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Selective synthesis of 2-substituted 4-carboxy oxazoles, thiazoles and thiazolidines from serine or cysteine amino acids

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ABSTRACT

The synthesis of new 4-carboxy oxazoles, thiazoles and thiazolidines by condensation of serine or cysteine with aldehydes or acids is described. Due to the optimization of a mild and selective procedure, which takes advantage of the positive effect of microwave irradiation on the MnO_2 mediated oxidation step, the 2-substituted-4-carboxy derivatives can be obtained in multi-gram scale. Examples of coordination chemistry to Ni(II) and Co(II) are described.

1. Introduction

The development of macromolecular architectures having defined structural motifs is a subject of intense research in different fields: molecular and ion recognition,[1–3] supramolecular chemistry,[4] drug design[5,6] and material science.[7] In this regard nitrogen-containing heterocycles have been widely used as ligands as they may favour the assembly of polymeric, polydimensional architectures also by establishing a variety of non-covalent interactions, such as dipole–dipole and hydrogen-bonding via chelation or coordination to different metal centres.

In particular, mixed N, S- or N, O-heterocycles, such as thiazolidines, thiazoles and oxazoles have received large attention. These heterocycles exhibit an interesting biological activity. Their structural motifs are present in thiopeptide antibiotics,[8,9] and are recognized as signature metal binding sites, common to many clinically important macrocyclic peptides.[10,11] Many oxazole and/or thiazole-containing macrocycles are naturally occurring molecules, *i.e.*, Bistratamides,[12] Didmolamides A and B,[13] Lyngbyabellin A,[14] Calyculins,[14,15] and show cytotoxic, antimicrobial and multiple drug resistance activities. Furthermore, these compounds have shown wide practical applications in material science; they exhibit favourable fluorescence,[16,17] solvatochromic, electrochemical, NLO and photochromic properties and have been used for organic light-emitting diodes (OLEDs) and semiconductor materials, as well as in optical data storage devices, and second-harmonic generators.[18–21] Finally, they can be used as stabilizers for polymeric materials,[22] as photosensitizers[23] and, once coordinated to technetium or rhenium, as radiopharmaceuticals for tumour imaging and/or radiotherapy.[24]

Recently, thiazole-based nicotinate and isonicotinate derivatives were chosen as promising organic connectors in crystal engineering, as the coexistence of thiazole-spaced pyridyl and carboxylate moieties could afford a rich variety of coordination modes, resulting in interesting polymetallic architectures.[25] These studies suggest that such flexible ligands may be quite versatile to stabilise metallorganic supramolecular systems.[25] Obviously the screening of a wider class of thiazole(oxazole)-based ligands would be very important to obtain a better insight on the substituent effects on the 3D self-assembly when coordinating transition metal moieties. For this reason, a general, mild and selective procedure for preparing 4-carboxy oxazole, thiazole and thiazolidine compounds in large quantities would be very desirable.

Herein, we report on the preparation and full characterization of some new carboxy thiazole(oxazole)-based ligands using a simple synthetic approach, which starts from easily available building blocks and has been optimized to allow for multi-gram scale preparation of a variety of 2-substituted, 4-carboxy heterocycles, and examples of the coordination chemistry towards Ni(II) and Co (II) salts.

2. Results and discussion

Cyclisation of cysteine side-chains onto carbonyl groups yielding thiazole five-membered heterocycles is a well established

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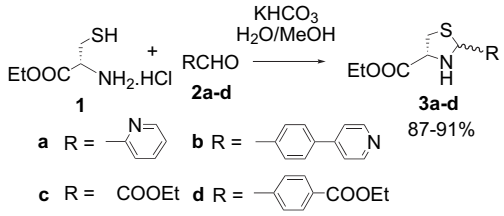
procedure,[26] which has found many applications.[27–29] Following this approach, L-cysteine ethyl ester **1** was reacted with different pyridyl- and carboxaldehydes **2a**–**d** to afford the corresponding thiazolidine derivative **3a**–**d** as shown in Scheme 1.

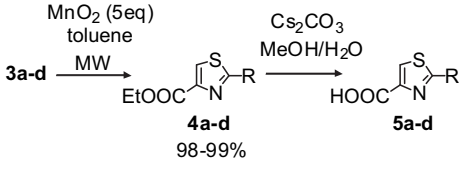


Scheme 1.

Condensation reactions were carried out in aqueous methanol containing potassium bicarbonate and, as expected, mixtures of two diastereoisomers were obtained, due to the presence of a new stereogenic centre generated at the C-2 atom of the thiazolidine ring.

The thiazolidines **3a**–**d** synthesised by this procedure were converted into the corresponding thiazoles via oxidative dehydrogenation. Several methods are described to perform this transformation albeit drawbacks, such as low yields, limited stability to reaction conditions, loss of optical purity in the case of some chiral thiazoles and hazardous reaction conditions hamper large scale synthesis. Our aim was to improve the existing procedures to obtain the targeted thiazoles in large scale and high yields. First attempts using a mixture of $CBrCl_3$/DBU[10,30] yielded as expected the thiazole derivatives **4a**–**d**, albeit in poor yields. DDQ[31] and NiO_2.[27,32,33] were also effective, however the yields were very poor and partially reduced thiazolines were found as by-products in some cases. Oxidation was most conveniently performed with manganese dioxide,[12–14,26,34–41] which provided the desired thiazoles in very good yields, although under rather harsh conditions. Best conditions required benzene as solvent in the presence of pyridine for 24 h at 55 °C, using a 25-fold excess of the commercially available activated MnO_2.[26,40]

In order to find milder and more general reaction conditions for our synthetic protocol, we decided to investigate the effect of microwave irradiation on the oxidation step, since the efficiency of microwave flash heating in accelerating oxidation processes has been successfully demonstrated[42] and beneficial effects have been reported in MnO_2 mediated oxidations.[43,44] In keeping with our expectations, the microwave-assisted reaction shortened the reaction time significantly and, although an excess of MnO_2 was still necessary (5 equiv), under optimised conditions, (30 s irradiation, 300 W microwave source, 100 °C), using toluene instead of benzene and without the need of pyridine, led to quantitative formation of thiazoles **4a**–**d** (Scheme 2) irrespective of the substituent at the C-2 position. The absence of added base, made possible by the use of microwave (MW) irradiation, results in turn in a wider scope of this protocol, potentially applicable to the synthesis of optically active thiazoles, where the presence of bases in the reaction mixture should be avoided being responsible, in some cases, of product racemization.[27,45]



Scheme 2.

Finally, ester saponification with Cs_2CO_3 in aqueous methanol afforded the corresponding carboxythiazoles **5a**–**d**, which were isolated after crystallization from acidic water and fully characterized in solution by conventional NMR and MS techniques. Suitable crystals of **5a**·0.5H_2O were grown from diluted water solutions and the corresponding X-ray crystal structure is presented in Fig. 1.

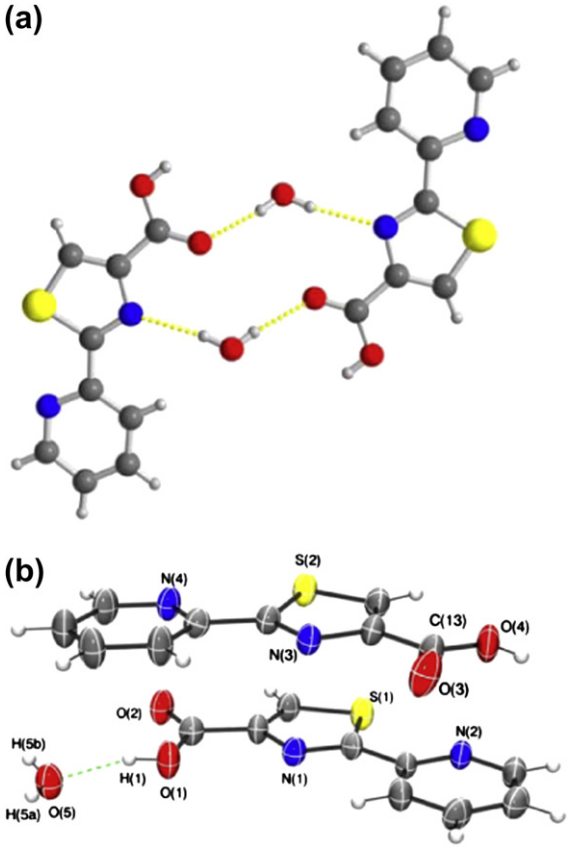
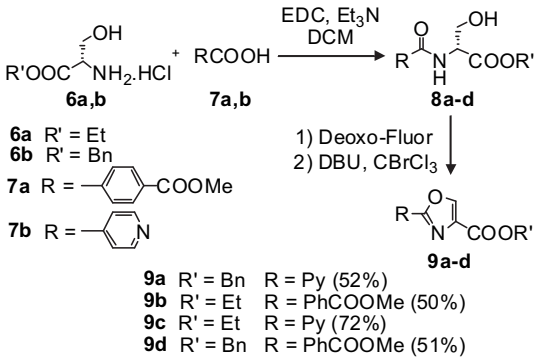


Fig. 1. Double hydrogen bonding of water to neighbouring thiazole molecules in the lattice of **5a**·0.5H_2O (**a**) and X-ray crystal structure of its asymmetric unit (**b**). Thermal ellipsoids in (**b**) are drawn at 40% probability.

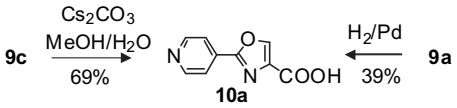
The asymmetric unit consists of two thiazoles and a clathrated water molecule hydrogen-bonded to one carboxylic group {d[O(1)···O(5)]=2.582(4) Å} that reduces the overall symmetry (Fig. 1b). Additional hydrogen bonding with the N atom of the thiazole ring of the neighbouring molecule is present {d[O(5)···N(3)]=3.032(5) Å, Fig. 1a}, thus creating a 3D network. The distance between two adjacent thiazole rings is 3.73 Å, thus confirming the existence of a strong π-stacking in the lattice. Surprisingly, the Cambridge Crytallographic Database includes only one organic structure containing the thiazole ring, *i.e.*, the (oxythiamineH)(picrolonate)$_2$·2H_2O.[46] However, in such derivative, the N atom of the five-membered heterocycle is alkylated, and the overall charge is positive (thiazolium ion). This situation slightly modifies the bond lengths with respect to the neutral ring, without strong deviations from the ordinary C=C and C=N bonds. (see Supplementary data).

4-Carboxyoxazolidines analogues were also prepared. Many methodologies have been developed in the past for oxazoles formation.[47] We decided to prepare β-hydroxyamides **8a**–**d** from serine ethyl or benzyl esters **6a**,**b** by EDC-mediated coupling with terephthalic acid monomethyl ester (**7a**) or isonicotinic acid (**7b**). One-pot cyclization and oxidation with bis(2-methoxyethyl)aminosulfur trifluoride solution (Deoxo-Fluor) and $CBrCl_3$ and DBU led to oxazole **9a**–**d** without the need to isolate the intermediate oxazoline (Scheme 3).[48,30]



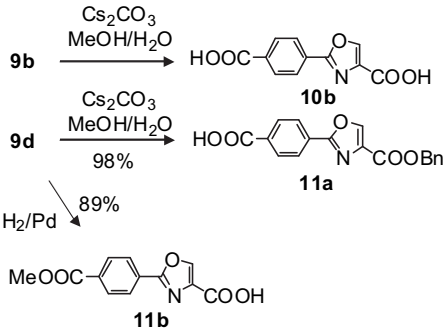
Scheme 3.

In particular, serine benzyl ester was used to evaluate a different protecting group, which might be especially useful in view of demanding orthogonally protected carboxy moieties, as in compounds **9b** or **9d**. Saponification of **9c** with Cs_2CO_3 gave the corresponding carboxazole **10a**, which was isolated after crystallization from acidic water and characterized by elemental analysis and spectroscopic methods. Alternatively, **10a** was obtained by palladium(0)-catalyzed hydrogenation of **9a**, albeit in significantly lower yield (Scheme 4).



Scheme 4.

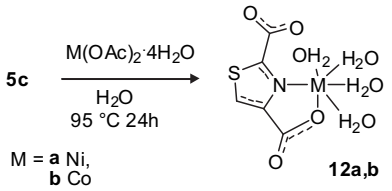
The dicarboxylic acid **10b** was prepared by saponification of **9b** with Cs_2CO_3 in aqueous methanol as above, while the monoprotected oxazoles **11a** and **11b** could in turn be obtained by saponification or hydrogenolysis of **9d**, respectively. These results confirm that in such compounds the benzyl ester can be advantageously used as orthogonal protective group for obtaining monocarboxy derivatives (Scheme 5).



Scheme 5.

As an example of the coordination ability of these new ligands, thiazole-2,4-dicarboxylic acid **5c** was reacted with several transition metals using solvotermic conditions.[49] Interesting results have been obtained in the case of nickel and cobalt acetate tetrahydrate, which under hydrothermal conditions at 90 °C gave the two new complexes **12a**,**b** (Scheme 6).

Suitable crystals of **12a**·H_2O were grown from diluted water solutions and the corresponding X-ray crystal structure is presented in Fig. 2. The resulting complex [Ni(**5c**)$(H_2O)_4$·H_2O] shows an (N,O)-chelating coordination mode of the (deprotonated) **5c** to the Ni(II) ion. The octahedral geometry is completed by four aquo



Scheme 6.

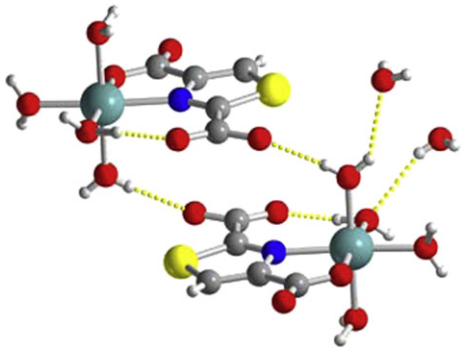


Fig. 2. 3D solid state packing and hydrogen bonding network in the lattice of **12a**. Hydrogen bonds drawn in yellow dotted lines.

ligands, in a cis-disposition. One carboxylic group is linked to the metal, while the other is 'pendant', engaging in extensive hydrogen bonding with the neighbouring water molecules and with the carboxylic groups of the adjacent molecules in the crystal lattice (see Fig. 3 and Supplementary data for details).

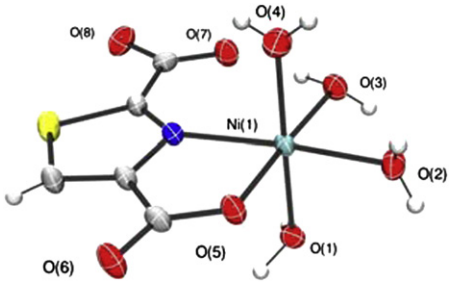


Fig. 3. X-ray crystal structure of complex **12a**. Thermal ellipsoids are drawn at 40% probability. The same colour code of Fig. 1 has been used.

Suitable crystals of **12a**·H_2O were grown from diluted water solutions and the corresponding X-ray crystal structure is presented in Fig. 2. The resulting complex [Ni(**5c**)$(H_2O)_4$·H_2O] shows an (N,O)-chelating coordination mode of the (deprotonated) **5c** to the Ni(II) ion. The octahedral geometry is completed by four aquo ligands, in a cis-disposition. One carboxylic group is linked to the metal, while the other is 'pendant', engaging in extensive hydrogen bonding with the neighbouring water molecules and with the carboxylic groups of the adjacent molecules in the crystal lattice (see Fig. 3 and Supplementary data for details).

A crystallization water molecule is included in the asymmetric unit, interacting through additional hydrogen bonding to the coordinated aquo ligands. The presence of an extended hydrogen bonding network due to the presence of several polar groups in the asymmetric unit confers a 'pseudo-polymeric' nature to these solids, being insoluble in all solvents.

3. Conclusions

We have reported a selective and general procedure for the synthesis of 4-carboxythiazoles, showing that both reaction time

and the need of polluting reagents can be dramatically reduced by MW activation during the oxidation step. The corresponding 4-carboxy oxazoles have also been prepared *via* a similar synthetic protocol, while the use of a benzyl moiety as protective group has been exploited to prepare orthogonally protected carboxy moieties. The coordination ability of **5c** towards nickel(II) and Co(II) in aqueous environment has been analysed, leading to (N,O)-bidentate chelation in two new complexes in which an extensive 3D network is created through hydrogen bonding. Different transition metal ions and the possible assembly of thiazole/oxazole-based metal-organic frameworks are currently under investigation.

4. Experimental section

4.1. General

All manipulations were performed under a dry nitrogen atmosphere using vacuum-lines and standard Schlenk techniques. Dichloromethane, benzene and methanol were dried by standard methods and distilled under nitrogen before use. All the other solvents were dried and degassed by MB SPS solvent purification system (http://solventpurifier.com). All reagents were obtained from commercial suppliers and used without further purification. Reactions were monitored by TLC on SiO_2 plates; detection was made using a $KMnO_4$ basic solution. Flash column chromatography was performed using glass columns (10–50 mm wide) and SiO_2 (230–400 mesh).

Microwave irradiation experiments were performed using a single-mode Discover System BenchMate 220VAC750 Hz from CEM Corporation,[50] using standard Pyrex vessels or flasks in open vessel mode.

Deuterated solvents for routine NMR measurements were dried over molecular sieves. ^{1}H NMR spectra were recorded operating at 300.13 and 400.1 MHz; ^{13}C NMR spectra were recorded operating at 75.48 and 100.61 MHz. Peak positions are relative to tetramethylsilane (^{1}H) and were calibrated against the residual solvent resonance. Coupling constants (J) were reported in hertz. When a mixture of diastereoisomers is present, signals of the minor diastereoisomer are reported in parentheses. FTIR spectra were measured using KBr pellets or solution cells.

Mass spectra were obtained at a 70 eV ionization potential and are reported in the form m/z (intensity relative to base=100).

ESI-MS spectra were done on an LCQ Orbitrap mass spectrometer equipped with a conventional ESI source by direct injection of the sample solution 80 scans were accumulated and averaged for each spectrum.

4.2. General procedure to ethyl 2(*R*,*S*)-substituted-thiazolidine-4(*R*)-carboxylate (3a–d)

Aldehydes **2a–d** (1.1 equiv) were suspended in MeOH, then a solution of the commercially available L-cysteine ethyl ester hydrochloride **1b** (1.1 equiv) dissolved in H_2O together with $KHCO_3$ (1.0 equiv) was added and the resulting mixture was stirred at room temperature overnight. After evaporation of MeOH the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine (100–200 mL depending on the reaction scale) and dried over Na_2SO_4. Evaporation of the solvent afforded compounds **3a–d**, which were used without further purification.

*4.2.1. (R,S)-Ethyl-2-(pyridin-2-yl-)thiazolidine-4-(R)-carboxylate (**3a**)*[51]. Reaction of **1** (7.70 g, 41.5 mmol) with 2-pyridinecarboxaldehyde (4.00 mL, 49.8 mmol) and $KHCO_3$ (41.5 g, 41.5 mmol) in MeOH (210 mL) and H_2O (210 mL) gave 9.85 g of **3a** (99%) as a yellow oil containing a 1:1 mixture of diastereoisomers. The mixture (100 mg) were purified by flash column chromatography to get an analytically pure sample. R_f=0.5 (petroleum ether/AcOEt=2/1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 8.64–8.61 (8.58–8.55) (m, 1H), 7.70–7.62 (m, 1H), 7.35–7.16 (m, 2H), 5.85 (5.65) [br s (d, J=11.25 Hz), 1H], 4.51 (br s, 1H), 4.27 (4.26) (q, J=7.1 Hz, 2H), 3.48–3.29 (m, 2H+1H), 1.32 (1.31) (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 171.6 (170.6), 158.7 (156.6), 149.8 (149.6), 136.7, 123.3 (122.9), 122.1 (121.4), 71.6 (71.0), 66.3 (65.6), 61.6 (61.5), 39.4 (38.7), 14.13; IR (KBr): ν 3290 (NH), 1747 (CO) cm^{-1}; MS, m/z (%): 238(3) [M$^+$], 166(100) [(M−COOEt)$^+$]. $C_{11}H_{14}N_2O_2S$ (238.31): calcd C, 55.44; H, 5.92; N, 11.76, found C 55.73, H 5.93, N 11.78.

*4.2.2. (R,S)-Ethyl-2-(4-(pyridin-4-yl)-phenyl)-thiazolidine-4-(R)-carboxylate (**3b**).* Reaction of **1** (2.00 g, 10.8 mmol,) with 4-(4-formylphenyl)-pyridine (2.18 g, 11.9 mmol) and $KHCO_3$ (10.8 g, 10.8 mmol) in MeOH (54.0 mL) and H_2O (54.0 mL) gave 9.75 g (99%) of **3a** as a yellow solid containing a 1:1.5 mixture of diastereoisomers. The mixture (100 mg) were purified by flash column chromatography to get an analytically pure sample. R_f=0.4 (petroleum ether/AcOEt=1/3); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.63–8.60 (m, 2H), 7.70–7.62 (m, 4H), 7.47–7.44 (m, 2H), 5.86 (5.58) (s, 1H), 4.24 (4.23) (q, J=7.1 Hz, 2H), 3.99–3.94 (4.16–4.12) (m, 1H), 3.48–3.44 (3.40–3.35) (m, 1H), 3.17–3.13 (3.14–3.08) (m, 1H), 2.74 (br s, 1H), 1.29 (1.28) (t, J=7.1 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 170.9 (171.4), 150.02, 147.3 (147.5), 138.2 (142.6), 139.1 (137.2), 128.0 (127.4), 127.0 (126.8), 121.3, 71.8 (70.0), 65.5 (64.2), 61.5 (61.4), 39.1 (38.1), 14.0; IR (KBr): ν 3255 (NH), 1730 (CO) cm^{-1}; MS, m/z (%): 314(3) [M$^+$], 241(52) [(M−COOEt)$^+$], 214(100). $C_{17}H_{18}N_2O_2S$ (314.40): calcd C, 64.94; H, 5.77; N, 8.91, found C 65.09, H 5.75, N 8.92.

*4.2.3. (S,R)-Diethyl thiazolidine-2,4-(R)-dicarboxylate (**3c**).* Reaction of **1** (8.00 g, 43.1 mmol) with ethyl glyoxalate (50% in toluene) (9.00 mL, 90.5 mmol) and $KHCO_3$ (4.31 g, 43.1 mmol) in MeOH (215 mL) and H_2O (215 mL) gave 9.23 g (92%) of **3c** as a yellow oil containing a 1:3 mixture of diastereoisomers. The mixture (100 mg) were purified by flash column chromatography to get an analytically pure sample. R_f=0.7 (hexane/AcOEt=3/2); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 5.07 (4.88) (s, 1H), 4.26–4.17 (m, 2H+2H), 4.15–4.13 (4.40–4.36) (m, 1H), 3.84–3.78 (3.7–3.71) (dd, J_{AB}=6.0, J_{BX}=10.2 Hz, 1H), 3.29–3.23 (3.23–3.17) (dd, J_{Ax}=10.2, J_{AB}=6.0 Hz, 1H), 2.75 (t, J_{app}=10.2 Hz, 1H), 1.26 (1.25) (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 170.8 (171.0), 169.8 (170.3), 66.4 (65.4), 64.6 (65.2), 61.6 (62.0), 37.7 (37.4), 14.0, 13.9; IR (KBr): ν 3293 (NH), 1740 (CO) cm^{-1}; MS, m/z (%): 233(2) [M$^+$], 160(100) [(M−COOEt)$^+$]. $C_9H_{15}NO_4S$ (233.28): calcd C, 46.34; H, 6.48; N, 6.00, found C 46.46, H 6.45, N 5.09.

*4.2.4. (R,S)-Ethyl-2-[4-(methoxycarbonyl)phenyl]-thiazolidine-4(R)-carboxylate (**3d**).* Reaction of **1** (8.00 g, 43.1 mmol) with methyl 4-formylbenzoate (7.78 g, 47.4 mmol) and $KHCO_3$ (4.31 g, 43.1 mmol) in MeOH (215 mL) and H_2O (215 mL) gave 12.4 g (98%) of **3d** as a yellow oil containing a 1:1 mixture of diastereoisomers. The mixture (100 mg) were purified by flash column chromatography to get an analytically pure sample. R_f=0.4 (hexane/AcOEt=2/1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.91 (7.95)(d, J=8.3 Hz, 2H), 7.54(7.47) (d, J=8.3 Hz, 2H), 5.80 (5.51) (s, 1H), 4.28 (4.30) (q, J=7.1 Hz, 2H), 3.94–3.88 (4.08–4.05) (m, 1H), 3.84 (3.83) (s, 3H), 3.43–3.37 (3.31–3.24) (dd, J_{AB}=10.3, J_{AX}=7.1 Hz, 1H), 3.11–3.04 (m, 1H), 2.91 (br s, 1H), 1.24 (1.23) (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 171.3 (170.2), 166.4 (166.3), 146.8 (143.1), 129.4 (129.7), 129.2, 127.3 (126.5), 69.8 (71.7), 64.2 (65.4), 61.5 (61.4), 51.9 (51.8), 38.0 (39.0), 13.9; IR (KBr): ν 3290 (NH), 1725 (CO) cm^{-1}; MS, m/z (%): 295 (8) [M$^+$], 223(100) [(M−COOEt)$^+$].

$C_{14}H_{17}NO_4S$ (295.35): calcd C, 56.93; H, 5.80; N, 4.74, found C 56.84, H 5.82, N 4.75.

4.3. General MnO_2 oxidation procedure (4a–d)

To a solution of the (*S*,*R*)-2-substituted-4-(*R*)-carbethoxy-1,3-thiazolidine **3a**–**d** (1.0 equiv) in toluene, activated MnO_2 (5.0 equiv) was added. The sealed flask was inserted into the cavity of a Discovery Microwave System apparatus and heated for 30 s at 100 °C and 300 W irradiation (value preset on the Microwave oven). The reaction mixture was then filtered through Celite and washed with toluene. The filtrate and washings were put together and concentrated under vacuum to afford thiazoles **4a**–**d**, which were purified by flash chromatography.

*4.3.1. Ethyl-2-(pyridin-2-yl)-thiazole-4-carboxylate (**4a**)*[52]. Reaction of **3a** (10.0 g, 42.1 mmol) with MnO_2 (18.3 g, 210 mmol) in toluene (420 mL) gave 6.87 g (70%) of **3a** as white solid. R_f=0.5 (petroleum ether/AcOEt=2/1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 8.56 (ddd, *J*=4.8, 1.7, 1.1 Hz, 1H), 8.28 (dt_{app}, *J*=7.7, 1.1 Hz, 1H), 8.21 (s, 1H), 7.77 (t_{app}d, *J*=7.7, 1.7 Hz, 1H), 7.31 (ddd, *J*=7.7, 4.8, 1.1 Hz, 1H), 4.40 (q, *J*=7.1 Hz, 2H), 1.38 (t, *J*=7.1 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 161.3, 169.8, 150.3, 149.3, 148.1, 137.0, 129.4, 125.0, 120.1, 61.4, 14.2 ppm; IR (KBr): ν 1724 (CO) cm^{-1}; MS, *m*/*z* (%): 234(5) [M^+], 161(100) [$(M-COOEt)^+$]; $C_{11}H_{10}N_2O_2S$ (234.27): calcd C, 56.39; H, 4.30; N, 11.96, found C 56.22, H 4.61, N 12.01.

*4.3.2. Ethyl-2-[4-(pyridin-4-yl)phenyl]-thiazole-4-carboxylate (**4b**).* Reaction of **3b** (2.90 g, 9.20 mmol) with MnO_2 (4.00 g, 46.0 mmol) in toluene (92.0 mL) gave 1.86 g (65%) of **3a** as yellow solid. R_f=0.3 (petroleum ether/AcOEt=2/1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.67 (dd, *J*=4.6, 1.6 Hz, 2H), 8.17 (s, 1H), 8.11 (dd, *J*=8.4, 1.1 Hz, 2H), 7.70 (dd, *J*=6.6, 1.8 Hz, 2H), 7.52 (dd, *J*=4.6, 1.6 Hz, 2H), 4.44 (q, *J*=7.1 Hz, 2H), 1.42 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 167.8, 161.3, 150.3, 148.2, 147.0, 140.1, 133.2, 127.6, 127.5, 127.3, 121.4, 61.5, 14.3; IR (KBr): ν 1720 (CO) cm^{-1}; MS, *m*/*z* (%): 238(100) [$(M-COOEt)^+$]; $C_{17}H_{14}N_2O_2S$ (310.37): calcd C, 65.79; H, 4.55; N, 9.03, found C 66.01, H 4.56, N 9.02.

*4.3.3. Diethyl thiazole-2,4-dicarboxylate (**4c**).* Reaction of **3c** (6.10 g, 26.1 mmol) with MnO_2 (11.35 g, 130.5 mmol) in toluene (261.0 mL) gave 4630 mg (77%) of **4c** as white solid. R_f=0.7 (hexane/AcOEt=3/2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.30 (s, 1H), 4.25 (q, *J*=7.0 Hz, 2H), 4.19 (q, *J*=7.0 Hz, 2H), 1.20 (t, *J*=7.0 Hz, 3H), 1.16 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 180.0, 158.8, 158.4, 148.1, 132.0, 62.3, 61.0, 13.6, 13.5; IR (KBr): ν 1731 (CO) cm^{-1}; MS, *m*/*z* (%): 229(5) [M^+]; 157(100) [$(M-CO_2Et)^+$]. $C_9H_{11}NO_4S$ (229.25): calcd C, 47.15; H, 4.84; N, 6.11, found C 47.25, H 5.02, N 6.02.

*4.3.4. Ethyl-2-[4-(methoxycarbonyl)phenyl]-thiazole-4-carboxylate (**4d**).* Reaction of **3d** (12.0 g, 40.8 mmol) with MnO_2 (17.7 g, 204 mmol) in toluene (410 mL) gave 8.25 g (69%) of **4d** as yellow solid. R_f=0.4 (hexane/AcOEt=2/1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 8.20 (s, 1H), 8.11–8.05 (m, 4H), 4.44 (q, *J*=7.1 Hz, 2H), 3.93 (s, 3H), 1.42 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 167.4, 166.2, 161.2, 148.4, 136.4, 131.8, 130.2, 127.8, 126.8, 61.6, 52.3, 14.3; IR (KBr): ν 1720 (CO) cm^{-1}; MS, *m*/*z* (%): 291(100) [M^+], 218 (100) [$(M-CO_2Et)^+$]; $C_{14}H_{13}NO_4S$ (291.32): calcd C, 57.72; H, 4.50; N, 4.81, found C 58.01, H 4.48, N 5.00.

4.4. General procedure of saponification (5a–d)

2-Substituted-4-carbethoxy-1,3-thiazole **4a**–**d** (1 equiv) was dissolved in MeOH. A solution of cesium carbonate (2 equiv) in H_2O was added and the mixture was stirred at room temperature overnight. The reaction mixture was then concentrated in vacuo to remove MeOH. The aqueous phase was washed with ethyl acetate then acidified with concentrated HCl ($1 \le pH \le 4$) to let carboxylic acid gradually precipitate from the reaction medium. The solid was collected by filtration on paper and washed several times with EtOH, H_2O and Et_2O to afford the pure acids **5a**–**d**.

*4.4.1. 2-(Pyridin-4-yl)-thiazole-4-carboxylic acid (**5a**).* Reaction of **4a** (6.88 g, 29.5 mmol) with Cs_2CO_3 (19.2 g, 59.0 mmol), in MeOH (295 mL) and H_2O (295 mL) gave 4.41 g (72%) of **5a** as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C): δ 8.66 (dm, *J*=4.8 Hz, 1H), 8.57 (s, 1H), 8.15 (dm, *J*=7.9 Hz, 1H), 8.00 (dt_{app}, *J*=7.8, 1.7 Hz, 1H), 7.54 (ddd, *J*=7.8, 4.8, 1.1 Hz, 1H); ^{13}C NMR (100.6 MHz, DMSO-d_6, 25 °C): δ 168.8, 162.1, 149.9, 149.8, 148.4, 138.0, 130.9, 125.7, 119.4; IR (KBr): ν 3114 (OH), 1709 (CO) cm^{-1}; ESI-MS, *m*/*z* (%): 206(100) [M^+]; $C_9H_6N_2O_2S \cdot 1/2H_2O$ (215.23): calcd C, 50.02; H, 3.28; N, 13.02, found C 50.07, H 3.31, N 12.98.

*4.4.2. 2-[4-(Pyridin-4-yl)phenyl]-thiazole-4-carboxylic acid (**5b**).* Reaction of **4b** (1.76 g, 5.70 mmol) with Cs_2CO_3 (3.70 g, 11.3 mmol), in MeOH (50.0 mL) and H_2O (50.0 mL) gave 1.25 g (78%) of **5b** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C): δ 13.25 (br s, 1H), 8.68 (d, *J*=5.9 Hz, 2H), 8.55 (s, 1H), 8.12 (d, *J*=8.3 Hz, 2H), 8.00 (d, *J*=8.3 Hz, 2H), 7.80 (d, *J*=5.9 Hz, 2H); ^{13}C NMR (100.6 MHz, DMSO-d_6, 25 °C): δ 167.0, 162.5, 150.8, 148.9, 146.2, 139.5, 133.5, 129.5, 128.2, 127.6, 121.6; IR (KBr): ν 3122 (OH), 1690 (CO) cm^{-1}; ESI-MS, *m*/*z* (%): 283(100) [$(M+H)^+$]; $C_{15}H_{10}N_2O_2S \cdot 1/2H_2O$ (282.32): calcd C, 61.84; H, 3.81; N, 9.62, found C 61.71, H 3.84, N 9.56.

*4.4.3. Thiazole-2,4-dicarboxylic acid (**5c**).* Reaction of **4c** (3.90 g, 17.0 mmol) with Cs_2CO_3 (22.2 g, 68.0 mmol) in MeOH (170 mL) and H_2O (170 mL) gave 2.46 g (83%) of **5c** as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C): δ 8.73 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6, 25 °C): δ 162.8, 161.6, 160.7, 149.7, 135.0; IR (KBr): ν 3140 (OH), 1719 (CO) cm^{-1}; ESI-MS, *m*/*z* (%): 173(100) [M^+], 128(30) [$(M-CO_2H)^+$]; $C_5H_3NO_4S \cdot H_2O$ (191.16): calcd C, 31.41; H, 2.64; N, 7.33, found C 31.68, H 2.66, N 7.35.

*4.4.4. 2-(4-Carboxyphenyl)thiazole-4-carboxylic acid (**5d**).* Reaction of **4d** (8.25 g, 28.3 mmol) with Cs_2CO_3 (36.9 g, 113 mmol) in MeOH (280 mL) and H_2O (280 mL) gave 5.39 g (76%) of **5d** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.55 (s, 1H), 8.11–8.05 (m, 4H); ^{13}C NMR (100.6 MHz, DMSO-d_6, 25 °C): δ 167.3, 166.5, 162.7, 136.4, 133.3, 130.7, 130.6, 129.5, 126.9; IR (KBr): ν 3134 (OH), 1695 (CO) cm^{-1}; ESI-MS, *m*/*z* (%): 249(15) [M^+], 248(100) [$(M-H)^+$]; $C_{11}H_7NO_4S \cdot H_2O$ (267.26): calcd for C, 49.43; H, 3.39; N, 5.24, found C 49.76, H 3.30, N 5.21.

4.5. General procedure to methyl 2(*R*)-amido-3-hydroxypropanoate3-hydroxy amide (8a–d)[48]

L-Serine methyl ester hydrochloride **6a**,**b** (1.0 equiv) was dissolved in CH_2Cl_2 together with acids **7a**,**b** (1.1 equiv), Et_3N (1.1 equiv) and EDC (1.1 equiv). After stirring overnight, the solution was washed with H_2O, $NaHCO_3$ satd sol and brine, then dried over Na_2SO_4. Evaporation of the solvent gave amide **8a**–**d**, which were used without further purification.

*4.5.1. (S)-Benzyl 3-hydroxy-2-(isonicotinamido)-propanoate (**8a**).* Reaction of **6a** (2.47 g, 10.6 mmol) with **7a** (1.44 g, 11.7 mmol), Et_3N (1.60 mL, 11.7 mmol), EDC (2.24 g, 11.7 mmol) in CH_2Cl_2 (90.0 mL) gave 2.28 g (72%) of **8a** as a white solid. 100 mg of the amide were purified by flash column chromatography to get an analytically pure sample. R_f=0.3 (hexane/AcOEt=1/2); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 8.73 (dd, *J*=4.5, 1.6 Hz, 2H), 7.64 (dd, *J*=4.5, 1.6 Hz,

2H), 7.37 (br s, 5H), 7.19 (br d, J=3.2 Hz, 1H), 5.26 (s, 1H), 4.92–4.87 (m, 1H), 4.15 (dd, J_{AB}=11.3, J_{AX}=3.4 Hz, 1H), 4.06 (dd, J_{AB}=11.3, J_{BX}=3.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 170.1, 165.5, 150.7, 141.0, 135.1, 128.7, 128.3, 127.6, 121.0, 67.9, 63.1, 55.2; IR (KBr): ν 3289 (NH), 3250 (OH), 1748 (CO), 1644 (CO) cm^{-1}; ESI-MS, m/z (%): 301(100) [(M+H)$^+$]. $C_{16}H_{16}N_2O_4$ (300.31): calcd C, 63.99; H, 5.37; N, 9.33, found C 64.07, H 5.34, N 9.29.

*4.5.2. (R)-Methyl 4-(1-ethoxy-3-hydroxy-1-oxopropan-2-ylcarbamoyl)benzoate (**8b**).* Reaction of **6b** (2.14 g, 12.6 mmol) with **7a** (2.50 g, 13.9 mmol), 0.70 mL of Et_3N (13.9 mmol) and EDC (2.66 g, 13.9 mmol) in CH_2Cl_2 (90.0 mL) gave 3.56 g (95%) of **8b** as a white solid. 100 mg of the amide were purified by flash column chromatography to get an analytically pure sample. R_f=0.6 (hexane/AcOEt=1/2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.05 (d, J=8.3 Hz, 2H), 7.88 (d, J=8.3 Hz, 2H), 7.38 (br d, J=3.2 Hz, 1H), 4.85–4.79 (m, 1H), 4.68 (br s, 1H), 4.28 (q, J=7.1 Hz, 2H), 4.10 (dd, J_{AB}=11.3, J_{AX}=3.6 Hz, 1H), 4.05 (dd, J_{AB}=11.3, J_{BX}=3.2 Hz, 1H), 3.9 (s, 3H), 1.31 (t, J=7.1 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ=170.4, 166.8, 166.2, 137.4, 132.9, 129.7, 127.2, 63.1, 62.0, 55.3, 52.4, 14.1; IR (film): ν 3547 (NH), 3277 (OH), 1723 (CO), 1640 (CO) cm^{-1}; ESI-MS, m/z (%): 296(100) [(M+H)$^+$]. $C_{14}H_{17}NO_6$ (295.29): calcd C, 56.94; H, 5.80; N, 4.74, found C 56.87, H 5.84, N 4.76.

*4.5.3. (R)-Ethyl 3-hydroxy-2-(isonicotinamido)-propanoate (**8c**).* Reaction of **6b** (5.00 g, 29.5 mmol) with **7b** (3.99 g, 32.4 mmol), Et_3N (4.50 mL, 32.4 mmol) and EDC (6.21 g, 32.4 mmol) in CH_2Cl_2 (250 mL) gave 6.55 g (93%) of **8c** as a white solid. 100 mg of the amide were purified by flash column chromatography to get an analytically pure sample. R_f=0.6 (hexane/AcOEt=1/2); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 8.75 (dd, J=4.4, 1.7 Hz, 2H), 7.66 (dd, J=4.4, 1.7 Hz, 2H), 7.12 (br d, J=3.0 Hz, 1H), 4.85–4.81 (m, 1H), 4.29 (q, J=7.1 Hz, 2H), 4.13 (dd, J_{AB}=11.3, J_{AX}=3.5 Hz, 1H), 4.07 (dd, J_{AB}=11.3, J_{BX}=3.2 Hz, 1H), 1.33 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 170.2, 165.5, 150.6, 140.7, 121.0, 63.2, 62.3, 55.2, 14.14; IR (KBr): ν 3328 (NH), 3260 (OH), 1749 (CO), 1644 (CO) cm^{-1}; ESI-MS, m/z (%): 239(100) [(M+H)$^+$]. $C_{11}H_{14}N_2O_4$ (238.24): calcd C, 55.46; H, 5.92; N, 11.76, found C 55.52, H 5.91, N 11.73.

*4.5.4. (R)-Methyl 4-(1-(benzyloxy)-3-hydroxy-1-oxopropan-2-ylcarbamoyl)benzoate (**8d**).* Reaction of **6a** (2.42 g, 10.4 mmol) with 2.06 g of monomethyl terephthalate **7b** (11.4 mmol), 1.60 mL of Et_3N (11.4 mmol) and EDC (2.18 g, 11.4 mmol) in CH_2Cl_2 (110 mL) gave 2.75 g (74%) of **8d** as a white solid. 100 mg of the amide were purified by flash column chromatography to get an analytically pure sample. R_f=0.6 (hexane/AcOEt=1/2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.08 (d, J=8.7 Hz, 2H), 7.86 (d, J=8.7 Hz, 2H), 7.35 (br s, 5H), 7.22 (bd, J=7.2 Hz, 1H), 5.24 (s, 2H); 4.93–4.88 (m, 1H), 4.12 (dd, J_{AB}=11.3, J_{AX}=3.6 Hz, 1H), 4.05 (dd, J_{AB}=11.3, J_{BX}=3.3 Hz, 1H), 3.9 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 170.3, 166.7, 166.2, 137.3, 135.0, 133.1, 129.8, 128.7, 128.6, 128.2, 127.2, 67.7, 63.3, 55.3, 52.4; IR (KBr): ν 3495 (NH), 3285 (OH), 1724 (CO), 1628 (CO) cm^{-1}; ESI-MS, m/z (%): 358(100) [(M+H)$^+$]. $C_{19}H_{19}NO_6$ (357.36): calcd C, 63.86; H, 5.36; N, 3.92, found C 63.78, H 5.37, N 3.91.

4.6. General procedure to 2-substituted oxazole-4-carboxylate (9a–d)

A solution of **8a**–**d** (1.0 equiv) in CH_2Cl_2 was cooled to −20 °C. Deoxo-Fluor (50% in THF) (2.2 equiv) was added dropwise, and the mixture was stirred at −20 °C for 50 min. After addition of $BrCCl_3$ (3.6 equiv) and DBU (3.6 equiv) the reaction was left at 0 °C for 5 h and then quenched with $NaHCO_3$ satd sol and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4. Evaporation of the solvent and purification by flash chromatography gave compounds **9a**–**d**.

*4.6.1. Benzyl 2-(pyridin-4-yl)oxazole-4-carboxylate (**9a**).* Reaction of **8a** (2.27 g, 7.60 mmol) with Deoxo-Fluor (3.50 mL, 16.1 mmol), $BrCCl_3$ (2.70 mL, 27.4 mmol) and DBU (4.10 mL, 27.4 mmol) in CH_2Cl_2 (76.0 mL) gave 1.10 g (52%) of **9a** as a white solid (hexane/AcOEt=grad). R_f=0.25 (hexane/AcOEt=1/1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.77 (d, J=6.0 Hz, 2H), 8.35 (s, 1H), 7.96 (dd, J=6.0 Hz, 2H), 7.35–7.44 (m, 5H), 5.41 (s, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 160.3, 159.9, 150.4, 144.6, 135.0, 134.6, 132.9, 128.4, 128.3, 120.0, 67.0; IR (KBr): ν 1734 (CO) cm^{-1}; MS, m/z (%): 280(5) [M$^+$], 146(100) [(M−CO_2Bn)$^+$]; $C_{16}H_{12}N_2O_3$ (280.28): calcd C, 68.56; H, 4.32; N, 9.99, found C 68.38, H 4.31, N 10.09.

*4.6.2. Ethyl 2-(4-(methoxycarbonyl)phenyl)-oxazole-4-carboxylate (**9b**).* Reaction of **8b** (3.72 g, 12.6 mmol) with Deoxo-Fluor (5.70 mL, 26.5 mmol), $BrCCl_3$ (4.50 mL, 45.4 mmol) and DBU (6.80 mL, 45.4 mmol) in CH_2Cl_2 (125 mL) gave 1.72 g (50%) of **9b** as a white solid. R_f=0.35 (hexane/AcOEt=1/2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.35 (s, 1H), 8.17 (d, J=8.4 Hz, 2H), 8.12 (d, J=8.4 Hz, 2H), 4.42 (q, J=7.0 Hz, 2H), 3.93 (s, 3H), 1.40 (t, J=7.0 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 160.2, 161.4, 161.1, 144.1, 132.2, 130.5, 130.1, 130.0, 126.8, 61.4, 52.3, 14.3; IR (KBr): ν 1721 (CO) cm^{-1}; MS, m/z (%): 275(30) [M$^+$], 163(100); $C_{14}H_{13}NO_5$ (275.26): calcd C, 61.09; H, 4.76; N, 5.09, found: C 61.05, H 4.73, N 5.06.

*4.6.3. Ethyl 2-(pyridin-4-yl)oxazole-4-carboxylate (**9c**).* Reaction of **8c** (1.70 g, 7.10 mmol) with Deoxo-Fluor (3.40 mL, 15.7 mmol), $BrCCl_3$ (2.50 mL, 25.7 mmol) and DBU (3.80 mL, 25.7 mmol) in CH_2Cl_2 (75.0 mL) gave 1.02 g (72%) of **9c** as a white solid. R_f=0.6 (hexane/AcOEt=1/2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.77 (d, J=6.0 Hz, 2H), 8.35 (s, 1H), 7.96 (d, J=6.0 Hz, 2H), 4.43 (q, J=7.2 Hz, 2H), 1.40 (t, J=7.2 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 160.8, 160.1, 150.7, 144.5, 135.3, 133.3, 120.3, 61.5, 14.3; IR (KBr): ν 1734 (CO) cm^{-1}; MS, m/z (%): 218(22) [M$^+$], 106(100); $C_{11}H_{10}N_2O_3$ (218.21): calcd C, 60.55; H, 4.62; N, 12.84, found C 60.68, H 4.65, N 12.91.

*4.6.4. Benzyl 2-(4-(methoxycarbonyl)phenyl)-oxazole-4-carboxylate (**9d**).* Reaction of **8d** (2.70 g, 7.60 mmol) with Deoxo-Fluor (3.50 mL, 16.1 mmol), $BrCCl_3$ (2.70 mL, 27.4 mmol) and DBU (4.10 mL, 27.4 mmol) in CH_2Cl_2 (75.0 mL) gave 1.30 g (51%) of **9d** as a white solid. R_f=0.6 (hexane/AcOEt=1/1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.32 (s, 1H), 8.21–8.12 (m, 4H), 7.48–7.34 (m, 5H), 5.41 (s, 2H), 3.95 (s, 3H); ^{13}C NMR (100.6 MHz, CD_2Cl_2, 25 °C): δ 166.1, 161.4, 160.8, 144.7, 135.6, 134.7, 132.4, 130.2, 130.0, 129.9, 128.6, 128.5, 126.7, 66.8, 52.3; IR (KBr): ν 1722 (CO) cm^{-1}; MS, m/z (%): 246 (2) [(M−CO_2Bn)$^+$], 163(100); $C_{19}H_{15}NO_5$ (337.33): calcd C, 67.65; H, 4.48; N, 4.15, found: C 67.86, H 4.49, N 4.13.

4.7. General procedure for debenzylation

A solution of carbobenzyloxy-oxazole **9a**,**d** (1 equiv) in MeOH was purged with N_2 and Pd (10 wt %) on carbon was added. H_2 (1 atm) was bubbled through the solution for 10 min, then the mixture was stirred under H_2 for 3 h. Filtration through Celite and evaporation of the solvent gave **10a** or **11b**.

*4.7.1. 2-(2-Pyridyl)-1,3-oxazole-4-carboxylic acid (**10a**).* Reaction of **9a** (1.93 g, 6.90 mmol) and Pd/C (193 mg) in MeOH (140 mL) gave, after filtration, 513 mg (39%) of **10a** as white solid. ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C): δ 8.93 (s, 1H), 8.79 (d, J=3.5 Hz, 2H), 7.93 (d, J=3.5 Hz, 2H); ^{13}C NMR (100.6 MHz, DMSO-d_6, 25 °C): δ 162.2, 159.4, 151.3, 146.7, 146.6, 133.5, 120.4; IR (film): ν 3378 (OH),

1726 (CO) cm^{-1}; ESI-MS, *m/z* (%): 191(100) [$(M+H)^+$]; $C_9H_6N_2O_3$ (190.16): calcd C, 56.85; H, 3.18; N, 14.73, found: C 56.82, H 3.20, N 14.74.

*4.7.2. 2-(4-(Methoxycarbonyl)phenyl)oxazole-4-carboxylic acid (**11b**).* Reaction of **9d** (900 mg, 2.70 mmol) and Pd/C (9.03 mg) in MeOH (55.0 mL) gave, after filtration, 600 mg (89%) of **11b** as white solid. ^1H NMR (400 MHz, DMSO-d_6, 25 °C): δ 8.92 (s, 1H), 8.16–8.10 (m, 4H), 3.89 (s, 3H); ^{13}C NMR (100.6 MHz, DMSO-d_6, 25 °C): δ 165.9, 162.3, 160.6, 132.3, 132.0, 130.5, 129.5, 128.2, 127.0, 52.8; IR (film): ν=2958 (OH), 1718 (CO), 1687(CO) cm^{-1}; ESI-MS, *m/z* (%): 246(100) [$(M-H)^+$]; $C_{12}H_9NO_5$ (247.20): calcd C, 58.30; H, 3.67; N, 5.67, found: C 58.31, H 3.60, N 5.77.

4.8. General procedure to 2-substituted oxazole-4-carboxylic acids

Compound **9b**–**d** (1 equiv) was dissolved in MeOH and reacted with a solution of cesium carbonate (2.0 equiv) in H_2O. The mixture was stirred at room temperature overnight, then MeOH was removed. The aqueous phase was washed with ethyl acetate, then acidified with concentrated HCl ($1 \leq pH \leq 4$) to let carboxylic acid gradually precipitate from the reaction medium. The solid was collected by filtration and washed several times with EtOH, H_2O and Et_2O to afford products **10b**,**c** or **11a**.

*4.8.1. 2-(4-Carboxyphenyl)oxazole-4-carboxylic acid (**10b**).* Reaction of **9b** (1.72 g, 6.20 mmol) and Cs_2CO_3 (8.15 g, 25.0 mmol) in MeOH (50.0 mL) and H_2O (50.0 mL) gave 1.45 g (98%) of **10b** as a yellow solid. ^1H NMR (400 MHz, DMSO-d_6, 25 °C): δ 8.88 (s, 1H), 8.09 (m, 2H), 8.02 (br s, 2H); ^{13}C NMR (100.6 MHz, DMSO-d_6, 25 °C): δ=167.2, 167.1, 162.4, 146.4, 134.9, 133.3, 130.6, 129.9, 126.9; IR (film): ν 3000 (OH), 1696 (CO) cm^{-1}; ESI-MS, *m/z* (%): 248(100) [$(M-H)^+$], 249(15) [M^+]; $C_{11}H_7NO_5 \cdot H_2O$ (251.19): calcd C, 52.60; H, 3.61; N, 5.58, found C 52.43, H 3.58, N 5.62.

*4.8.2. 4-(4-(Benzyloxycarbonyl)oxazol-2-yl)benzoic acid (**11a**).* Reaction of **9d** (1.30 g, 3.90 mmol) and Cs_2CO_3 (2.54 g, 7.90 mmol) in MeOH (40.0 mL) and H_2O (40.0 mL) gave 310 mg (25%) of **11a** as a white solid. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.97 (s, 1H), 8.40–7.98 (m, 9H), 5.12 (s, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 167.0, 162.3, 160.8, 146.5, 135.2, 133.3, 130.6, 130.1, 129.9, 128.1, 126.9, 63.3; IR (film): ν 3378 (OH), 1725 (CO) cm^{-1}; ESI-MS, *m/z* (%): 248(100) [$(M-H)^+$], 322(100) [M^+]; $C_{18}H_{13}NO_5 \cdot 1/2(H_2O)$ (332.30): calcd C, 65.06; H, 4.25; N, 4.21; found C 65.11, H 4.32, N 4.17.

*4.8.3. 2-(2-Pyridyl)-1,3-oxazole-4-carboxylic acid (**10a**).* Reaction of **9c** (1.00 g, 4.60 mmol) and Cs_2CO_3 (3.00 g, 9.20 mmol) in MeOH (40.0 mL) and H_2O (40.0 mL) gave 605 mg (69%) of **10a** as a white solid.

4.9. General procedure to M(5c)$(H_2O)_4 \cdot H_2O$ (12a,b) complexes

A twofold excess of metal precursor (1 equiv) was dissolved together with **5c** (2 equiv) in H_2O. The clear solution was transferred to a Teflon-lined stainless steel autoclave, which was sealed and heated under autogenous pressure at 90 °C for 24 h. After slow overnight cooling, crystals of **12a**,**c** were collected, washed with ethanol, petroleum ether and dried under a nitrogen stream at room temperature.

*4.9.1. [Ni(**5c**)$(H_2O)_4 \cdot H_2O$] (**12a**).* Reaction of $Ni(OAc)_2 \cdot 4H_2O$ (0.72 g, 2.89 mmol) and **5c** (0.25 g, 1.44 mmol) in 5 mL of H_2O gave 0.25 g of **12a** as aquamarine prismatic crystals (55% calculated with respect to the ligand). IR (KBr): 3436 (H_2O), 3232 (OH), 1638 (CO); $C_5H_{11}NNiO_9S \cdot H_2O$ (337.92): calcd C, 17.77; H, 3.88; N, 4.15, found: C 17.70, H 3.62, N 4.43.

*4.9.2. [Co(**5c**)$(H_2O)_4 \cdot H_2O$] (**12b**).* Reaction of $Co(OAc)_2 \cdot 4H_2O$ (0.72 g, 2.89 mmol) and **5c** (0.25 g, 1.44 mmol) in 5 mL of H_2O gave 0.254 g of **12b** as pink solid (29% calculated with respect to the ligand). IR (KBr): 3394 (H_20), 3214 (OH), 1617 (CO); $C_5H_{11}NCoO_9S \cdot H_2O$ (338.16): calcd C, 17.76; H, 3.87; N, 4.14, found: C 17.94, H 3.93, N 4.09.

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Supplementary data

^1H and ^{13}C NMR spectra of new compounds **3a**–**d**, **4a**–**d**, **5a**–**d**, **8a**–**d**, **9a**–**d**, **10a**,**b**, **11a**,**b**. Crystallographic tables and details for **5a** and **12a**. The crystallographic data file (.cif) for **5a** (CCDC number 748497) and **12a** (CCDC number 783690) have been deposited. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.09.104. These data include MOL files and InChiKeys of the most important compounds described in this article.

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