Synthesis of 2,3 and 4,5-Dihydro-hydroxy-isoxazoles and Isoxazoles Under Different pH Conditions

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Abstract: Reaction between aryl 1,3-diketoesters **2a-e** and hydroxylamine hydrochloride has been investigated under different experimental conditions. Whereas acid conditions gave principally 3,5-isoxazole esters (**3a-e**), reactions under neutral and basic conditions led to different 4,5 and 2,3-dihydro-hydroxy-isoxazoles **4a-e** and **5a-e**.

Keywords: Isoxazoles, dihydro-hydroxy-isoxazoles, aryl 1,3-diketoesters, hydroxylamine.

INTRODUCTION

The isoxazole scaffold has shown considerable interest in the synthesis of numerous drug candidates: indeed, compounds containing this five-membered ring exhibit a broad spectrum of biological activities such as antibacterial [1, 2], anti-inflammatory [3], or anti-cancer properties [4]. As part of our ongoing research program [5-7] to develop new derivatives of biological interest we were interested in the synthesis of 3,5-disubstitued isoxazole bearing an aryl group in C-5 and an amide function in C-3.

To date, numerous synthetic methods have been described for the preparation of isoxazoles and one of the most frequently used is a 1,3-dipolar cycloaddition between an alkyne and a nitrile oxide [8]. Other synthetic methods involve oxidative aromatization of isoxazolines [9] preparations from *N*-acetoacetyl derivatives [10] or 1,1-disubstitued bromoalkene [11]. The coupling of an appropriate non-symmetrical 1,3-diketone with hydroxylamine is usually described as leading to the formation of two regioisomers (3,5 and 5,3 isoxazole) during the reaction [12]. In some cases when this reaction is carried out with amines, the regioselectivity of this reaction can be controlled by adjusting pH of the reaction medium [13, 14]. Thus, to develop new anti-inflammatory compounds, we focused our attention on the coupling of different 1,3-diketoesters with hydroxylamine under various experimental conditions.

As depicted in Scheme **1**, the various arylketones **1a-e** (See Table **1**) were oxalylated by diethyl oxalate in the presence of sodium ethanolate, producing aryl 1,3-diketoesters **2a-e** in high yields in their enol forms. However, we have noticed that yields varied according to the electronic nature of the substituent bearing by the aromatic moiety. Indeed, the best yields were obtained when the substituent borne by the aromatic moiety possessed an electronic withdrawing character. Because of their capacity to increase the acidity of the ketonic protons, withdrawing substituents are able to increase the electrophilic character of the ketonic carbone.

Treatment of the aryl 1,3-diketoesters **2a-e** was next investigated under three different conditions: i) alkaline (procedure A), ii) neutral (only with hydroxylammonium chloride, procedure B), and iii) acid (procedure C). During the cyclization step, LC/MS analysis showed a M+18 peak, depending on the pH of the reaction and which could correspond to different dihydro-hydroxy-isoxazoles. Synthesis and characterization of such dihydro-hydroxy-isoxazoles bearing an aryl ring and an ester function have not been reported thus far. Pei and Wickham [15] have just indicated that when the reaction is carried out in the presence of base (Et_3N or $NaHCO_3$), the desired isoxazole ester was obtained in very low yield (<10%). In addition, on similar compounds, Manning and Coleman [16] revealed that condensation of 1 eq. of hydroxylamine with 3,3-disubstituted 2,4-pentanediones led to 4,5-dihydro-hydroxy-isoxazoles as a single alcohol. Then, as regards of the pharmaceutical interest of isoxazole ring, we wished to

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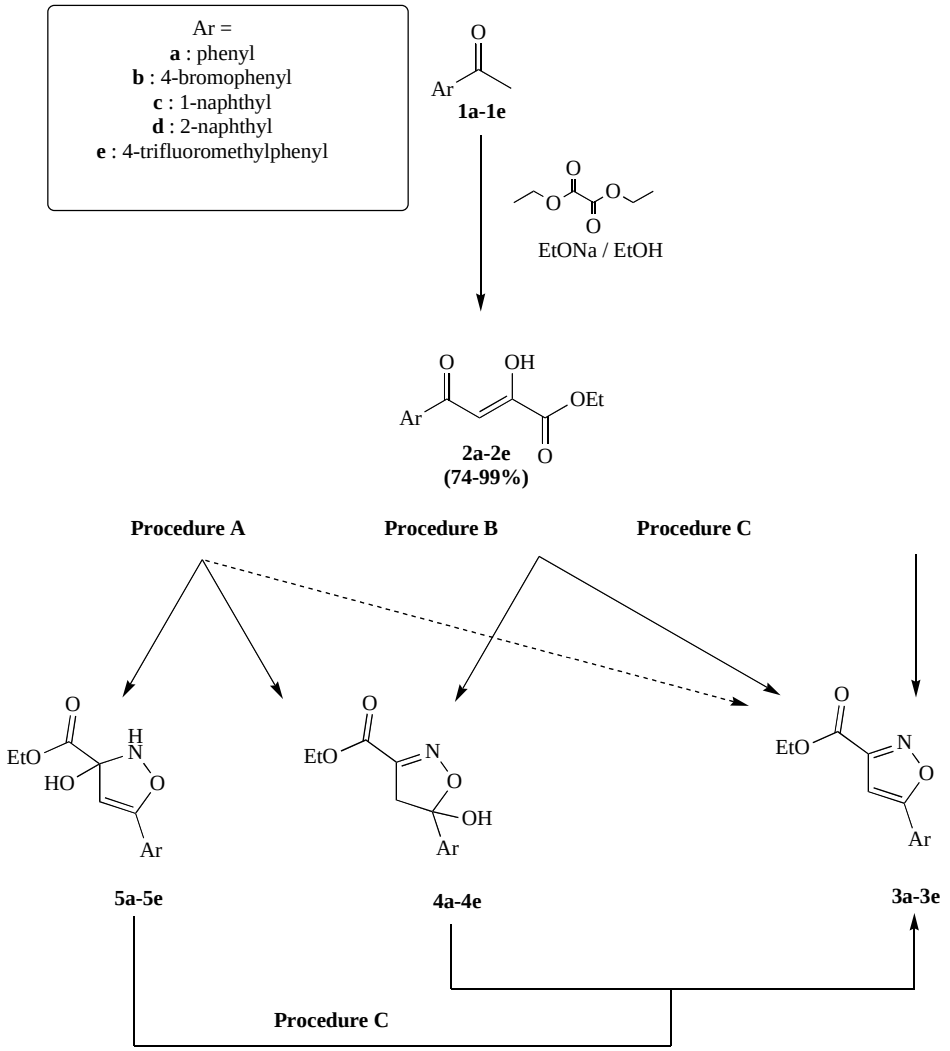

Scheme 1. Synthetic pathway for the obtention of isoxazoles and isoxazolines.

Reagents and conditions:

-Procedure A: $NH_2OH.HCl$, DIPEA (3eq), EtOH, reflux, 2h.

-Procedure B: $NH_2OH.HCl$, EtOH reflux, 2h.

-Procedure C: $NH_2OH.HCl$, PTSA, toluene, Dean-Stark conditions, reflux, 2h.

elucidate the structure of such regioisomers and proved that the reaction can be compatible with different aryl 1,3-diketoesters. The two different dihydro-hydroxy-isoxazole rings could constitute an attractive building block in the design of drug candidates.

RESULTS AND DISCUSSION

Firstly, since crystallization of **3a** was difficult, assignment of 3,5-isoxazole ester ring (*versus* 5,3) was achieved by crystallographic data obtained on 5-phenyl-*N*-(3-phenylpropyl)isoxazole-3carboxamide (**6**). Thanks to a recrystalization in absolute ethyl alcohol of this compound obtained from **3a** by a rapid saponification of ester function followed by a coupling reaction with phenylpropylamine under peptidic conditions (HOBt, HBTU), the structure was unambiguously secured by an X-Ray crystal [17] (Fig. **1**) and a NMR ^{1}H analysis. These data confirm that the electronic effects on the group ester render the position adjacent to the ester most susceptible to attack by nucleophiles and effectively, the 3,5-regioisomer was generated.

Secondly, in order to optimize the cyclization step and to explain the origin of M+18 peak, three different procedures were explored. Under alkaline conditions (procedure A), a mixture of dihydro-hydroxy-isoxazoles and isoxazoles (**3a-e**) was obtained. Neutral conditions (procedure B) gave isoxazole (**3a-e**) and a single dihydro-hydroxy-isoxazole**.** Isoxazoles and dihydro-hydroxy-isoxazoles were purified and separated by flash-chromatography (cyclohexane / AcOEt ; 8:2). Reaction between **2a-e** and hydroxylamine hydrochloride with PTSA (procedure C) generated only the isoxazole esters (**3a-e**) in good yields (see General Procedure of Synthesis). The first NMR ^{1}H analysis of M+18 peak from the procedure A highlighted the presence of two compounds which have not been separated by flash

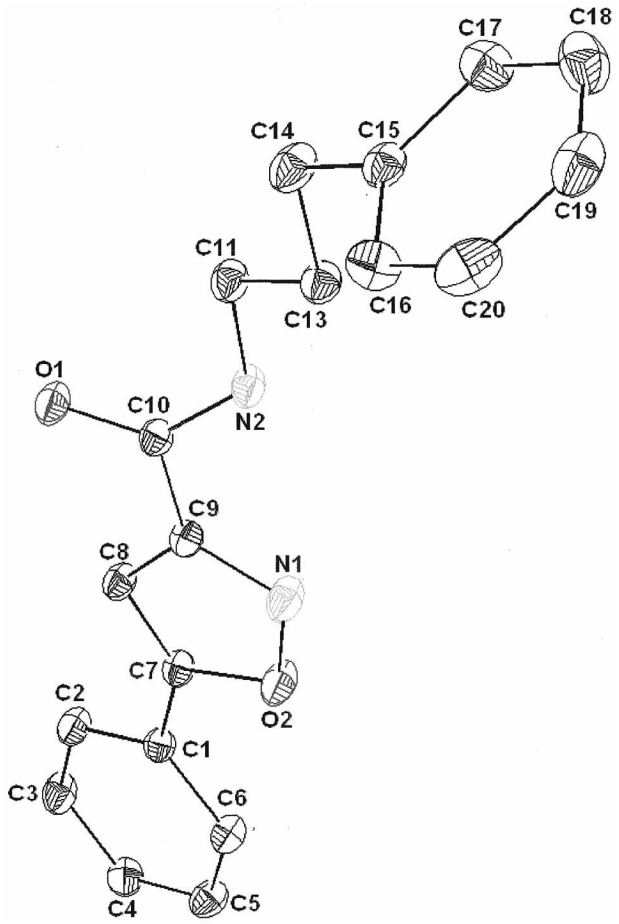

Fig. (1). ORTEP plot of the isoxazole amide 6.

chromatography. Then, to unambiguously determinate the structure of the obtained products (alcohols **4a** and **5a**) the cyclization step was monitored by HPLC and CE. HPLC analysis was carried out by means of a Daicel Chiralcel OD-H column [18, 19], with an eluent of hexane/ethanol (90:10). Following this method, two peaks were obtained on the chromatogram at 12.55 and 8.90 min, respectively (Fig. **2**).

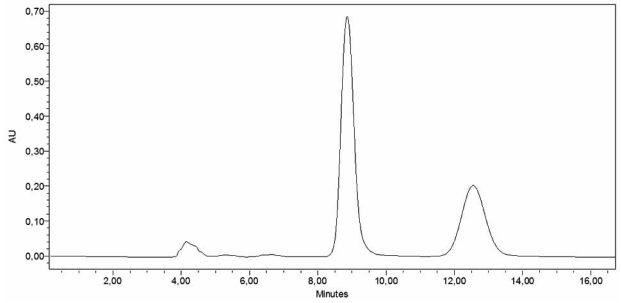

Fig. (2). UV_{207nm} chromatogram of **4a** and **5a** alcohols. Columm OD-H 4.6 x 250 mm, 5 µm; mobile phase hexane/ethanol (90:10 v/v); flow-rate, 0.8 ml/min; temperature, 25 ˚C.

The alcohol **4a** originally from procedure B was also analyzed by HPLC and presented a retention times at 12.50 min. For compound **3a** (procedure B), one peak was observed at 6.80 min and (procedure C) one peak at 6.77 min. Some further chromatographic analyses showed that alcohols were eluted later than the ester isoxazole. It can be explained by supplementary H-bondings between the alcohol solute and the stationary phase. CE confirmed results obtained from HPLC and was run with anionic cyclodextrins (highly sulfated-β-CD) as driving selectors. Cyclodextrins were chosen because of their remarkable ability to form inclusion complexes with a wide variety of molecules [20, 21]. Analysis was carried out with a 25 mM phosphate buffer, pH 2.5. The electropherogram obtained for **4a** and **5a** (procedure A) presented two peaks at 7.03 and 4.69 min, respectively (Fig. **3**). The alcohol **4a** migrated after the alcohol **5a**, as in HPLC. For compound **4a** (procedure B), one peak was observed at 6.92 min. For compound **3a** (procedure B), one peak was observed at 6.80 min and (procedure C) one peak at 3.65 min.

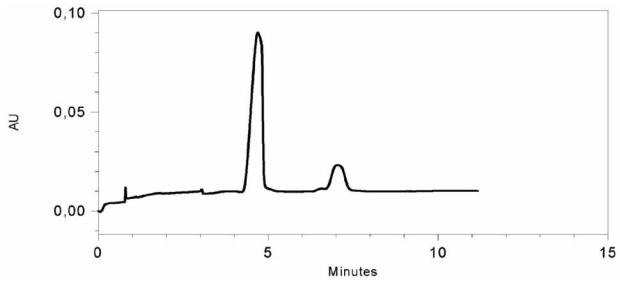

Fig. (3). UV_{207nm} electropherogram of **4a** and **5a** alcohols. Fused-silica capillary coated with PEO 50.2 cm (effective length 10 cm) x 50 µm I.D.; normal polarity, long end; BGE, 25 mM phosphate buffer pH 2.5 (H3PO4 + TEA) containing 3% of HS-β-CD; cathodic injection, 0.5 psi pressure for 5 s of 0.25 mM solution; applied voltage, 25 kV; temperature, 25 ˚C.

The structure of the isoxazole esters **3a** and the two alcohols **4a** and **5a** was confirmed by ^{1}H NMR spectra. The most important difference between alcohols **4a** and **5a** lies in the observation of two doublets confirming the presence of two nonequivalent protons (-CH_2-) for **4a** and one singulet showing the presence of one ethylenic proton (-CH=) for **5a**. The rotary power of compounds **4a** and **5a** also confirmed that compounds were obtained as racemate.

The procedures A-C were found to be compatible with different aromatic groups such as 4-bromophenyl, 1-naphthyl, 2-naphthyl, or 4-trifluorophenyl groups. Then, procedure A led to mainly 4,5-dihydro-hydroxy-isoxazoles **4a-e** (71-93% yields) than 2,3-dihydro-hydroxy-isoxazoles **5a-e** (6-24% yields). Compounds **5a**, **5c,** and **5e** were obtained in the same range (19-24%). Lower yields (6% and 10%) were obtained for **5b** and **5d**, respectively. Steric and electronic effects seem to have no influence on the reactivity and starting material was not recovered. We also observed the formation of isoxazole (**3a-e**) with a low yield. Procedure B furnished principally isoxazoles **3a-d** (78-92%) than 4,5-dihydro-hydroxy-isoxazoles **4a**-d (8-22%). An exception was observed for **3e** and **4e** where the ratio was 56/44. Substrate with bromine seems to be less favorable and reactive for the dehydration step. Finally, procedure C furnished exclusively **3a-e** in 82-95% of isolated yields.

Table 1. Dihydro-hydroxy-isoxazoles 4a-e, 5a-e and 3,5-isoxazole Esters 3a-e Produced *Via* Scheme 1 from five aryl β-diketoesters 2a-e

Compounds	Ar	Ratio 3: 4: 5 (Yields %)		
		$NH_2OH.HCl$, 3 eq. DIEA	$NH_2OH.HCl$	$NH_2OH.HCl$, PTSA
		Procedure A	Procedure B	Procedure C
3a, **4a**, **5a**	**a** = phenyl	5 ; 71; 24	82; 16; 0	95; 0; 0
3b, **4b**, **5b**	**b** = 4-bromophenyl	1 ; 93; 6	85; 15; 0	84; 0; 0
3c, **4c, 5c**	**c** = 1-naphthyl	5 ; 76; 19	78; 22; 0	80; 0; 0
3d, **4d**, **5d**	**d** = 2-naphthyl	5 ; 85; 10	92; 8; 0	90; 0; 0
3e, **4e**, **5e**	**e** = 4-trifluoromethylphenyl	5 ; 74; 21	56; 44; 0	82; 0; 0

To validate and conclude this study, compounds **4a-e** and **5a-e** were refluxed in toluene in the presence of PTSA (0.5 equiv) with a Dean-Stark apparatus. After 2h, we observed only the formation of the 3,5-isoxazole **3a-e**.

CONCLUSION

In summary, we have investigated the reaction of hydroxylamine with a set of aryl 1,3-diketoesters **2a-e** and unambiguously determined the structure of obtained products under different reactions conditions. The procedure showed to be compatible with a set of aryl 1,3-diketoesters. In acid conditions, only the isoxazoles are formed, whereas in neutral or in alkaline conditions the formation of isoxazoles is paired of the generation of dihydro-hydroxy-isoxazoles. We described for the first time characterization of such compounds. The use of alkaline conditions furnished a mixture of two 2,3 and 4,5-dihydro-hydroxy-isoxazoles (**5a-e** and **4a-e**). The same reaction carried with hydroxylammonium chloride gave only 4,5-dihydro-hydroxy-isoxazoles (**4a-e**).

EXPERIMENTAL SECTION

All commercial reagents and solvents were used without further purification. Analytical thin-layer chromatography was performed on precoated Kieselgel 60F254 plates (Merck); the spots were located by UV (254 and 366 nm) and/or with iodine. Silica gel 60 230-400 mesh purchased from Merck was used for column chromatography. All melting points were determined with a Büchi 535 capillary apparatus and remain uncorrected. The IR spectra were recorded in a potassium bromide pellet with a Bruker Vector 22 spectrophotometer; absorbances were reported in ν (cm^{-1}). 1H NMR spectra were obtained using a Brücker 300 MHz spectrometer, chemical shift (δ) were expressed in ppm relative to tetramethylsilane used as an internal standard, J values were in hertz, and the splitting patterns were designated as follow: s singlet, d doublet, t triplet, m multiplet. All compounds were analyzed by HPLC-MS on a HPLC combined with a Surveyor MSQ (Thermo Electron) equipped with an APCI+ source.

General Procedure for the Synthesis of Ethyl 2-hydroxy-4-oxo-but-2-enoates (Compounds 2a-e)

To a solution of freshly prepared sodium ethanolate (obtained from sodium (66.0 mmol, 2 equiv.) in 50 mL of absolute ethyl alcohol) a solution of aromatic ketone (33.0 mmol, 1 equiv.) and diethyl oxalate (66.0 mmol, 2 equiv.) was added dropwise at 50°C in 30 mL of absolute ethyl alcohol. Then, the reaction mixture was heated at reflux for 2 h. At the end of the reaction, solvent was evaporated under reduced pressure. The residue obtained was diluted with 100 mL of an aqueous solution of hydrochloric acid (1N) and stirred at room temperature for 1 h. The product was then extracted with 100 mL of ethyl acetate and washed by 100 mL of distilled water. The organic phase was dried with $MgSO_4$, filtered and concentrated under reduced pressure. Next, the residue obtained was triturated with cyclohexane to give compounds **2a-e**.

Ethyl 2-hydroxy-4-oxo-4-phenyl-2-butenoate (2a)

Orange oil; 5.45 g (75%). IR (ν, cm^{-1}) 1736 (CO), 1600 (enol). ^{1}H NMR (300 MHz; DMSO): δ 1.12 ppm (t, C*H*$_3$-CH$_2$-, 3H, *J*= 6.4 Hz), 3.98 ppm (q, CH$_3$-C*H*$_2$-, 2H, *J*= 6.4 Hz), 7.08 ppm (s, -C*H*=, 1H), 7.54 ppm (t, Ar*H*, 2H, *J*= 7.8 Hz), 7.67 ppm (t, Ar*H*, 1H, *J*= 7.9 Hz), 8.02 (d, Ar*H*, 2H, *J*= 7.7 Hz), 10.68 ppm (s, -O*H*, 1H). LC/MS (APCI+) calcd for $C_{12}H_{12}O_4$, m/z: 221 (MH+).

Ethyl 4-(4-bromophenyl)-2-hydroxy-4-oxo-2-butenoate (2b)

Yellow solid; 7.30 g (74%); Mp 65-66°C. IR (ν, cm^{-1}) 1721 (CO), 1592 (enol). ^{1}H NMR (300 MHz; DMSO): δ 1.47 ppm (t, C*H*$_3$-CH$_2$-, 3H, *J*= 7.2 Hz), 4.42 (q, CH$_3$-C*H*$_2$-, 2H, *J*= 7.2 Hz), 6.99 (s, -C*H*=, 1H), 7.88-8.07 ppm (m, Ar*H*, 4H), 10.68 ppm (s, -O*H*, 1H). LC/MS (APCI+) calcd for $C_{12}H_{11}BrO_4$, m/z: 299 (MH) and 301 (MH)2+.

Ethyl 2-hydroxy-4-(1-naphthyl)-4-oxo-2-butenoate (2c)

Yellow solid; 7.57 g (85%); Mp 61-62°C. IR (ν, cm–1) 1728 (CO), 1610 (enol). ^{1}H NMR (300 MHz; DMSO): δ 1.43 ppm (t, C*H*$_3$-CH$_2$-, 3H, *J*= 7.2 Hz), 4.42 ppm (q, CH$_3$-C*H*$_2$-, 2H, *J*= 7.2 Hz), 7.30 ppm (s, -C*H*=, 1H), 7.52-7.68 ppm (m, Ar*H*, 3H), 7.88-7.97 ppm (m, Ar*H*, 2H), 8.06 ppm (d, Ar*H*, 1H, *J*= 8.2 Hz), 8.61 ppm (d, Ar*H*, 1H, *J*= 8.2 Hz), 10.69 ppm (s, -O*H*, 1H). LC/MS (APCI+) calcd for $C_{16}H_{14}O_4$, m/z: 271 (MH)+.

Ethyl 2-hydroxy-4-(2-naphthyl)-4-oxo-2-butenoate (2d)

Yellow solid; 6.59 (74%); Mp 79-80°C. IR (ν, cm^{-1}) 1722 (CO), 1601 (enol). ^{1}H NMR (300 MHz; DMSO): δ 1.47 ppm (t, C*H*$_3$-CH$_2$-, 3H, *J*= 7.2 Hz), 4.42 ppm (q, CH$_3$-C*H*$_2$-, 2H, *J*= 7.2 Hz), 7.25 ppm (s, -C*H*=, 1H), 7.55-7.68 ppm (m, Ar*H*, 2H), 7.88-8.07 ppm (m, Ar*H*, 4H), 8.57 ppm

(s, Ar*H*, 1H), 10.68 ppm (s, -O*H*, 1H). LC/MS (APCI+) calcd for $C_{16}H_{14}O_4$, m/z: 271 (MH)+.

Ethyl 2-hydroxy-4-oxo-4-[4-(trifluoromethyl)phenyl]-2-butenoate (2e)

Yellow solid; 9.40 g (99%); Mp 50-51°C. IR (ν, cm^{-1}) 1702 (CO), 1613 (enol). ^{1}H NMR (300 MHz; DMSO): δ 1.30 ppm (t, C*H*$_3$-CH$_2$-, 3H, *J*= 7.3 Hz), 4.19 ppm (q, CH$_3$-C*H*$_2$-, 2H, *J*= 7.3 Hz), 6.98 ppm (s, -C*H*=, 1H), 7.64 ppm (d, Ar*H*, 2H, *J*= 8.2 Hz), 8.02 ppm (d, Ar*H*, 2H, *J*= 8.2 Hz), 10.68 ppm (s, -O*H*, 1H). LC/MS (APCI+) calcd for $C_{13}H_{11}F_3O_4$, m/z: 289 (MH)+.

General Procedure for the Cyclisation in Alkaline Conditions, Procedure A (Compounds 3a-e, 4a-e and 5a-e)

A mixture of compounds **2a-e** (7.41 mmol, 1 equiv.), hydroxylamine hydrochloride (7.41 mmol, 1 equiv.) and DIPEA (22.2 mmol, 3 equiv.) in 50 mL of absolute ethyl alcohol was refluxed for 2h. After cooling to room temperature, the solvent was evaporated and the residue obtained was purified by flash chromatography (cyclohexane / AcOEt ; 8:2).

General Procedure for the Cyclisation in Neutral Conditions, Procedure B (Compounds 3a-e and Compounds 4a-e)

A mixture of compounds **2a-e** (7.41 mmol, 1 equiv.) and hydroxylamine hydrochloride (7.41 mmol, 1 equiv.) in 50 mL of absolute ethyl alcohol was refluxed and stirred for 2h. After cooling to room temperature, the solvent was evaporated and the residue obtained was purified by flash chromatography (cyclohexane / AcOEt; 8:2).

General Procedure for Dehydration. Procedure C (Compounds 3a-e)

(a) From benzoylpyruvates **2a-e**. A mixture of compounds **2a-e** (7.41 mmol, 1 equiv.), hydroxylamine hydrochloride (7.41 mmol, 1 equiv.) and PTSA (3.71 mmol, 0.5 equiv) in 50 mL of toluene was heated at reflux in a Dean-Stark apparatus for 2h. At the end of reaction, the mixture was cooled to room temperature, then the solvent was evaporated. The residue was diluted with 50 mL dichloromethane and successively washed by 50 mL of $NaHCO_3$ (5%) and 50 mL of water. The organic phase was dried with $MgSO_4$, filtered and concentrated under reduced pressure.

(b) From alcohols **4a-4e** or **5a-5e.** Compounds **4a-4e** or **5a-5e** (3.54 mmol, 1 equiv.) were refluxed in 30 mL of toluene in presence of PTSA (1.77 mmol, 0.5 equiv) with Dean-Stark apparatus for 2h. After cooling to room temperature, toluene was evaporated and residue diluted with dichloromethane before to be washed by 30 mL of $NaHCO_3$ (5%), then by 30 mL of water. The organic phase was dried, filtered and evaporated.

Ethyl 5-phenyl-3-isoxazolecarboxylate (3a)

White solid; procedure A: 81 mg (5%), procedure B: 1.32 g (82%), procedure C: 1.53 g (95%); Mp 59-60°C. IR (ν, cm^{-1}) 1731 (CO). ^{1}H NMR (300 MHz; DMSO): δ 1.30 ppm (t, C*H*$_3$-CH$_2$-, 3H, *J*= 7.2 Hz), 4.29 ppm (q, CH$_3$-C*H*$_2$-, 2H, *J*= 7.3 Hz), 7.13 ppm (s, -C*H*=, 1H), 7.48-7.52 ppm (m, Ar*H*, 5H). LC/MS (APCI+) calcd for $C_{12}H_{11}NO_3$, m/z: 218 (MH)+.

Ethyl 5-(4-bromophenyl)-3-isoxazolecarboxylate (3b)

White solid; procedure A: 0.02 g (1%), procedure B: 1.86 g (85%), procedure C: 1.84 g (84%); Mp 133-134°C. IR (ν, cm–1) 1725 (CO). ^{1}H NMR (300 MHz; DMSO): δ 1.34 ppm (t, C*H*$_3$-CH$_2$-, 3H, *J*= 7.1 Hz), 4.39 ppm (q, CH$_3$-C*H*$_2$-, 2H, *J*= 7.1 Hz), 7.58 ppm (s, -C*H*=, 1H), 7.78 ppm (d, Ar*H*, 2H, *J*= 8.5 Hz), 7.93 ppm (d, Ar*H*, 2H, *J*= 8.5 Hz). LC/MS (APCI+) calcd for $C_{12}H_{10}BrNO_3$, m/z: 296 (MH) and 298 (MH)2+.

Ethyl 5-(1-naphthyl)-3-isoxazolecarboxylate (3c)

White solid; procedure A: 102 mg (5%), procedure B: 1.54 g (78%), procedure C: 1.58 g (80%); Mp 64-65°C. IR (ν, cm^{-1}) 1735 (CO). ^{1}H NMR (300 MHz; DMSO): δ 1.36 ppm (t, C*H*$_3$-CH$_2$-, 3H, *J*= 7.2 Hz), 4.43 ppm (q, CH$_3$-C*H*$_2$-, 2H, *J*= 7.2 Hz), 7.42 ppm (s, -C*H*=, 1H), 7.63-7.71 ppm (m, Ar*H*, 3H), 7.96 ppm (d, Ar*H*, 1H, *J*= 6.7 Hz), 8.07 ppm (d, Ar*H*, 1H, *J*= 7.8 Hz), 8.16 ppm (d, Ar*H*, 1H, *J*= 8.2 Hz), 8.22 ppm (d, Ar*H*, 1H, *J*= 7.9 Hz). LC/MS (APCI+) calcd for $C_{16}H_{13}NO_3$, m/z: 268 (MH)+.

Ethyl 5-(2-naphthyl)-3-isoxazolecarboxylate (3d)

White solid; procedure A: 102 mg (5%), procedure B: 1.82 g (92%), procedure C: 1.78 g (90%); Mp 107-108°C. IR (ν, cm^{-1}) 1718 (CO). ^{1}H NMR (300 MHz; DMSO): δ 1.36 ppm (t, C*H*$_3$-CH$_2$-, 3H, *J*= 7.1 Hz), 4.41 ppm (q, CH$_3$-C*H*$_2$-, 2H, *J*= 7.0 Hz), 7.61 ppm (s, -C*H*=, 1H), 7.62-7.64 ppm (m, Ar*H*, 2H), 7.98-8.03 ppm (m, Ar*H*, 1H), 8.06-8.11 ppm (m, Ar*H*, 3H), 8.60 ppm (s, Ar*H*, 1H). LC/MS (APCI+) calcd for $C_{16}H_{13}NO_3$, m/z: 268 (MH)+.

Ethyl 5-[4-(trifluoromethyl)phenyl]-3-isoxazolecarboxylate (3e)

White solid; procedure A: 0.13 g (5%), procedure B: 1.18 g (56%), procedure C: 1.73 g (82%); Mp 136-137°C. IR (ν, cm^{-1}) 1723 (CO). ^{1}H NMR (300 MHz; DMSO): δ 1.38 ppm (t, C*H*$_3$-CH$_2$-, 3H, *J*= 7.2 Hz), 4.39 ppm (q, CH$_3$-C*H*$_2$-, 2H, *J*= 7.2 Hz), 7.85 ppm (s, -C*H*=, 1H), 8.36 ppm (d, Ar*H*, 2H, *J*= 8.2 Hz), 8.42 ppm (d, Ar*H*, 2H, *J*= 8.2 Hz). LC/MS (APCI+) calcd for $C_{13}H_{10}F_3NO_3$, m/z: 286 (MH)+.

Ethyl 5-hydroxy-5-phenyl-4,5-dihydro-3-isoxazolecarboxylate (4a)

Colourless oil; procedure A: 1.24 g (71%), procedure B: 0.29 g (16%). IR (ν, cm^{-1}) 1729 (CO), 1125 (C-OH). 1H NMR (300 MHz; DMSO): δ 1.24 ppm (t, C*H*$_3$-CH$_2$-, 3H, *J*= 7.2 Hz), 3.40 ppm (d, -C*H*$_2$-C(OH)-, 1H, *J*= 18.1 Hz), 3.85 ppm (d, -C*H*$_2$-C(OH)-, 1H, *J*= 18.1 Hz), 4.21 ppm (q, CH$_3$-C*H*$_2$-, 2H, *J*= 7.2 Hz), 7.47 ppm (m, Ar*H*, 3H), 7.71 ppm (m, Ar*H*, 2H), 7.87 (s, -O*H*, 1H). LC/MS (APCI+) calcd for $C_{12}H_{13}NO_4$, m/z: 236 $(MH)^+$.

Ethyl 5-(4-bromophenyl)-5-hydroxy-4,5-dihydro-3-isoxazolecarboxylate (4b)

Colourless oil; procedure A: 2.16 g (93%), procedure B: 0.35 g (15%). IR (ν, cm^{-1}) 1725 (CO), 1134 (C-OH). 1H NMR (300 MHz; DMSO): δ 1.26 ppm (t, C*H*$_3$-CH$_2$-, 3H, *J*= 7.2 Hz), 3.44 ppm (d, -C*H*$_2$-C(OH)-, 1H, *J*= 18.2 Hz), 3.91 ppm (d, -C*H*$_2$-C(OH)-, 1H, *J*= 18.2 Hz), 4.22 ppm (q, CH$_3$-C*H*$_2$-, 2H, *J*= 7.2 Hz), 7.48 ppm (d, Ar*H*, 2H, *J*= 8.2 Hz), 7.71 ppm (d, Ar*H*, 2H, *J*= 8.2 Hz), 7.86 (s, -O*H*, 1H). LC/MS (APCI+) calcd for $C_{12}H_{12}BrNO_4$, m/z: 314 (MH) and 316 $(MH)^{2+}$.

Ethyl 5-hydroxy-5-(1-naphthyl)-4,5-dihydro-3-isoxazolecarboxylate (4c)

Colourless oil; procedure A: 1.61 g (76%), procedure B: 0.46 g (22%). IR (ν, cm-1) 1722 (CO), 1120 (C-OH). 1H NMR (300 MHz; DMSO): δ 1.22 ppm (t, C*H*$_3$-CH$_2$-, 3H, *J*= 7.2 Hz), 3.32 ppm (d, -C*H*$_2$-C(OH)-, 1H, *J*= 18.2 Hz), 3.85 ppm (d, -C*H*$_2$-C(OH)-, 1H, *J*= 18.2 Hz), 4.20 ppm (q, CH$_3$-C*H*$_2$-, 2H, *J*= 7.2 Hz), 7.46-7.51 ppm (m, Ar*H*, 3H), 7.56 ppm (d, Ar*H*, 1H, *J*= 7.0 Hz), 7.59 ppm (d, Ar*H*, 1H, *J*= 7.9 Hz), 7.68 ppm (d, Ar*H*, 1H, *J*= 8.2 Hz), 7.71 ppm (d, Ar*H*, 1H, *J*= 7.9 Hz) 7.87 (s, -O*H*, 1H). LC/MS (APCI+) calcd for $C_{16}H_{15}NO_4$, m/z: 286 (MH)+.

Ethyl 5-hydroxy-5-(2-naphthyl)-4,5-dihydro-3-isoxazolecarboxylate (4d)

Colourless oil; procedure A: 1.79 g (85%), procedure B: 0.17 g (8%). IR (ν, cm^{-1}) 1726 (CO), 1154 (C-OH). ^{1}H NMR (300 MHz; DMSO): δ 1.24 ppm (t, C*H*$_3$-CH$_2$-, 3H, *J*= 7.2 Hz), 3.38 ppm (d, -C*H*$_2$-C(OH)-, 1H, *J*= 18.2 Hz), 3.79 ppm (d, -C*H*$_2$-C(OH)-, 1H, *J*= 18.2 Hz), 4.20 ppm (q, CH$_3$-C*H*$_2$-, 2H, *J*= 7.2 Hz), 7.46-7.54 ppm (m, Ar*H*, 2H), 7.68-7.70 ppm (m, Ar*H*, 1H), 7.71-7.73 ppm (m, Ar*H*, 3H), 7.75 ppm (s, Ar*H*, 1H), 7.88 (s, -O*H*, 1H). LC/MS (APCI+) calcd for $C_{16}H_{15}NO_4$, m/z: 286 (MH)+.

Ethyl 5-hydroxy-5-[4-(trifluoromethyl)phenyl]-4,5-dihydro-3-isoxazolecarboxylate (4e)

Colourless oil; procedure A: 1.65 g (74%), procedure B: 0.98 g (44%). IR (ν, cm^{-1}) 1730 (CO), 1156 (C-OH). ^{1}H NMR (300 MHz; DMSO): δ 1.27 ppm (t, C*H*$_3$-CH$_2$-, 3H, *J*= 7.2 Hz), 3.44 ppm (d, -C*H*$_2$-C(OH)-, 1H, *J*= 18.1 Hz), 3.91 ppm (d, -C*H*$_2$-C(OH)-, 1H, *J*= 18.1 Hz), 4.25 ppm (q, CH$_3$-C*H*$_2$-, 2H, *J*= 7.2 Hz), 7.48 ppm (d, Ar*H*, 2H, *J*= 8.2 Hz), 7.71 ppm (d, Ar*H*, 2H, *J*= 8.2 Hz), 7.86 (s, -O*H*, 1H). LC/MS (APCI+) calcd for $C_{13}H_{12}F_3NO_4$, m/z: 303 (MH)+.

Ethyl 3-hydroxy-5-phenyl-2,3-dihydro-3-isoxazolecarboxylate (5a)

Colourless oil; procedure A: 0.42 g (24%). IR (ν, cm^{-1}) 1724 (CO), 1112 (C_OH). ^{1}H NMR (300 MHz; DMSO): δ 1.22 ppm (m, C*H*$_3$-CH$_2$-, 3H), 4.18 ppm (q, CH$_3$-C*H*$_2$-, 2H, *J*= 7.2 Hz), 4.28 ppm (s, -C*H*=, 1H), 7.38-7.90 ppm (m, Ar*H*, 4H), 7.89 (s, -O*H*, 1H), *7*.98 ppm (d, Ar*H*, 1H, *J*= 7.2 Hz), 12.55 (s, -N*H*, 1H). LC/MS (APCI+) calcd for $C_{12}H_{13}NO_4$, m/z: 236 $(MH)^+$.

Ethyl 5-(4-bromophenyl)-3-hydroxy-2,3-dihydro-3-isoxazolecarboxylate (5b)

Colourless oil; procedure A: 0.14 g (6%). IR (ν, cm^{-1}) 1723 (CO), 1156 (C-OH). 1H NMR (300 MHz; DMSO): δ 1.23 ppm (t, C*H*$_3$-CH$_2$-, 3H, *J*= 7.2 Hz), 4.19 ppm (q, CH$_3$-C*H*$_2$-, 2H, *J*= 7.2 Hz), 4.26 ppm (s, -C*H*=, 1H), 7.39 ppm (d, Ar*H*, 2H, *J*= 8.2 Hz), 7.89 ppm (s, -O*H*, 1H), 8.00 (d, Ar*H*, 2H, *J*= 8.2 Hz), 12.55 (s, -N*H*, 1H). LC/MS (APCI+) calcd for $C_{12}H_{12}BrNO_4$, m/z: 314 (MH) and 316 $(MH)^{2+}$.

Ethyl 3-hydroxy-5-(1-naphthyl)-2,3-dihydro-3-isoxazolecarboxylate (5c)

Colourless oil; procedure A: 0.40 g (19%). IR (ν, cm^{-1}) 1726 (CO), 1135 (C-OH). 1H NMR (300 MHz; DMSO): δ 1.27 ppm (m, C*H*$_3$-CH$_2$-, 3H), 4.22 ppm (q, CH$_3$-C*H*$_2$-, 2H, *J*= 7.2 Hz), 4.25 (s, -C*H*=, 1H), 7.39-7.42 ppm (m, Ar*H*, 3H), 7.54 ppm (d, Ar*H*, 1H, *J*= 7.1 Hz), 7.64 ppm (d, Ar*H*, 1H, *J*= 8.2 Hz), 7.66 ppm (d, Ar*H*, 1H, *J*= 7.9 Hz), 7.90 (s, -N*H*, 1H), 8.02 ppm (d, Ar*H*, 1H, *J*= 8.2 Hz) 12.54 (s, -O*H*, 1H). LC/MS (APCI+) calcd for $C_{16}H_{15}NO_4$, m/z: 286 (MH)+.

Ethyl 3-hydroxy-5-(2-naphthyl)-2,3-dihydro-3-isoxazolecarboxylate (5d)

Colourless oil; procedure A: 0.21 (10%). IR (ν, cm^{-1}) 1724 (CO), 1152 (C-OH). ^{1}H NMR (300 MHz; DMSO): δ 1.23 ppm (m, C*H*$_3$-CH$_2$-, 3H), 4.18 ppm (q, CH$_3$-C*H*$_2$-, 2H, *J*= 7.2 Hz), 4.29 (s, -C*H*=, 1H), 7.39-7.51 ppm (m, Ar*H*, 2H), 7.54-7.56 ppm (m, Ar*H*, 1H), 7.61-7.65 ppm (m, Ar*H*, 3H), 7.89 ppm (s, -N*H*, 1H), 8.00 (s, Ar*H*, 1H), 12.55 ppm (s, -O*H*, 1H). LC/MS (APCI+) calcd for $C_{16}H_{15}NO_4$, m/z: 286 (MH)+.

Ethyl 3-hydroxy-5-[4-(trifluoromethyl)phenyl]-2,3-dihydro-3-isoxazolecarboxylate (5e)

Colourless oil; procedure A: 0.48 (21%). IR (ν, cm^{-1}) 1728 (CO), 1154 (C-OH). ^{1}H NMR (300 MHz; DMSO): δ 1.29 ppm (t, C*H*$_3$-CH$_2$-, 3H, *J*= 7.2 Hz), 4.17 ppm (q, CH$_3$-C*H*$_2$-, 2H, *J*= 7.2 Hz), 4.28 (s, -C*H*=, 1H), 7.54 ppm (d, Ar*H*, 2H, *J*= 8.2 Hz), 7.89 (s, -N*H*, 1H), 8.02 ppm (d, Ar*H*, 2H, *J*= 8.2 Hz), 12.54 ppm (s, -O*H*, 1H). LC/MS (APCI+) calcd for $C_{13}H_{12}F_3NO_4$, m/z: 303 (MH)+.

ABBREVIATIONS

DIPEA = diisopropylethylamine

PTSA = paratoluene sulfonic acid

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