12th International Electronic Conference on Synthetic Organic Chemistry (ECSOC-12) 1-30 November 2008
http://www.usc.es/congresos/ecsoc/12/ECSOC12.htm & http://www.mdpi.org/ecsoc-12

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Solvent-mediated reactivity of β-aminoalcohols against dialkyloxalate: synthesis of tetrasubstituted oxalamide *and*/ *or* morpholin-2,3-dione derivatives.

Maria Luisa Testa [(a)], Elena Zaballos-Garcia [(b)] and Ramón J. Zaragozá [(c)]

[(a)] Istituto per lo Studio dei Materiali Nanostrutturati, CNR, via Ugo La Malfa 153, 90146 Palermo, Italy; [(b)]Departamento Química Orgánica, Universidad de Valencia, Av. Vicente Andres Estelles, E-46100 Burjassot, Valencia, Spain; [(c)]Departamento Química Orgánica, Universidad de Valencia, Dr. Moliner 50, E-46180 Burjassot, Valencia, Spain.
email address: marialuisa.testa@ismn.cnr.it

Abstract: The reactivity of various β-aminoalcohols with diethyloxalate, in several reaction conditions, has been investigated. Lineal or cyclic derivatives were obtained depending on the nature of the solvent used and the starting material.
Keywords: tetrasubstituted oxalamide, morpholin-2,3-dione, theoretical calculations.

Introduction.

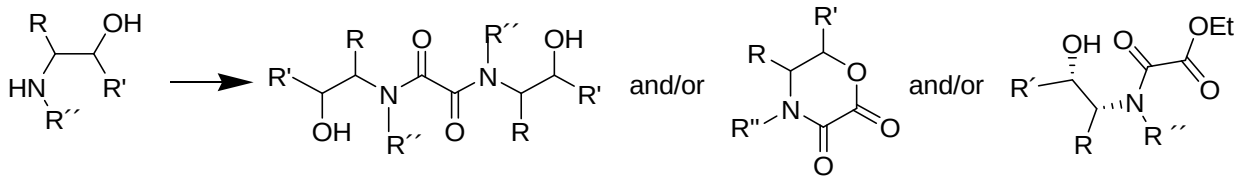
Oxalamides and morpholin-2,3-diones are important substructures in compounds that show biological activity including HIV-1 protease inhibitors, [1] cephalosporin bactericides, [2] and chemioterapic agents. [3] The literature describing these structures is rather plentiful. As concern oxalamide function, it has been established that the synthesis occurs in a variety of ways, among them, the reaction of primary amines and dialkyloxalate. [4] Since secondary amines react only slowly and incompletely with diethyloxalate, the tetraalkyloxalamides were prepared from amines and oxalyl chloride in the presence of a tertiary amine. [5] Frequently, in order to afford *N*-substituted oxalamides, the synthetic approach involves *N*-alkylation, once oxalamide was formed, or several steps, whereas the synthesis concerns unsymmetric oxalamide compounds. [6] When a *N*-substituted β-aminoalcohol is used, the reaction affords cyclic compounds identified as morpholin-2,3-diones. [7] Morpholin-2,3-dione ring can be disconnected to a β-aminoalcohol and a oxalate derivative and, using this procedure, a variety of *N*-substituted morpholin-2,3-diones could be obtained. Nevertheless, there are no reports in the literature of a detailed study on the reactivity of β-aminoalcohols towards dialkyloxalate in different reaction conditions.

Results and Discussion

In a previous paper [8] we presented the synthesis of C-2 symmetric polidentate oxalamide derivatives obtained by the reaction between aminodiols and diethyloxalate in toluene at reflux temperature. Herein, as a continuation of our interest in the synthesis of polyfunctionalized molecules, [9] we wish to report a full account of our recent results on a different solvent-mediated reactivity of β-aminoalcohols in presence of dialkyloxalate.

In order to prepare new C-2 symmetric polidentate aminoalcohols, a serie of aminoalcohol (see Scheme 1) were studied in the reaction with diethyloxalate in different molar ratio (2:1 and 1:1)

using toluene or ethanol as solvent. We observed a quite different behaviour of *N*-substituted β-aminoalcohols with respect to primary β-aminoalcohols.



1 **2** **3** **4**

a	R = H	R´ = H	R´´ = H	
b	R = H	R´ = H	R´´ = CH_3	
c	R=H	R´ = Ph	R´´ = H	
d	R = H	R´ = Ph	R´´ = CH_3	
e	R = (2*S*)-CH_3	R´ = (1*R*)-Ph	R´´ = H	Norephedrine
f	R = (2*R*)-CH_3	R´ = (1*S*)-Ph	R´´ = CH_3	Ephedrine
g	R = (2*S*)-CH_3	R´ = (1*S*)-Ph	R´´ = CH_3	Pseudoephedrine
h	R = (3*R*)-Ph	R´ = (2*R*)-CH_2OH	R´´ = H	
i	R = (3*R*)-Ph	R´ = (2*R*)-CH_2OH	R´´ = CH_3	
j	R = (3*R*)-Ph	R´ = (2*R*)-CH_2OH	R´´ = CH_2CH_3	

Scheme 1. Reaction between aminoalcohol **1** and diethyloxalate (1:1 or 2:1) in ethanol or toluene afforded oxalamide derivatives **2** and/or morpholine-2,3-diones **3**

We have firstly investigated the condensation of diethyloxalate with primary β-aminoalcohols **1a, 1c, 1e** and **1h**, [10] both in toluene and ethanol, at room or reflux temperature, using different molar ratio (2:1 and 1:1). As it was expected, all the reactions afforded as only compound, the corresponding C-2 symmetric oxalamides **2a, 2c, 2e** and **2h** in yields 67-96% and no traces of the corresponding morpholine-2,3-diones **3** were detected. The analytical and spectroscopic data for compounds **2a** [4, 11], **2e** [12] and **2h** [8] resulted identical to those previously reported, whereas, the structure of **2c** was elucidated by spectroscopic methods.

It is remarkable that in the reaction of (1*R*,2*S*)-(-)-norephedrine (**1e**), when toluene was used as solvent, the *N*,*N'*-Bis-[(1*R*,2*S*)-(-)-norephedrine]oxalamide (**2e**) [12] was isolated in high yields along with traces of the corresponding oxamidic ester **4e** [13] (Table 1) which appears to result from failed condensation to bis-oxalamide. In contrast, using ethanol, the oxamidic ester **4e** was isolated as major product **2e:4e** 1:2 .

Table 1. Products obtained of the reactions of β-aminoalcohols **1** with diethyl oxalate (*see experimental section)*

β-Aminoalcohol	**1a**	**1b**	**1c**	**1d**	**1e**	**1f**	**1g**	**1h**	**1i**	**1j**
In toluene (method A)*	**2a**	**2b**	**2c**	**2d**	**2e:4e** (10:1)	**2f: 3f** (10:0.2)	**2g: 3g** (9:1)	**2h**	**3i**	**3j**
In ethanol (method B)*	**2a**	**2b:3b** (1:1)	**2c**	**2d:3d** (10:2.7)	**2e:4e** (1:2)	**3f**	**2g: 3g** (1:1)	**2h**	**3i**	**3j**

The reaction of *N*-substituted β-aminoalcohols **1b, d, f, g, i, j** with diethyloxalate (molar ratio 1:1 and 2:1) showed different trends depending on either starting material or the solvent used. Whereas the literature reports that *N*-substituted β-aminoalcohols afforded morpholin-2,3-diones **3**, as only compound, we found also the corresponding linear derivatives, bis-oxalamides **2**.

In particular, the reaction of 2-methylaminoethanol (**1b**) and 2-(methylamino)-1-phenylethanol (**1d**) in toluene, at room or reflux temperature, afforded as only compound the tetraalkyloxalamides **2b** and **2d,** respectively. No traces of the corresponding six membered ring cyclization products were detected. The results were different when ethanol was used as solvent of the reaction, in the same reaction conditions, a mixture of the corresponding linear (**2b** or **2d**) and cyclic compounds (**3b** or **3d**) was obtained (Table 1). The corresponding morpholin-2,3-dione **3b** and **3d** were previously synthesised by other methods as the palladium-catalyzed carbonylations. [14] The structures of **2b** and **2d** were elucidated by spectroscopy.

Remarkable results were obtained when chiral β–aminoalcohols (1*S*, 2*R*)-(+)-ephedrine (**1f)** and (1*S*, 2*S*)-(+)-pseudoephedrine (**1g**) were used as starting materials. When (1*S*, 2*R*)-(+)-ephedrine (**1f)** was allowed to react with diethyloxalate using ethanol as solvent: only cyclic compound **3f** [15] (60%) was isolated. In contrast, both linear oxalamide **2f** and traces of cyclic compound **3f** were isolated when the reaction was carried out in toluene, thereby confirming the role of the solvent in the reaction trend. To the best of our knowledge, only one reference [16] reports the synthesis of this compound **2f**. However, when we carried out the reaction in the experimental condition furnished by authors, we obtained the cyclic derivative **3f** without any traces of linear bis-oxalamide **2f**. So, this is the first synthesis of the ephedrine derived oxalamide **2f**.

Using as starting material (1*S*, 2*S*)-(+)-pseudoephedrine (**1g**), when the reaction was carried out in toluene, a mixture (10:0.2) of lineal (**2g**) and cyclic (**3g**) derivatives was obtained. When ethanol was used as solvent, an equimolar mixture of lineal /cyclic derivatives was found (Table 1).

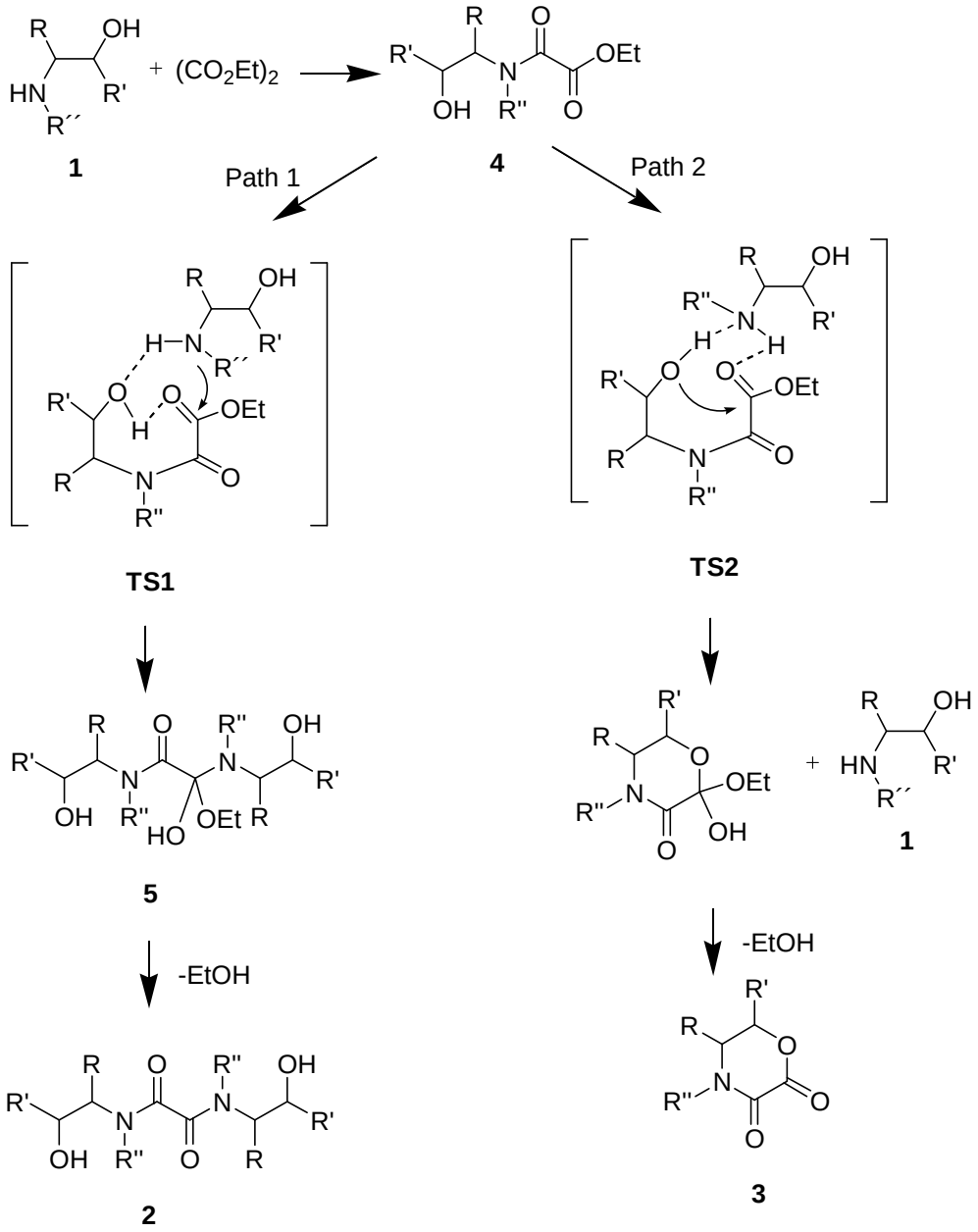
Finally, *N*-substituted β-aminodiols, (2*R*, 3*R*)-3-methylamino-3-phenylpropane-1,2-diol **(1i)** [9d] and (2*R*, 3*R*)-3-ethylamino-3-phenylpropane-1,2-diol (**1j)** [9d] afforded, in either toluene or ethanol and in different molar ratios, the corresponding cyclic morpholine-2,3-dione derivatives **3i** and **3j** respectively, as only reaction product.

The structures of **2-4** were confirmed by ^{1}H and ^{13}C NMR.

It is necessary to emphasize the difference in the ^{1}H and ^{13}C NMR spectrum of the N-H linear structures **(2a**, **2c, 2e** and **2h)** or the N-alkyl substituted (**2b, 2d**, **2f** and **2g**). Whereas the derivatives N-H showed simple spectra, due to only one conformation present. This conformation is stabilized by intramolecular hydrogen bonding between the amidic proton and the β-carbonyl group [6a, 12b, 17]. On the other hand, the tetralkyl-substituted oxalamides showed great complexity in ^{1}H and ^{13}C NMR due to the different conformations that these compounds adopt.

The different reactivity observed in the reaction of diethyloxalate with primary β-aminoalcohols and N-alkyl β-aminoalcohols encourages us to perform and theoretical study of the possible mechanism.

The suggested mechanism is presented in Scheme 2, the energies and geometries of preliminary transition states (TS1 and TS2) involved in the mechanism are in Table 2 and Figure 1, respectively.



Scheme 2. Mechanism reaction between aminoalcohol **1** and diethyloxalate

The aminolysis of the diethyloxalate through nucleophilic attack of aminoalcohol **1** gives in a first stage the oxamidic ester **4**. Another aminolysis process (Path 1) by a second molecule of aminoalcohol **1**, and intramolecular catalysis of the hydroxyl group present in oxamidic ester **4** [18] would afford the neutral tetrahedral intermediate **5**, which by expulsion of ethanol would give finally the bis-oxalamide **2**. On the other hand (Path 2), intramolecular attack of the hydroxyl group to the ester moiety of **4** catalyzed by a second molecule of aminoalcohol **1** [19] and finally expulsion of ethanol would give the morpholin-2,3-dione **3**.

The preliminary theoretical study of this transformation has been made using the ethanolamine **1a** (R=R'=R"=H) and the N-metyl ethanolamine **1b** (R=R'=H, R"=Me) with the oxamidic ester **4** (methyl replace the ethyl group). All calculations were carried out with the Gaussian 03 suite of programs. [20] The study has been made using density functional theory (DFT) [21] by means of B3LYP/6-31G** [22] energy calculations.

Table 2. Total (*E* in a.u.) and relative (ΔE in kcal mol^{-1}) energies of the initial products and some TS involved in the reaction of aminoalcohols **1a** and **1b** with dimethyloxalate *in vacuo*.

	E	ΔE
R"=H		
4a+**1a**	-762.014368	0.00
TS1a	-761.986228	17.66
TS2a	-761.981726	20.48
R"=Me		
4b+**1b**	-840.627713	0.00
TS1b	-840.600586	17.02
TS2b	-840.601525	16.43

As we can see in the Table 2, the formation of the bis-oxalamide **2a** is favored kinetically. The transition state **TS1a** is 2.8 kcal mol^{-1} lower than **TS2a**. However, with the N-methyl aminoalcohol **1b**, the formation of the morpholin-2,3-dione **3b** is a little more favored. The transition state **TS2b** is 0.6 kcal mol^{-1} lower than **TS1b**.

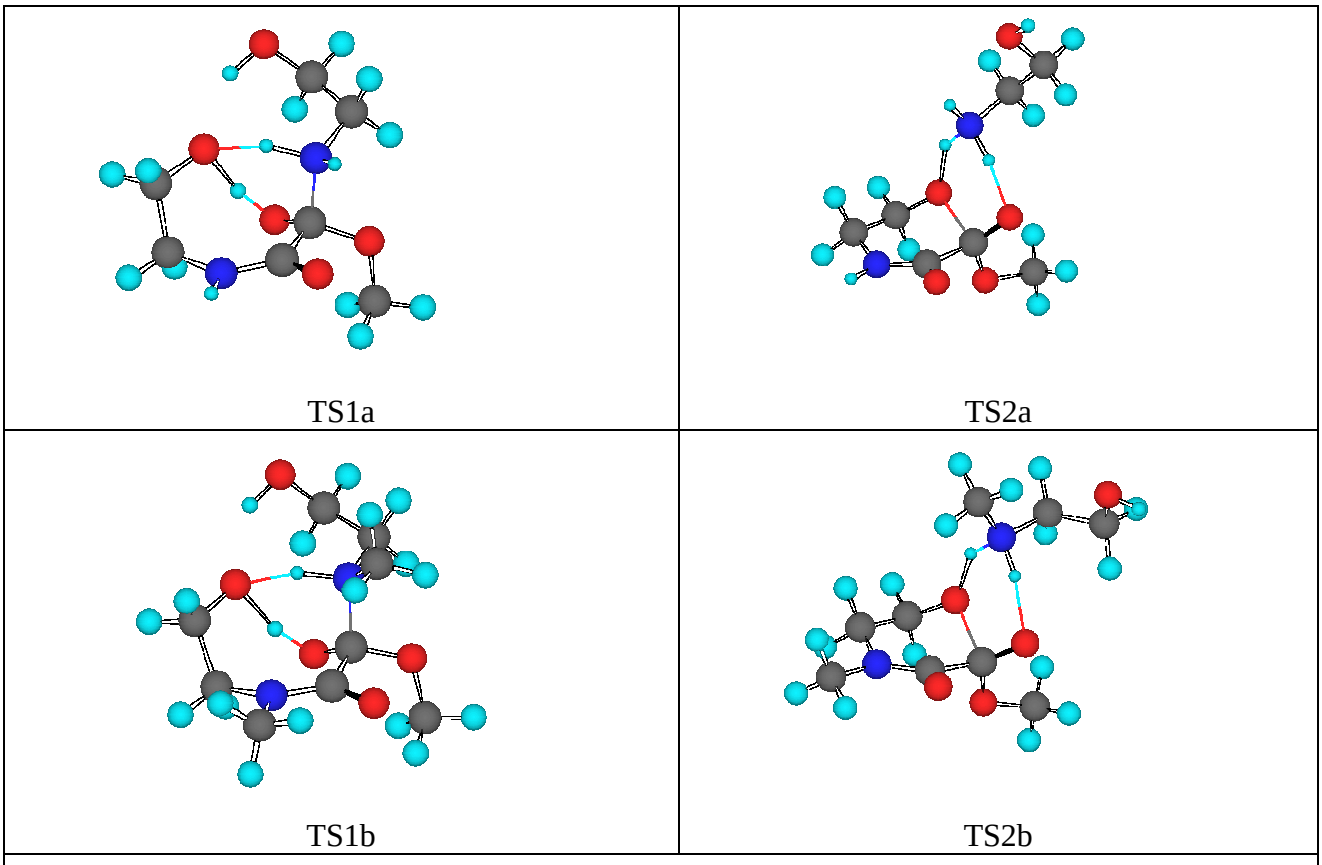


Figure 1. Geometries of the transition structures **TS1a**, **TS2a**, **TS1b** and **TS2b** involved in the reaction of aminoalcohols **1a** and **1b** with dimethyloxalate

Conclusion.

In summary, we have presented a different reactivity of various β-aminoalcohols mediated by the solvent used. The performed experiments showed that the use of a polar medium reaction such as ethanol encourages the synthesis of cyclic morpholin-2,3-diones, on the other hand, the synthesis of N-substitued bis-oxalamide derivatives can be afforded using apolar solvent as toluene. Here we present theoretical preliminary calculations.

Experimental Section.

Unless otherwise specified, materials were purchased from commercial suppliers and used without further purification. Solvents were distilled prior to use. Thin-layer chromatography was performed on Merck PL60 F_{254} sheets. Preparative column chromatography was performed on Merck Kieselgel 60 (230–240 mesh) silica gel. Melting points were determined with a Sanyo-Gallencamp capillary apparatus and are uncorrected. IR spectra were recorded on a Jasco FT-IR 5300 spectrometer. Optical rotations were measured at room temperature in a Perkin Elmer 241 polarimeter. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Avance DRX Bruker 300 MHz spectrometer, in DMSO-d_6 and in $CDCl_3$ solutions. Chemical shifts were recorded in parts per million (ppm), downfield from internal Me_4Si. The one-bond multiplicity of carbon atoms was determined by DEPT experiments. High-resolution mass spectral data were obtained on a VG Autospec, TRIO 1000 (Fisons) instrument. Electron impact (EI) or Fast Atom Bombardment (FAB) at 70 eV were used as ionisation mode in mass spectra. The structure of all the compounds was determined by analytical and spectroscopic methods and by comparison with data of the compounds reported in literature.

1.1 General procedure for the synthesis of oxalamide compounds 2 or morpholine 2,3-diones 3

Method A. Diethyloxalate (0.5 mmol) was added to a solution of the appropriate aminodiol **1a-j** (1 mmol) in toluene or ethanol (4 ml). The mixture was stirred or heated at reflux temperature until disappearence of the starting material (TLC monitorage) and, after cooling at room temperature. If a solid appears was filtered under reduced pressure and the filtrate was concentrated to dryness and the residue was purified by column chromatography. When not turn out to be precipitated the reaction mixture was concentrated to dryness and the residue was purified by column chromatography. The isolated products were identified as the corresponding oxalamide derivative **2** and/or morpholine-2,3-dione **3** (*see Table 1*).

Method B. Diethyloxalate (1 mmol) was added to a solution of the appropriate aminodiol **1a-1j** (1 mmol) in toluene or ethanol (4 ml). The mixture was stirred at room temperature or heated at reflux temperature until disappearence of the starting material (TLC monitorage) and, after cooling at room temperature, the procedure continues in the same way that the *method A*.

1.2 Using as β-aminoalcohol 2-Aminoethanol (1a)

Method A: toluene, 25°C, afforded *N,N'-Bis-(2-hydroxy-ethyl)-oxalamide* **(2a)**, yield: 94%. *Method B*: ethanol, 25°C, afforded **2a**, yield: 67%

N,N'-Bis-(2-hydroxy-ethyl)-oxalamide **(2a)**

Analytical and spectroscopic data were coincident to those previously reported [4,11] and ^{13}C NMR data together with MS data, not previously reported, are now described.

White solid, mp. 169-170°C. IR (KBr) ν_{max}: 3292; 1651; 1543 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 3.20 (q, *J* = 6.0 Hz, 4H), 3.57 (t, *J* = 6.0 Hz, 4H), 4.20 (bs, 2H), 8.59 (bs, 2H).^{13}C-NMR (75.4 MHz, DMSO-d_6): δ 41.8 (t), 59.4 (t), 160.2 (s). HMRS (EI) *m/z* calcd for $[M]^+$ $C_6H_{12}N_2O_4$ 176.0797, found: 176.0794.

1.3 Using as β-aminoalcohol N-Methylethanolamine (1b)

Method A: toluene, 25°C, afforded *N,N'-Bis-(2-hydroxy-ethyl)-N,N'-dimethyl-oxalamide* **(2b)**, yield: 72%. *Method A*: ethanol, 25°C, afforded **2b**, yield: 67%. *Method B*: ethanol, 25°C, afforded a mixture of *N,N'-Bis-(2-hydroxy-ethyl)-N,N'-dimethyl-oxalamide* **(2b)** : *4-Methylmorpholine-2,3-dione* **(3b)** (1 : 1), yield: 85%.

N,N'-Bis-(2-hydroxy-ethyl)-N,N'-dimethyl-oxalamide **(2b)**

Oil colourless. IR (KBr) ν_{max}: 3420; 1631 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.03 (s, 3H); 3.09 (s, 3H); 3.49 (m, 2H); 3.59-3.65 (m, 4H); 3.73-3.79 (m, 2H); 3.80-3.85 (m, 2H). ^{13}C-NMR (75.4

MHz, $CDCl_3$) δ 31.6 (q); 36.4 (q); 49.2 (t); 52.4 (t); 58.5 (t); 59.5 (t); 165.8 (s); 166.4 (s). HMRS (EI) *m/z* calcd for $[M]^+$ $C_8H_{16}N_2O_4$ 204.1110, found: 204.1111

4-Methylmorpholine-2,3-dione **(3b)**

Analytical and spectroscopic data for compound **3b** were consistent to those previously reported. [14]

1.4 Using as β-aminoalcohol 2-Amino-1-phenylethanol (1c)

Method A: toluene, 25°C, afforded *N,N'-Bis-(2-hydroxy-2-phenyl-ethyl)-oxalamide* **(2c)**, yield: 96%. *Method B*: ethanol, 25°C, afforded **2c**, yield: 67%.

N,N'-Bis-(2-hydroxy-2-phenyl-ethyl)-oxalamide **(2c)**

White solid, mp. 186-187°C. IR (KBr) ν_{max}: 3302; 1649; 1537 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 3.23-3.43 (m, 2H); 4.73 (m, 1H); 5.58 (sbr, 1H, exchangeable with D_2O); 7.23-7.34 (m, 5H); 8.51 (t, *J* = 6.0 Hz, 1H, exchangeable with D_2O).^{13}C-NMR (75.4 MHz, DMSO-d_6): δ 47.2 (t); 71.0 (d); 126.3 (d); 127.5 (d); 128.4 (d); 143.5 (s); 160.1 (s). HMRS (FAB) *m/z* calcd for $[M-OH]^+$ $C_{18}H_{19}N_2O_3$ 311.1395, found: 311.1387.

1.5 Using as β-aminoalcohol 2-(Methylamino)-1-phenylethanol (1d)

Method A: toluene, 25°C, afforded *N,N'-Bis-(2-hydroxy-2-phenyl-ethyl)-N,N'-dimethyl-oxalamide* **(2d)**, yield: 58%. *Method A*: ethanol, 25°C, afforded a mixture of *N,N'-Bis-(2-hydroxy-2-phenyl-ethyl)-N,N'-dimethyl-oxalamide* **(2d)** : *4-Methyl-6-phenylmorpholine-2,3-dione* **(3d)** (10:2.2), yield: 68%. *Method B*: toluene, reflux temperature, afforded **2d**, yield: 65%. *Method B:* ethanol, 25ºC, afforded a mixture of **2d** : **3d** (10 : 2.7), yield: 75%

N,N'-Bis-(2-hydroxy-2-phenyl-ethyl)-N,N'-dimethyl-oxalamide **(2d)**

White solid, mp. 132-133°C. IR (KBr) ν_{max}: 3476; 3369; 1651; 1631 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.82 (s, 3H); 2.94 (s, 3H); 3.14-3.75 (m, 4H); 4.07 (sbr, 1H, exchangeable with D_2O); 4.65 (sbr, 1H, exchangeable with D_2O); 4.79-4.93 (m, 2H); 7.29 (m, 10H). ^{13}C-NMR (75.4 MHz, DMSO-d_6): δ 33.0 (q); 36.0 (q), 54.1 (t); 57.5 (t); 71.0 (d); 126.3 (d); 126.4 (d); 126.7 (d); 127.9 (d); 128.7 (d); 128.9 (d); 143.7 (s), 143.9 (s); 165.6 (s); 166.9 (s). HRMS (FAB) *m/z* calcd for $[M+H]^+$ $C_{20}H_{25}N_2O_4$ 357.1814, found: 357.1811.

4-Methyl-6-phenylmorpholine-2,3-dione **(3d)**

Analytical and spectroscopic data for compound **3d** were consistent to those previously reported. [14]

1.6 Using as β-aminoalcohol (1*R*,2*S*)-(-)-norephedrine (1e)

Method A: toluene, reflux temperature, afforded a mixture of *N,N'-Bis-[(1R,2S)-(-)-norephedrine]oxalamide* **(2e)** : *N-[(1R,2S)-(2-Hydroxy-1-methyl-2-phenyl-ethyl)]oxalamic acid ethyl ester* **(4e)** (10:1), yield: 94%. *Method B:* ethanol, 25°C, afforded a mixture of **2e**: **4e** (1:2), yield: 85%

N,N'-Bis-[(1R,2S)-(-)-norephedrine]oxalamide **(2e)**

Analytical and spectroscopic data for compound **2e** were consistent to those previously reported. [12]

N-[(1R,2S)-(2-Hydroxy-1-methyl-2-phenyl-ethyl]-oxalamic acid ethyl ester **(4e)**

Analytical and spectroscopic data for compound **4e** were consistent to those previously reported. [13]

1.7 Using as β-aminoalcohol (1*S*,2*R*)-(+)-ephedrine (1f)

Method A: toluene, 25°C, afforded a mixture of *N,N'-Bis-[(1S,2R)-(+)-ephedrine]oxalamide* (**2f)** : *(5R,6S)-4,5-Dimethyl-6-phenylmorpholine-2,3-dione* **(3f)** (10:0.2) yield: 90%. *Method A*: ethanol, 25°C, afforded **3f**, yield: 70%. *Method B*: 25°C, 3 days, afforded **3f**, yield: 60%.

N,N'-Bis-[(1S,2R)-(+)-ephedrine]oxalamide **(2f)**

White solid, mp. 146-147ºC. IR (KBr) ν_{max}: 3404, 1620, 1599 cm^{-1}. NMR (300 MHz, DMSO-d_6) δ 0.90-0.99 (m, 6H), 2.69 (s, 3H); 2.85 (s, 3H); 3.99 (m, 1H); 4.34 (m, 1H); 4.88 (m, 1H); 5.13 (d, *J*= 2.0 Hz, 1H); 7.20-7.38 (m, 10H). ^{13}C NMR (75.4 MHz, DMSO-d_6) δ 10.7 (q); 11.5 (q); 26.7 (q); 31.5 (q); 52.8 (d); 59.5 (d); 74.8 (d); 76.2 (d); 126.3 (d); 126.5 (d); 127.6 (d); 128.1 (d); 128.2 (d); 128.5 (d); 141.6 (s); 144.0 (s); 169.0 (s); 170.6 (s). HMRS (FAB) *m/z* calcd for $[M+1]^+$ $C_{22}H_{29}N_2O_4$ 385.2127, found: 385.2137

(5R,6S)-4,5-Dimethyl-6-phenylmorpholine-2,3-dione **(3f)**

Analytical and spectroscopic data for compound **3f** were consistent to those previously reported. [15]

1.8 Using as β-aminoalcohol (1*S*,2*S*)-(+)-pseudoephedrine (1g)

Method A: toluene, 25°C, afforded a mixture of *N,N'-Bis-[(1S,2S)-(+)-pseudoephedrine]oxalamide* **(2g)** : *(5R,6R)-4,5-Dimethyl-6-phenylmorpholine-2,3-dione* **(3g)** (9:1), yield: 75% *Method B*: ethanol, 25°C, afforded mixture **2g:3g** (1:1), yield: 73%.

N,N'-Bis-[(1S,2S)-(+)-pseudoephedrine]oxalamide **(2g)**

White solid, mp. 174-175°C. IR (KBr) ν_{max}: 3472, 3377, 1643, 1620 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 0.90-0.95 (m, 6H); 2.50 (s, 3H); 2.53 (s, 3H); 2.95-3.03 (m, 2H); 4.50-4.60 (m, 2H); 7.20-7.50 (m, 10H). ^{13}C-NMR (75.4 MHz, DMSO-d_6) δ 14.0 (q); 15.1 (q); 29.3 (q); 30.2 (q); 52.3 (d); 59.4 (d); 73.4 (d); 73.6 (d); 126.9 (d); 127.2 (d); 127.5 (d); 127.7 (d); 128.2 (d); 128.3 (d); 128.4 (d); 128.5 (d); 128.7 (d); 129.2 (d); 142.6 (s); 143.6 (s); 165.8 (s); 166.0 (s). HMRS (EI) *m/z* calcd for $[M+1]^+$ $C_{22}H_{29}N_2O_4$ 385.2127, found: 385.2130.

(5R,6R)-4,5-Dimethyl-6-phenylmorpholine-2,3-dione **(3g)**

White solid, mp. 94-96°C. IR (KBr) ν_{max}: 3456, 1765, 1689 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.45 (d, *J* = 6.1 Hz, 3H); 2.90 (s, 3H); 3.87 (m, 1H); 5.40 (d, *J* = 5.0 Hz, 3H); 7.12-7.50 (m, 5H). ^{13}C-NMR (75.4 MHz, $CDCl_3$) δ 17.7 (q); 33.0 (q); 57.4 (d); 82.0 (d); 126.3 (d); 129.4 (d); 129.6 (d); 136.1 (s); 153.9 (s); 156.9 (s). HMRS (EI) *m/z* calcd for $[M]^+$ $C_{12}H_{13}NO_3$ 219.0895, found: 219.0898.

1.9 Using as β-aminoalcohol (2*R*, 3*R*)-3-Amino-3-phenylpropane-1,2-diol (1h) [10]

Method A: toluene, reflux temperature, afforded *N,N'-Bis-[(1R, 2R) 2,3–dihydroxy–1-phenylpropyl]oxalamide* **(2h)**, yield: 96%. *Method A*: toluene, 25°C, afforded compound **2h**, yield: 90%. *Method B*: ethanol, 25°C, afforded compound **2h**, yield: 82%

N,N'-Bis-[(1R, 2R) 2,3–dihydroxy–1-phenylpropyl]oxalamide **(2h)**

Analytical and spectroscopic data for compound **2h** were consistent to those previously reported.[8]

1.10 Using as β-aminoalcohol (2*R*, 3*R*)-3-Methylamino-3-phenylpropane-1,2-diol (1i) [9d]

Method A: toluene, reflux temperature, afforded *(5S, 6S)-6-Hydroxymethyl-4-methyl-5-phenyl-morpholine-2,3-dione* **(3i)**, yield: 76%. *Method A*: ethanol, 25°C afforded compound **3i**, yield: 70%. *Method B*: toluene, 25°C, afforded compound **3i**, yield: 74%.

(5S, 6S)-6-Hydroxymethyl-4-methyl-5-phenyl-morpholine-2,3-dione **(3i)**

White solid, mp. 167-168°C. $[\alpha]^{25}_D$ = +58.3 (*c* 1.56, CH_3OH). IR (KBr) ν_{max}: 3460; 1767; 1687 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 2.89 (s, 3H); 3.26 (m, 2H); 3.40 (sbr, 1H, exchangeable with D_2O); 4.94 (d, *J* = 3.2 Hz, 1H); 5.23 (dt, *J* = 6.6 and 3.4 Hz, 1H); 5.29 (t, *J* = 5.3 Hz, 1H, exchangeable with D_2O); 7.15 (dd, *J* = 7.9 e 1.9 Hz, 2H); 7.39-7.47 (m, 3H).^{13}C-NMR (DMSO-d_6): δ 33.6 (q); 59.7 (t); 61.6 (d); 77.9 (d); 127.9 (d); 129.1 (d); 129.2 (d); 133.5 (s); 154.1 (s); 157.1 (s). HMRS (FAB) *m/z* calcd for $[M]^+$ $C_{12}H_{13}NO_4$ 235.8391, found: 235.8388.

1.11 Using as β-aminoalcohol (2*R*, 3*R*)-3-(ethylamino)-3-phenylpropane-1,2-diol (1j) [9d]
Method A: toluene, reflux temperature, afforded *(5S, 6S)-6-Hydroxymethyl-4-ethyl-5-phenyl-morpholine-2,3-dione* **(3j)**, yield: 72%. *Method A*: ethanol, 25°C, afforded compound **3j**, yield: 70%. *Method B*: toluene, 25°C, afforded compound **3j**, yield: 68%.
(5S, 6S)-6-Hydroxymethyl-4-ethyl-5-phenyl-morpholine-2,3-dione **(3j)**
White solid, mp. 190-191°C. $[\alpha]^{25}_{D}$ = +35.7 (*c* 1.32, CH_3OH). IR (KBr) ν_{max}: 3431; 1765; 1682 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.13 (t, *J* = 7.1 Hz, 3H); 3.14 (dt, *J* = 7.1 and 20.7 Hz, 1H); 3.42 (dd, *J* = 6.7 and 11.50 Hz, 1H); 3.53 (dd, *J* = 6.6 and 11.6 Hz, 1H); 3.73 (dt, *J* = 7.1 and 20.9 Hz, 1H); 4.81 (d, *J* = 3.2 Hz, 1H); 5.08 (dt, *J* = 6.6 and 3.2 Hz, 1H); 7.17-7.19 (2H, m); 7.39-7.47 (m, 3H).^{13}C-NMR (DMSO-d_6): δ 12.8 (q); 42.6 (d); 60.7 (t); 60.9 (d); 79.2 (d); 128.6 (d); 129.8 (d); 132.7 (s); 154.2 (s); 157.6 (s). HMRS (EI) *m/z* calcd for $[M]^+$ $C_{13}H_{15}NO_4$ 249.1001, found: 249.1005.

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