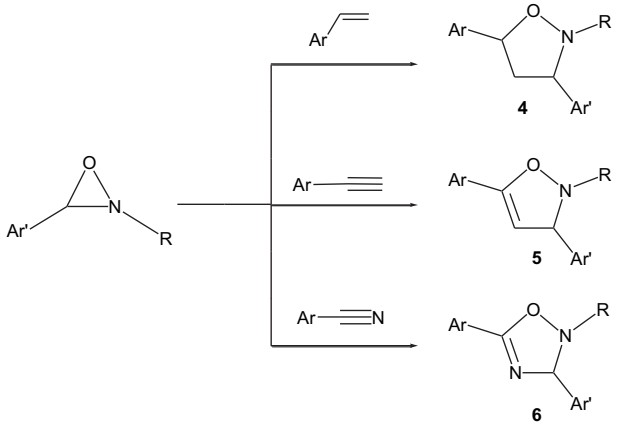


Scheme 3. Azodioxy compounds from oxaziridines.

reactions with alkenes,[14,15] alkynes[16] and nitriles,[17] to generate stable isoxazolidines **4**, isoxazolines **5** and 2,3-dihydro-1,2,4-oxadiazoles **6**, respectively (Scheme 4).

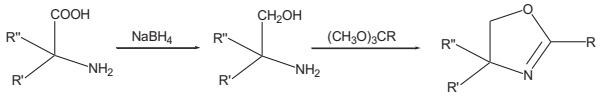


Scheme 4. [3+2] Cycloaddition between oxaziridines and dipolarophiles.

The oxaziridines have been prepared from the respective imines according to Emmons's methodology,[18] which is based on the addition of the *m*-CPBA (1.1 mmol) to an imine (1.0 mmol) in CH_2Cl_2 (20 mL) at 0 °C. No nitrosoalkane was ever isolated or observed in the various synthesis reactions.

2. Results and discussion

With the aim of synthesizing more reactive oxaziridines for cycloaddition reactions with various dipolarophiles, we turned our attention to the preparation of more strained oxaziridines (for example, condensed to other heterocycles), through the oxidation of cyclic imines, such as 4,5-dihydrooxazoles **7a**–**h** and 5-methyl-3,4-dihydro-2*H*-pyrrole **7i** (Table 1). Oxazolines **7a**–**h** were prepared through reduction of enantiomerically pure or racemic α-amino acids to the corresponding amino alcohols,[19] which were subsequently condensed with *ortho* esters[20] (Scheme 5).



Scheme 5. Oxazolines synthesis from amino acids.

From the previous literature we expected that **7a**–**i** would be converted into the corresponding **8a**–**i** (or **9a**–**i**), but surprisingly we got new and unexpected results that we report in this work.

Particularly, when to an ice-cooled solution of **7a** in CH_2Cl_2 was added *m*-CPBA (1.1 equiv), after a 10 h period, GC and GC–MS showed the formation of a new product, together with the 50% of unreacted starting material. The same reaction carried out with 2.2 equiv of *m*-CPBA instead produced the total conversion of the starting 2-phenyloxazoline into the new product. The reaction work-up was conducted in a non-aqueous way, according to a modified Emmons's procedure: the crude mixture was stirred with excess powdered anhydrous sodium carbonate (with neutralization of the acidic reaction mixture) until carbon dioxide evolution ceased. After filtration, the mixture was concentrated in vacuo at room temperature and after the addition of diethyl ether a white solid (99% yield) was obtained. The ^1H, ^{13}C NMR, GC–MS and the X-ray diffraction analysis of this product were in agreement with the structure of the *trans* dimer **12a** (Fig. 1).[21]

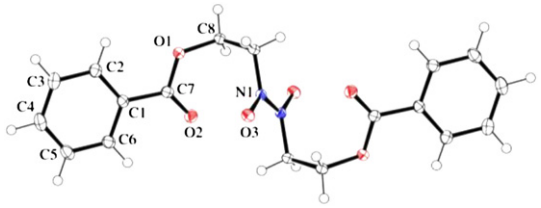


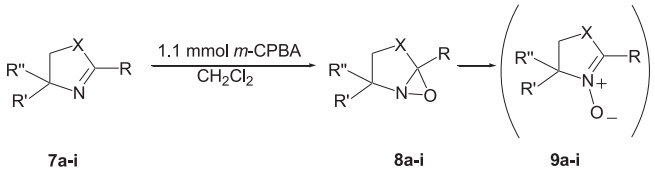
Fig. 1. Projection of compound **12a** at 93 K. The molecule lies on a crystallographic centre of symmetry; only the asymmetric unit was labelled. ADPs at 50% probability level; H atoms not to scale.

We hypothesize that the starting oxazoline **7a**, oxidized with *m*-CPBA, is initially converted into the corresponding unstable condensed 2,3-oxaziridine **8a**, which in the presence of the peroxy acid, quickly is further oxygenated generating **10a** as a transient intermediate (Scheme 6).

N-Oxide **10a** rearranges to monomeric *C*-nitroso compound **11a** that rapidly dimerizes to *trans* azodioxy ester **12a**. This last product was isolated and characterized. The dimer **12a**, dissolved in toluene and heated at reflux, after a few minutes underwent a thermal conversion into oxime **13a**, giving the *Z* and *E* isomeric forms (*Z*/*E* ratio 58:42, Scheme 6). Such rearrangement probably occurs via azodioxide monomerization to nitroso compounds, which subsequently undergo 1,3 hydrogen migration to form oximes.[22] The slight prevalence of the *Z* isomer respect to the *E* one was probably due to the possible formation of hydrogen bond between hydroxyl and carbonyl group in *Z* isomer. Indeed, calculations performed at the 6-31G*/B3LYP level (in the gas phase) showed only a small energy difference (0.47 kcal/mol) between the two isomers, that justified the result. NOESY measurements were in agreement with the assigned structures.

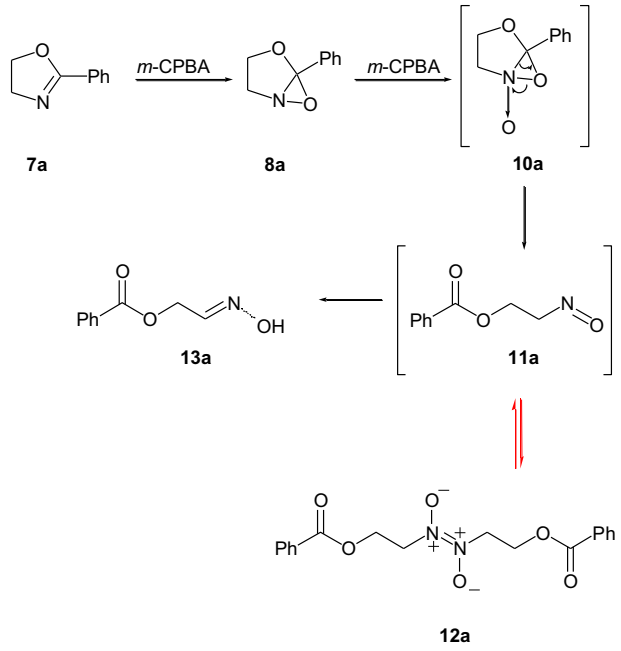
The same trend was found in a similar reaction carried out on the known (+)-(4*S*)-oxazoline **7b**;[23–25] the (−)-(*S*, *S*)-*trans* dimeric azodioxy ester **12b** ($[\alpha]_D^{24.0}$ −104.6, *c* 0.1, $CHCl_3$) was obtained in 50% yield using 1.1 equiv of *m*-CPBA and in quantitative yield using 2.2 equiv of *m*-CPBA, respectively (Table 2, entry 2). The dimer **12b**, isolated and heated at reflux in toluene, was converted into *Z* and *E* isomer of the oxime **13b** (*Z*/*E* ratio 70/30; Table 3, entry 2).

Table 1
Condensed oxaziridines synthesis



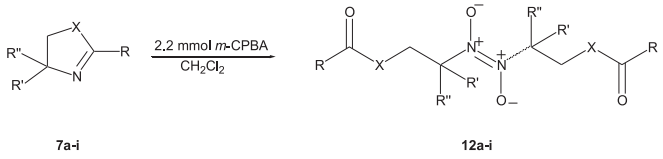
Entry	Starting material	R	R′	R″	X	Product	Total yield (%)
1	**7a**	Ph	H	H	O	**8a**[a]	—
2	**7b**	Ph	H	Bn	O	**8b**[a]	—
3	**7c**	Et	H	*i*-Pr	O	**8c**[a]	—
4	**7d**	Me	H	*i*-Pr	O	**8d**[a]	—
5	**7e**	Et	H	Bn	O	**8e**[a]	—
6	**7f**	Et	H	*i*-Bu	O	**8f**[a]	—
7	**7g**	Et	Me	Me	O	**8g**	97
8	**7h**	Me	Me	Me	O	**8h**	97
9	**7i**	Me	H	H	CH_2	**8i**	98

[a] Not isolated product.



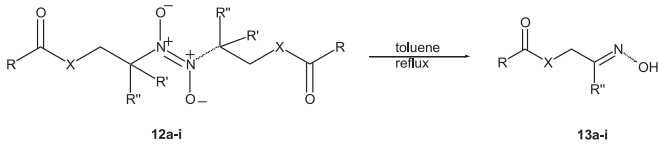
Scheme 6. Suggested mechanism for azodioxide and oxime synthesis.

Table 2
Azodioxy compounds synthesis



Entry	Starting material	R	R′	R″	X	Product	Ratio trans/cis	Total yield (%)
1	**7a**	Ph	H	H	O	**12a**	100/0	99
2	**7b**	Ph	H	Bn	O	**12b**	100/0	96
3	**7c**	Et	H	*i*-Pr	O	**12c**	100/0	99
4	**7d**	Me	H	*i*-Pr	O	**12d**	100/0	97
5	**7e**	Et	H	Bn	O	**12e**	100/0	98
6	**7f**	Et	H	*i*-Bu	O	**12f**	50/50	97
7	**7g**	Et	Me	Me	O	**12g**	80/20	98
8	**7h**	Me	Me	Me	O	**12h**	66/33	97
9	**7i**	Me	H	H	CH_2	**12i**	100/0	98

Table 3
Rearrangement of azodioxides to oximes



Entry	Starting material	R	R′	R″	X	Product	Ratio *Z*/*E*	Total yield (%)
1	**12a**	Ph	H	H	O	**13a**	58/42	99
2	**12b**	Ph	H	Bn	O	**13b**	70/30	96
3	**12c**	Et	H	*i*-Pr	O	**13c**	50/50	98
4	**12d**	Me	H	*i*-Pr	O	**13d**	50/50	97
5	**12e**	Et	H	Bn	O	**13e**	66/33	99
6	**12f**	Et	H	*i*-Bu	O	**13f**	66/33	99
7	**12g**	Et	Me	Me	O	—	—	—
8	**12h**	Me	Me	Me	O	—	—	—
9	**12i**	Me	H	H	CH_2	**13i**	66/33	98

The (−)-(4*S*)-oxazolines **7c**[26], **7d**[27] and **7e**[20] also produced similar results affording at first the *trans* dimers **12c** (Table 2, entry 3), **12d**[28] (Table 2, entry 4) and **12e** (Table 2, entry 5), which then, after the reflux, were transformed into **13c** (*Z*/*E* ratio 50:50), **13d** (*Z*/*E* ratio 50:50) and **13e** (*Z*/*E* ratio 66:33), respectively (Table 3, entries 3–5). Previously, Aitken et al., oxidizing the chiral oxazoline **7d** using 1.6 equiv of *m*-CPBA, isolated the dimer **12d** together with the *E*/Z mixture of the isomeric oximes **13d**.[28]

An equimolar mixture of *cis*/*trans* azodioxy-carbonyl dimer **12f** was instead obtained when the oxazoline **7f**[29] reacted under the same conditions described above (Table 2, entry 6). Both the *trans* and *cis* dimer, refluxed in toluene separately, provided a mixture of *Z*/*E* oxime **13f** with a diastereomeric ratio of 66:33 (Table 3, entry 6).

Oxazolines lacking hydrogen atoms at the 4 position produced different results. For instance, the 2-ethyl-4,4-dimethyl-4,5-dihydro-oxazole **7g** oxidized with *m*-CPBA (1.1 equiv) at 0 °C, after 3 h, afforded the stable condensed 2,3-oxaziridine **8g**, which did not need further purification (yield=97%; Table 1, entry 7). Therefore, we previously used **8g** in the [3+2] cycloaddition reactions with alkenes, alkynes and nitriles.[30] The stability of this condensed oxaziridine is probably caused by two alkyl groups in 4 position that, of course, provide an improved thermal stability to the molecule compared to previous cases. The 2,4,4-trimethyl-4,5-dihydro-oxazole **7h**, treated under the same conditions, led to stable oxaziridine **8h**,[31] too (Table 1, entry 8). However, **7** and **7h** treated with an excess of *m*-CPBA (2.2 equiv), produced the dimeric azodioxy esters **12** and **12h** in high yields, both in the two *cis*/*trans* isomeric forms with a diastereomeric ratio of 20:80 and of 33:66, respectively (Table 2, entries 7 and 8). The oxaziridines **8** and **8** oxidized with 1.1 equiv of *m*-CPBA, also gave the azodioxides **12** and **12**, respectively, with the same yield and ratio. Moreover, **12** and **12h**, when heated at reflux for few hours in toluene, retained the dimeric structure but the cis isomeric form showed a tendency to interconvert into the trans isomer. After about 1 h of reflux, the *cis*/*trans* ratio became 4:96 for **12** and 8:92 for **12h**. Furthermore, theoretical studies on the cis/trans-isomerization of azodioxy compounds have shown that, in a thermal reaction, the fragmentation of the cis form into two nitrosomonomers and their recombination to the trans form take place via the symmetry-allowed 'from step to step' mechanism (Fig. 2).[32] For the azodioxides **12g** and **12h**, oxime formation is precluded because their respective monomeric *C*-nitroso compounds contain no hydrogen α to nitrogen for migration.[22]

Finally, even the cyclic imine **7i**, 5-methyl-3,4-dihydro-2*H*-pyrrole, behaved similarly. The stable condensed oxaziridine **8i** and the *trans* azodioxy ketone **12i** were formed through oxidation of **7i** with 1.1 equiv and 2.2 equiv of *m*-CPBA, respectively (Table 1, entry 9; Table 2, entry 9). The *trans* dimer heated in toluene at 80 °C, after 10 min, gave the *Z* and *E* oxime **13i** (diastereomeric ratio 66:33; Table 3, entry 9).

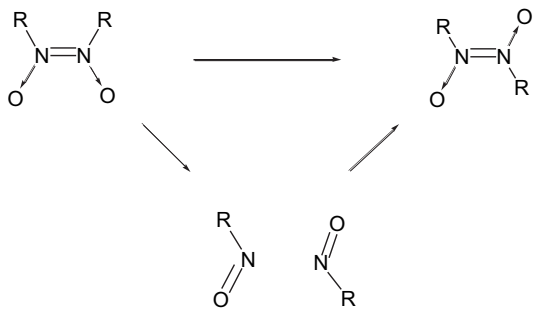


Fig. 2. cis/trans Interconversion of azodioxy dimer through the monomeric form.

3. Conclusions

In summary, we have carried out an efficient and simple synthesis of *C*-nitroso derivatives from enantiomerically pure or racemic α-amino acids.

4. Experimental section

4.1. General experimental methods

All reactions involving air-sensitive reagents were performed under an atmosphere of nitrogen in oven-dried glassware by using syringe/septum cap techniques. Et_2O, THF and toluene were purified by distillation from sodium before use. CH_2Cl_2 was distilled from calcium hydride before use. Petroleum ether refers to the 40–60 °C boiling fraction. Cyclic imines, **7a** and **7g**–**i**, and *m*-chloroperbenzoic acid (*m*-CPBA) were of commercial grade (Aldrich) and used without further purification. 2-Oxazolines, **7b**,[23–25] **7c**,[26] **7d**[27] and **7e**[20], **7f** were prepared according to the general literature procedure,[20] which involved condensation of *ortho* esters, as received commercially (Aldrich) and without further purification, with 2-amino alcohols in the presence of a catalyst (CF_3COOH). Amino alcohols were synthesized by reduction of the corresponding commercially available α-amino acids, following reported synthetic protocols.[19] The ^1H and the ^{13}C NMR spectra were recorded with a Bruker Avance 400 apparatus (400.13 and 100.62 MHz, for ^1H and ^{13}C, respectively) with $CDCl_3$ as the solvent and TMS as an internal standard (δ=7.26 ppm for ^1H spectra; δ=77.0 ppm for ^{13}C spectra). The IR spectra were recorded with an FTIR spectrophotometer Digilab Scimitar Series FTS 2000. Polarimetric measurements were performed by a Jasco P-120 polarimeter. GC–MS analyses were performed with an Agilent Technologies 6850 series II gas chromatograph (5% phenylpolymethylsiloxane capillary column, 30 m, 0.25 mm i.d.), equipped with a 5973 Network mass-selective detector operating at 70 eV. The electrospray ionization [HRMS (ESI)] experiments were carried out in a hybrid QqTOF mass spectrometer (PE SCIEX–Q-STAR) equipped with an ion-spray ionisation source. MS (+) spectra were acquired by direct infusion (5 μL min^{-1}) of a solution containing the appropriate sample (10 pmol μL^{-1}) dissolved in a solution 0.1% acetic acid, methanol/water (50:50) at the optimum ion voltage of 4800 V. The nitrogen gas flow was set at 30 psi (pounds per square inch) and the potentials of the orifice, the focussing ring and the skimmer were kept at 30, 50 and 25 V relative to ground, respectively. Melting points were determined with an Electrothermal melting point apparatus and are uncorrected. TLC was performed on Merck silica gel plates with F-254 indicator; viewing was by UV light (254 nm). Column chromatographies were performed on silica gel (63–200 mm) using petroleum ether/diethyl ether (Et_2O) or petroleum ether/ethyl acetate (AcOEt) mixtures as eluents.

4.2. General procedure for the synthesis of condensed oxaziridines 8g,[30] 8h[31] and 8i

To an ice cooled solution of the oxazolines **7g**–**h** or 2-methyl-1-pyrroline **7i** (1.0 mmol) in CH_2Cl_2 (10 mL) was added dropwise a small excess of *m*-CPBA (270 mg, 1.1 mmol, 70%) in CH_2Cl_2 (5 mL) previously cooled in an ice bath. The reaction was taken under stirring and cooling (0–5 °C) for about 3 h and monitored by gas-chromatography. When the reaction was completed, the organic mixture was washed once with a dilute cooled solution of $Na_2S_2O_3$ (5%, 10 mL), then three time with 10 mL of a cooled solution of Na_2CO_3 (5%). After drying over anhydrous Na_2SO_4, the mixture was concentrated in vacuo affording the condensed oxaziridine as pure compound.

*4.2.1. 5-Methyl-6-oxa-1-aza-bicyclo[3.1.0]hexane (**8i**).* Yield: 97 mg (98%), yellow oil. ^1H NMR (400.13 MHz, $CDCl_3$): δ=1.50 (3H, s, CH_3), 1.50–1.59 (2H, m, $CH_2CH_2CH_2$), 1.69–1.75 (1H, m, CH2*C*HHCO), 2.20 (1H, ddd, *J*=2.0 , 7.0 , 8.6 Hz, CH_2CHHCO), 2.82–2.89 (1H, m, N–C*H*H), 3.33 (1H, ddd, *J*=2.0 , 7.0 , 8.6 Hz, N–CH*H*) ppm; ^{13}C NMR (100.62 MHz, $CDCl_3$): δ=18.5, 19.9, 30.5, 55.4, 87.7 ppm; FTIR ($CHCl_3$): 2993, 2932 and 2862 (C–H aliph.), 1372 (C–O), 1221 (N–O) cm^{-1}; GC–MS (70 eV): *m*/*z* (%)=99 (100) $[M]^+$, 98 (63), 80 (10), 69 (39); HRMS (ESI): calcd for $C_5H_{10}NO$: (100.0762) $[M+H]^+$; found: (100.0760).

4.3. General procedure for the synthesis of azodioxy-carbonyl dimers 12a–i[28]

A solution of *m*-CPBA (540 mg, 2.2 mmol, 70%) in CH_2Cl_2 (10 mL), previously cooled in an ice bath, was added dropwise to an ice cooled solution of the cyclic imines **7a**–**i** (1.0 mmol) in CH_2Cl_2 (10 mL) The mixture was allowed to gradually warm to room temperature (with stirring) over a 12-h period. After further dilution with CH_2Cl_2 (10 mL), the solution was stirred with excess powdered anhydrous sodium carbonate until carbon dioxide evolution ceased. After filtration, the solvent was evaporated in vacuo at room temperature giving the dimers **12a**–**i** as pure compounds.

*4.3.1. trans-Benzoic acid 2-nitrosoethyl ester dimer (**12a**).* Yield: 177 mg (99%), bright white needle-like crystals with mp 74–75 °C (diethyl ether). ^1H NMR (400.13 MHz, $CDCl_3$): δ=4.72 (2H, t, *J*=5.1 Hz, O–CH_2), 4.81 (2H, t, *J*=5.1 Hz, N–CH_2), 7.39 (2H, t, *J*=7.6 Hz, Ph), 7.54 (1H, t, *J*=7.6 Hz, Ph.), 7.98 (2H, d, *J*=7.6 Hz, Ph) ppm; ^{13}C NMR (100.62 MHz, $CDCl_3$): δ=57.7, 58.8, 128.4, 129.3, 129.7, 133.3, 166.1 ppm; FTIR ($CHCl_3$): 3028 (C–H arom.), 2981 and 2950 (C–H aliph.), 1722 (C=O), 1219 (N–O) cm^{-1}; GC–MS (70 eV): *m*/*z* (%)=358 (<1) $[M]^+$, 179 (5), 161 (10), 123 (12), 105 (100), 77 (65), 57 (30); HRMS (ESI): calcd for $C_{18}H_{19}N_2O_6$: (359.1243) $[M+H]^+$; found: (359.1245).

*4.3.2. trans-(S)-Benzoic acid 2-nitroso-3-phenypropyl ester dimer (**12b**).* Yield: 258 mg (96%), bright white needle-like crystals with mp 110–111 °C (diethyl ether). ^1H NMR (400.13 MHz, $CDCl_3$): δ=2.94 (2H, dd, *J*=5.3 , 7.2 Hz, PhCH_2), 4.52 (1H, dd, *J*=3.4 , 11.7 Hz, OC*H*H), 4.61 (1H, dd, *J*=8.6 , 11.7 Hz, O–CH*H*), 6.02–6.09 (1H, m, N–CH), 7.19–7.30 (7H, m, Ph), 7.41 (1H, t, *J*=7.5 Hz, Ph), 7.80 (2H, d, *J*=7.9 Hz, Ph) ppm; ^{13}C NMR (100.62 MHz, $CDCl_3$): δ=34.5, 62.8, 66.1, 127.3, 128.2, 128.8, 129.2 (2C), 129.6, 133.1, 135.1, 165.8 ppm; FTIR ($CHCl_3$): 3031 (C–H arom.), 2958 and 2850 (C–H aliph.), 1722 (C=O), 1273 (N–O) cm^{-1}; GC–MS (70 eV): *m*/*z* (%)=538 (<1) $[M]^+$, 269 (6), 147 (43), 130 (72), 117 (31), 105 (100), 91 (51), 77 (72). $[\alpha]_D^{24}$ −104.6 (*c* 0.1, $CHCl_3$); HRMS (ESI): calcd for $C_{32}H_{31}N_2O_6$: (539.2182) $[M+H]^+$; found: (539.2185).

*4.3.3. trans-(S)-Propionic acid 3-methyl-2-nitrosobutyl ester dimer (**12c**).* Yield: 171 mg (99%), pale yellow oil. ^1H NMR (400.13 MHz, $CDCl_3$): δ=0.98 (3H, d, *J*=6.8 Hz, CHCH_3), 1.05 (3H, d, *J*=6.8 Hz, CHCH_3), 1.12 (3H, t, *J*=7.5 Hz, CH_2CH_3), 2.21–2.33 (3H, m, CH_2CH_3 and $CHCH_3$), 4.34 (1H,dd, *J*=9.5 , 11.7 Hz, O–C*H*H), 4.57 (1H, dd, *J*=3.0 , 11.7 Hz, O–CH*H*), 5.44 (1H, td, *J*=3.0 , 9.5 Hz, N–HC) ppm; ^{13}C NMR (100.62 MHz, $CDCl_3$): δ=8.7, 18.3, 19.4, 27.0, 28.0, 61.3, 70.7, 173.8 ppm; FTIR ($CHCl_3$): 2974 and 2885 (C–H aliph.), 1738 (C=O), 1211 (N–O) cm^{-1}; GC–MS (70 eV): *m*/*z* (%)=346 (<1) $[M]^+$,173 (3), 156 (4), 99 (27), 69 (89), 57 (100); $[\alpha]_D^{24}$ +1.9 (*c* 0.1, $CHCl_3$); HRMS (ESI): calcd for $C_{16}H_{31}N_2O_6$: (347.2182) $[M+H]^+$; found: (347.2181).

*4.3.4. trans-(S)-Propionic acid 2-nitroso-3-phenylpropyl ester dimer (**12e**).* Yield: 217 mg (99%), green oil. ^1H NMR (400.13 MHz,

$CDCl_3$): δ=1.10 (3H, t, J=7.5 Hz, CH_2CH_3), 2.26 (2H, q, J=7.5 Hz, CH_2CH_3), 2.78 (1H, dd, J=7.5 , 14.0 Hz, HHC–Ph), 2.88 (1H, dd, J=7.5 , 14.0 Hz, HHC–Ph), 4.32 (1H, dd, J=8.9 , 11.8 Hz, O–CHH), 4.39 (1H, dd, J=3.6 , 11.8 Hz, O–CHH), 5.81–5.87 (1H, m, N–CH), 7.14–7.27 (5H, m, Ph) ppm; ^{13}C NMR (100.62 MHz, $CDCl_3$): δ=8.8, 27.1, 34.2, 61.8, 66.1, 127.2, 128.6, 129.0, 129.7, 135.0, 173.6 ppm; FTIR ($CHCl_3$): 3027 (C–H arom.), 2945 (C–H aliph.), 1742 (C=O), 1181 (N–O) cm^{-1}; GC–MS (70 eV): m/z (%)=442 (<1) $[M]^+$, 221 (8), 147 (62), 130 (100), 117 (89), 91 (82), 57 (63); $[\alpha]_D^{24}$ −55.0 (c 0.1, $CHCl_3$); HRMS (ESI): calcd for $C_{24}H_{31}N_2O_6$: (443.2182) $[M+H]^+$; found: (443.2180).

*4.3.5. cis/trans Propionic acid 4-methyl-2-nitrosopentyl ester dimer mixture (**12f**).* Yield: 181 mg (97%), colourless oil. cis/trans Ratio 50:50 calculated by ^{1}H NMR. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ=0.92–0.96 (12H, m, $CHCH_3$), 1.07–1.16 (6H, m, CH_2CH_3), 1.30–1.42 (2H, m, $CHCH_2CH$), 1.49–1.52 (2H, m, $CHCH_2CH$), 1.84–1.91 (2H, m, CH_3CHCH_3), 2.23–2.32 (4H, m, CH_2CH_3), 4.20–4.26 (2H, m, O–CH_2), 4.39–4.44 (2H, m, O–CH_2), 5.76–5.89 (2H, m, N–CH) ppm; ^{13}C NMR (100.62 MHz, $CDCl_3$): δ=8.8, 21.7, 21.9, 22.7, 24.7, 24.8, 27.1, 36.9, 37.3, 63.1, 63.2, 63.7, 173.6, 173.8 ppm; FTIR ($CHCl_3$): 2962 and 2870 (C–H aliph.), 1742 (C=O), 1453 and 1385 (N–O *cis*), 1199 (N–O *trans*) cm^{-1}; GC–MS (70 eV): m/z (%)=374 (<1) $[M]^+$, 187 (1), 145 (10), 113 (21), 75 (35), 57 (100); HRMS (ESI): calcd for $C_{18}H_{35}N_2O_6$: (375.2495) $[M+H]^+$; found: (375.2491).

*4.3.6. Propionic acid 2-methyl-2-nitrosopropyl ester dimer (**12g**).* Total yield: 156 mg (98%). *trans*-Isomer: yield: 124 mg (78%), blue oil. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ=1.13 (3H, t, J=7.6 Hz, CH_2CH_3), 1.60 [6H, s, $C(CH_3)_2$], 2.32 (2H, q, J=7.6 Hz, CH_2CH_3), 4.39 (2H, s, O–CH_2) ppm; ^{13}C NMR (100.62 MHz, $CDCl_3$): δ=8.9, 23.1, 27.3, 68.1, 86.1, 173.5 ppm; FTIR (film): 2983 and 2944 and 2884 (C–H aliph.), 1745 (C=O), 1181 (N–O) cm^{-1}; GC–MS (70 eV): m/z (%)=318 (<1) $[M]^+$, 159 (1), 129 (10), 57 (100); HRMS (ESI): calcd for $C_{14}H_{27}N_2O_6$: (319.1869) $[M+H]^+$; found: (319.1871). *cis*-Isomer: yield: 32 mg (20%), blue oil. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ=1.13 (3H, t, J=7.6 Hz, CH_2CH_3), 1.15 [6H, s, $C(CH_3)_2$], 2.23 (2H, q, J=7.6 Hz, CH_2CH_3), 4.80 (2H, s, O–CH_2) ppm; ^{13}C NMR (100.62 MHz, $CDCl_3$): δ=8.9, 23.5, 27.5, 68.7, 97.3, 173.8 ppm; FTIR (film): 2983 and 2944 and 2884 (C–H aliph.), 1743 (C=O), 1375 and 1348 (N–O) cm^{-1}; GC–MS (70 eV): m/z (%)=318 (<1) $[M]^+$, 159 (1), 129 (10), 57 (100); HRMS (ESI): calcd for $C_{14}H_{27}N_2O_6$: (319.1869) $[M+H]^+$; found: (319.1870).

*4.3.7. Acetic acid 2-methyl-2-nitrosopropyl ester dimer (**12h**).* Total yield: 141 mg (97%). *trans*-Isomer: Yield: 93 mg (64%), green oil. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ=1.60 [6H, s, $C(CH_3)_2$], 2.05 (3H, s, CH_3CO), 4.38 (2H, s, O–CH_2) ppm; ^{13}C NMR (100.62 MHz, $CDCl_3$): δ=20.4, 23.1, 68.2, 86.0, 170.1; FTIR ($CHCl_3$): 2986 and 2850 (C–H aliph.), 1746 (C=O), 1213 (N–O) cm^{-1}; GC–MS (70 eV): m/z (%)=290 (<1) $[M]^+$, 115 (12), 55 (20), 43 (100); HRMS (ESI): calcd for $C_{12}H_{23}N_2O_6$: (291.1556) $[M+H]^+$; found: (291.1554). *cis*-Isomer: Yield: 48 mg (33%), green oil. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ=1.12 [6H, s, $C(CH_3)_2$], 1.94 (3H, s, CH_3CO), 4.77 (2H, s, O–CH_2) ppm; ^{13}C NMR (100.62 MHz, $CDCl_3$): δ=18.1, 24.7, 66.7, 97.2, 170.2; FTIR ($CHCl_3$): 2986 and 2850 (C–H aliph.), 1746 (C=O), 1377 and 1350 (N–O) cm^{-1}; GC–MS (70 eV): m/z (%)=290 (<1) $[M]^+$, 115 (12), 55 (20), 43 (100); HRMS (ESI): calcd for $C_{12}H_{23}N_2O_6$: (291.1556) $[M+H]^+$; found: (291.1555).

*4.3.8. trans-5-Nitrosopentan-2-one dimer (**12i**).* Yield: 112 mg (98%), orange oil. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ=2.14 (2H, quintet, J=6.7 Hz, $CH_2CH_2CH_2$), 2.16 (3H, s, CH_3CO), 2.60 (2H, t, J=6.7 Hz, CH_2CO), 4.27 (2H, t, J=6.7 Hz, N–CH_2) ppm; ^{13}C NMR (100.62 MHz, $CDCl_3$): δ=19.0, 29.9, 40.0, 58.1, 206.8 ppm; FTIR ($CHCl_3$): 2960 and 2862 (C–H aliph.), 1716 (C=O), 1213 (N–O) cm^{-1}; GC–MS (70 eV): m/z (%)=230 (<1) $[M]^+$, 98 (55), 85 (10), 72 (100); HRMS (ESI): calcd for $C_{10}H_{19}N_2O_4$: (231.1345) $[M+H]^+$; found: (231.1343).

4.4. General procedure for the synthesis of oximes 13a–f[28] and 13i

A solution of the azodioxy-carbonyl dimers **12a–f,i** (1.0 mmol) in toluene (5 mL) was heated at reflux under magnetic stirring for 10–50 min. After this time, TLC was used to monitor reaction progress. The solution was cooled to room temperature and evaporated to dryness to give a crude material. The reaction mixture was purified by chromatography on silica gel (petroleum ether/ethyl acetate=70:30 for entries 1 and 5 of Table 3; petroleum ether/diethyl ether=70:30 for entries 3 and 6 of Table 3).

*4.4.1. Benzoic acid 2-hydroxyiminoethyl ester (**13a**).* Total yield: 177 mg (99%). *Z*-Isomer: yield: 102 mg (57%), white solid with mp 62–63 °C (hexane). R_f (petroleum ether/ethyl acetate=70:30): 0.53; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ=4.93 (2H, d, J=5.6 Hz, O–CH_2), 7.45 (2H, t, J=7.5 Hz, Ph), 7.58 (1H, t, J=7.4 Hz, Ph), 8.07 (2H, t, J=7.5 Hz, Ph), 7.65 (1H, t, J=5.6 Hz, HC=N), 9.24 (1H, s, broad, OH, exchanges with D_2O) ppm; ^{13}C NMR (100.62 MHz, $CDCl_3$): δ=61.4, 128.4, 129.4, 129.8, 133.3, 146.4, 166.1 ppm; FTIR ($CHCl_3$): 3579 (free OH), 1722 (C=O), 1269 (C–O), 1113 (C=N), 920 (N–O) cm^{-1}; GC–MS (70 eV): m/z (%)=179 (5) $[M]^+$, 161 (9), 123 (11), 105 (100), 77 (5), 57 (25); HRMS (ESI): calcd for $C_9H_{10}NO_3$: (180.0660) $[M+H]^+$; found: (180.0661). *E*-Isomer: yield: 75 mg (42%), white solid with mp 65–66 °C (hexane). R_f (petroleum ether/ethyl acetate=70:30): 0.59; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ=5.18 (2H, d, J=3.9 Hz, O–CH_2), 6.99 (1H, t, J=3.9 Hz, HC=N), 7.48 (2H, t, J=7.5 Hz, Ph), 7.58 (1H, t, J=7.4 Hz, Ph), 8.07 (2H, t, J=7.5 Hz, Ph), 9.50 (1H, s, broad, OH, exchanges with D_2O) ppm; ^{13}C NMR (100.62 MHz, $CDCl_3$): δ=58.8, 128.5, 129.4, 129.7, 133.4, 148.4, 166.2 ppm; FTIR ($CHCl_3$): 3683 (free OH), 1723 (C=O), 1266 (C–O), 1117 (C=N), 920 (N–O) cm^{-1}; GC–MS (70 eV): m/z (%)=179 (5) $[M]^+$, 161 (9), 123 (11), 105 (100), 77 (5), 57 (25); HRMS (ESI): calcd for $C_9H_{10}NO_3$: (180.0660) $[M+H]^+$; found: (180.0662).

*4.4.2. Z/E Benzoic acid 2-hydroxyimino-3-phenylpropyl ester mixture (**13b**).* Total yield: 258 mg (96%), white low melting solid. R_f (petroleum ether/ethyl acetate=70:30): 0.55; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ=3.69 (2H, s, PhCH_2, *E* isomer), 3.88 (2H, s, PhCH_2, *Z* isomer), 4.84 (2H, s, O–CH_2, *Z* isomer), 5.20 (2H, s, O–CH_2, *E* isomer), 7.18–7.27 (10H, m, Ph), 7.38–7.45 (4H, m, Ph), 7.55 (2H, t, J=7.5 Hz, Ph), 7.92 (4H, d, J=8.2 Hz, Ph), 8.60 (2H, s, broad, OH, exchanges with D_2O) ppm; ^{13}C NMR (100.62 MHz, $CDCl_3$): δ=31.9, 37.4, 58.8, 64.2, 126.7, 126.8, 128.3, 128.6, 128.7, 128.8, 129.1, 129.5, 129.7, 133.2, 135.8, 136.0, 155.0, 156.6, 165.9 ppm; FTIR ($CHCl_3$): 3681 (free OH), 3309 (broad OH), 1722 (C=O), 1271 (C–O), 1113 (C=N), 940 (N–O) cm^{-1}; GC–MS (70 eV): m/z (%)=269 (7) $[M]^+$, 147 (43), 130 (72), 117 (76), 105 (100), 91 (51), 77 (80); HRMS (ESI): calcd for $C_{16}H_{16}NO_3$: (270.1130) $[M+H]^+$; found: (270.1128).

*4.4.3. Propionic acid 2-hydroxyimino-3-methylbutyl ester (**13c**).* Total yield 169 mg (98%). *Z*-Isomer: Yield: 84 mg (49%), pale yellow oil. R_f (petroleum ether/diethyl ether=70:30): 0.52; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ=1.11 [6H, d, J=7.0 Hz, $CH(CH_3)_2$], 1.12 (3H, t, J=7.6 Hz, CH_2CH_3), 2.36 (2H, q, J=7.6 Hz, CH_2CH_3), 3.37 [1H, eptet, J=7.0 Hz, $CH(CH_3)_2$], 4.66 (2H, s, O–CH_2), 8.75 (1H, s, broad, OH, exchanges with D_2O) ppm; ^{13}C NMR (100.62 MHz, $CDCl_3$): δ=8.9, 18.5, 25.9, 27.4, 62.2, 64.3, 159.9, 173.9 ppm; FTIR ($CHCl_3$): 3582 (free OH), 3305 (broad OH), 2975, 2941 and 2885 (C–H aliph.), 1737 (C=O), 1266 (C–O), 1182 and 1082 (C=N), 920 (N–O) cm^{-1}; GC–MS (70 eV): m/z (%)=173 (2) $[M]^+$, 156 (4), 99

(28), 69 (91), 57 (100); HRMS (ESI): calcd for $C_8H_{16}NO_3$: (174.1130) $[M+H]^+$; found: (174.1130). *E*-Isomer: Yield: 84 mg (49%), pale yellow oil. R_f (petroleum ether/diethyl ether=70:30): 0.59; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ=1.11 [6H, d, J=6.9 Hz, CH(CH_3)$_2$], 1.16 (3H,t, J=7.6 Hz, CH_2CH_3), 2.38 (2H, q, J=7.6 Hz, CH_2CH_3), 2.64 [1H, eptet, J=6.9 Hz, $CH(CH_3)_2$], 4.98 (2H, s, O–CH_2), 8.75 (1H, s, broad, OH, exchanges with D_2O) ppm; ^{13}C NMR (100.62 MHz, $CDCl_3$): δ=9.0, 19.8, 27.5, 30.5, 57.8, 160.7, 173.8 ppm; FTIR ($CHCl_3$): 3587 (free OH), 3283 (broad OH), 2974, 2939 and 2886 (C–H aliph.), 1738 (C=O), 1266 (C–O), 1182 and 1082 (C=N), 920 (N–O) cm^{-1}; GC–MS (70 eV): m/z (%)=173 (2) $[M]^+$, 156 (4), 99 (28), 69 (91), 57 (100); HRMS (ESI): calcd for $C_8H_{16}NO_3$: (174.1130) $[M+H]^+$; found: (174.1132).

*4.4.4. Propionic acid 2-hydroxyimino-3-phenylpropyl ester (**13e**).* Total yield: 219 mg (99%). *Z*-Isomer: yield: 146 mg (66%), yellow oil. R_f (petroleum ether/ethyl acetate=70:30): 0.51; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ=1.10 (3H, t, J=7.5 Hz, CH_2CH_3), 2.29 (2H, q, J=7.5 Hz, CH_2CH_3), 3.80 (2H, s, PhCH_2), 4.60 (2H, s, O–CH_2), 7.16–7.32 (5H, m, Ph), 8.75 (1H, s, broad, OH, exchanges with D_2O) ppm; ^{13}C NMR (100.62 MHz, $CDCl_3$): δ=8.9, 27.2, 31.8, 63.4, 126.7, 128.6, 129.0, 135.5, 154.9, 173.8 ppm; FTIR ($CHCl_3$): 3579 (free OH), 3295 (broad OH), 3028 (C–H arom.), 2941 (C–H aliph.), 1739 (C=O), 1266 (C–O), 1177 and 1083 (C=N), 920 (N–O) cm^{-1}; GC–MS (70 eV): m/z (%)= 221 (8) $[M]^+$, 147 (78), 130 (100), 117 (85), 91 (83), 57 (73); HRMS (ESI): calcd for $C_{12}H_{16}NO_3$: (222.1130) $[M+H]^+$; found: (222.1130); *E*-Isomer: yield: 73 mg (33%), yellow oil. R_f (petroleum ether/ethyl acetate=70:30): 0.56; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ=1.09 (3H, t, J=7.5 Hz, CH_2CH_3), 2.27 (2H, q, J=7.5 Hz, CH_2CH_3), 3.61 (2H, s, PhCH_2), 4.95 (2H, s, O–CH_2), 7.16–7.32 (5H, m, Ph), 8.75 (1H, s, broad, OH, exchanges with D_2O) ppm; ^{13}C NMR (100.62 MHz, $CDCl_3$): δ=8.9, 29.7, 37.4, 58.2, 126.8, 128.8, 129.0, 136.1, 156.6, 173.7 ppm; FTIR ($CHCl_3$): 3582 (free OH), 3289 (broad OH), 3028 (C–H arom.), 2941 (C–H aliph.), 1738 (C=O), 1266 (C–O), 1177 and 1084 (C=N), 920 (N–O) cm^{-1}; GC–MS (70 eV): m/z (%)=221 (8) $[M]^+$, 147 (78), 130 (100), 117 (85), 91 (83), 57 (73); HRMS (ESI): calcd for $C_{12}H_{16}NO_3$: (222.1130) $[M+H]^+$; found: (222.1129).

*4.4.5. Propionic acid 2-hydroxyimino-4-methylpentyl ester (**13f**).* Total yield: 185 mg (99%). *Z*-Isomer: yield: 123 mg (66%), pale green oil. R_f (petroleum ether/diethyl ether=70:30): 0.56; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ=0.87 [6H, d, J=6.7 Hz, CH(CH_3)$_2$], 1.08 (3H, t, J=7.7 Hz, CH_2CH_3), 1.93–2.03 [m, 1H, $CH(CH_3)_2$], 2.22 (2H, d, J=7.5 Hz, $CHCH_2$), 2.31 (2H, q, J=7.7 Hz, CH_2CH_3), 4.56 (2H, s, O–CH_2), 8.70 (1H, s, broad, OH, exchanges with D_2O) ppm; ^{13}C NMR (100.62 MHz, $CDCl_3$): δ=8.86, 22.6, 25.6, 27.3, 34.6, 64.1, 155.8, 173.9 ppm; FTIR ($CHCl_3$): 3583 (free OH), 3286 (broad OH), 2960 (C–H aliph.), 1730 (C=O), 1266 (C–O), 1183 and 1083 (C=N), 920 (N–O) cm^{-1}; GC–MS (70 eV): m/z (%)=187 (<1) $[M]^+$, 145 (9), 113 (21), 75 (33), 57 (100); HRMS (ESI): calcd for $C_9H_{18}NO_3$: (188.1286) $[M+H]^+$; found: (188.1285). *E*-Isomer: yield: 62 mg (33%), pale green oil. R_f (petroleum ether/diethyl ether=70:30): 0.61; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ=0.84 [6H, d, J=6.6 Hz, CH(CH_3)$_2$], 1.10 (3H, t, J=7.7 Hz, CH_2CH_3), 1.78–1.85 [1H, m, $CH(CH_3)_2$], 2.05 (2H, d, J=7.2 Hz, $CHCH_2$), 2.32 (2H, q, J=7.7 Hz, CH_2CH_3), 4.90 (2H, s, O–CH_2), 8.70 (1H, s, broad, OH, exchanges with D_2O) ppm; ^{13}C NMR (100.62 MHz, $CDCl_3$): δ=8.86, 22.3, 25.9, 27.3, 39.6, 58.8, 156.5, 173.7 ppm; FTIR ($CHCl_3$): 3586 (free OH), 3286 (broad OH), 2960 (C–H aliph.), 1738 (C=O), 1260 (C–O), 1183 and 1084 (C=N), 922 (N–O) cm^{-1}; GC–MS (70 eV): m/z (%)=187 (<1) $[M]^+$, 145 (9), 113 (21), 75 (33), 57 (100); HRMS (ESI): calcd for $C_9H_{18}NO_3$: (188.1286) $[M+H]^+$; found: (188.1283).

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Supplementary data

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21. Crystal data for compound **12a**: $\mathbf{C^{18}H^{18}N^2O^6}$, Fw=358.34, T=93 K, monoclinic, space group P21/c, a=5.5243 (4), b=8.6318 (8), c=17.6998 (16) Å, β=94.366 (3), V=841.56 (12) Å3, Z=2, Dx=1.414 Mg m−3, μ (Mo Kα)=0.108 mm−1; crystal dimensions 0.44×0.24×0.14 mm3, λ=0.71073 Å (Mo Kα) radiation, graphite monochromator, Bruker SMART-APEX CCD diffractometer, equipped with a Bruker KRYOFLEX low temperature device. Data collection: ω and φ scan mode, 2θ<60°; 9958 collected reflections, 3072 unique, merging R=0.0223. The structure was solved by SIR2002 (Burla, M. C.; Camalli, M.; Carrozzini, B.; Cascarano, G. L.; Giacovazzo, C.; Polidori, G.; Spagna, R. *J. Appl. Crystallogr.* **2003**, *36*, 1103) and refined by full-matrix least-squares based on F_o^2, using SHELXL97 (Sheldrick, G.M., *Acta Cryst*, **2008**, *A64*, 112–122). H atoms were refined isotropically. The final consistency index were R=0.0458 and wR=0.1028 [0.0367 and 0.0967, respectively for 2552 reflections with $I_o>2.\sigma(I_o)$]; goodness-of-fit=1.065. Detailed crystallographic data were deposited as CCDC 782701 with the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.
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