Tetrahedron 68 (2012) 608–613

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Investigation on the reactivity of isoxazol-5-ones towards 1,2-diaza-1,3-dienes: new entry to variously substituted (imidazol-2-yl)acetate and 1,3-oxazin-6-one derivatives

Orazio A. Attanasi [a], Silvia Bartoccini [a], Gianfranco Favi [a], Gianluca Giorgi [b], Francesca R. Perrulli [a], Stefania Santeusanio [a,*]

[a] Department DiSteVa, Organic Chemistry Section, Università degli Studi di Urbino 'Carlo Bo', Via I Maggetti 24, 61029 Urbino, Italy
[b] Department of Chemistry, Università degli Studi di Siena, Via Aldo Moro, 53100 Siena, Italy

ARTICLE INFO

Article history:
Received 10 August 2011
Received in revised form 17 October 2011
Accepted 31 October 2011
Available online 6 November 2011

Dedicated to Professor Francisco Palacios on the occasion of his 60th birthday

Keywords:
Isoxazoles
Michael addition
Imidazoles
Ring-opening
Ring enlargement

ABSTRACT

1,2-Diaza-1,3-dienes (DDs) undergo, under neutral conditions, *N*-nucleophilic attack from a 4-ethoxycarbonylisoxazol-5-one derivative. The first aza-Michael addition is followed by an intramolecular second, affording a fused heterobicyclic system that, upon ring opening and decarboxylation processes, gives rise to novel substituted imidazoles with an acetate functionality in the 2-position. On the contrary, under the same reaction conditions, 3-phenylisoxazol-5-one provides a double Michael addition at two units of DD involving first the C-4 and then the N-2 of the heterocycle. The resulting diadduct spontaneously undergoes ring-opening/ring-closing process that concludes with a ring enlargement of the heterocycle providing the 1,3-oxazin-6-one derivative.

1. Introduction

The development of new methods for the synthesis of *N*-containing heterocycles from α,β-unsaturated carbonyls[1] is of particular interest in organic chemistry since they occur in a wide variety of natural products[2] including essential amino acids and alkaloids.[3] In particular, imidazoles[4] are important as heterocyclic components in highly significant bio-active molecules.[5] One of our main targets is to employ 1,2-diaza-1,3-dienes (DDs)[6] as building blocks for imidazole skeletons through a preliminary aza-Michael addition followed by different ring closure processes.[7,8] Among heterocyclic imines, isoxazolin-5-ones have proven to be valuable intermediates in nucleophilic addition that in turn can afford different and interesting heterocyclic compounds[9] including imidazoles,[10] and therefore we were interested to explore their reactivity towards DDs. In particular, we focused our attention in the chemistry of monosubstituted isoxazol-5-one derivatives both for their ability to afford nucleophilic attack[9a,c,d] and to undergo ring-opening reaction by means of bases, nucleophiles,[9a,11] or by rearrangement or intramolecular reactions.[12]

Herein, we report the results of a study on the reactivity of DDs **1** with monosubstituted isoxazol-5-one pronucleophiles as a new route to variously functionalized 2-(2-ethoxy-2-oxoethyl)-1*H*-imidazoles and 2,2,4,5-tetrasubstituted 1,3-oxazin-6-one derivative, respectively.

2. Results and discussion

It is well known that isoxazol-5-one derivatives can exhibit different tautomeric forms. With exclusive reference to prototropic annular tautomerism, for typical substituted isoxazol-5-one **A** three tautomeric forms have been recognized and designated as CH-form **A′**, OH-form **A″** and NH-form **A‴**, each of them can traps electrophiles in different ways (Fig. 1).

Considering that an initial ^{1}H NMR study on ethyl 5-oxo-4,5-dihydroisoxazole-4-carboxylate (**2**) in $CDCl_3$ solution revealed the CH-form as predominant, whereas only the NH-form was observed in DMSO-d_6 solution, we wanted to test the

* Corresponding author. Tel.: +39 0722 303442; fax: +39 0722 303441; e-mail addresses: orazio.attanasi@uniurb.it (O.A. Attanasi), stefania.santeusanio@uniurb.it (S. Santeusanio).

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doi:10.1016/j.tet.2011.10.118

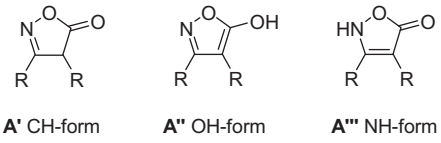
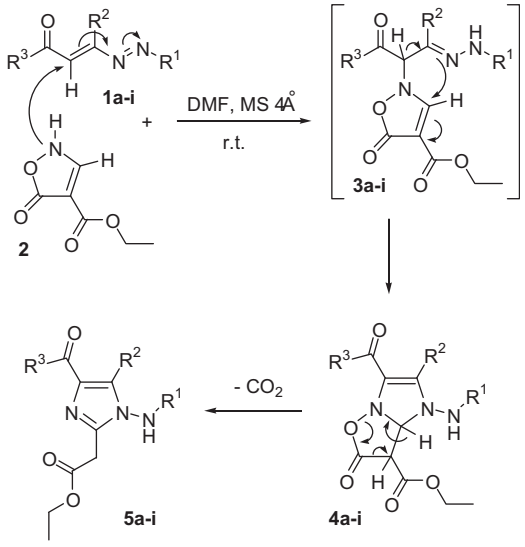


Fig. 1. Tautomerism of isoxazol-5-one derivatives.

nucleophilic behaviour of **2** towards DDs **1** in different solvents. Since the aza group in the conjugated heterodiene system exalts the electrophilic character of the terminal carbon of **1**, first we decided to investigate the reaction between DDs **1a**–**i** (1 equiv) and **2** (1 equiv) in DMF at room temperature, to determine which tautomeric form of **2** would attack the electrophile. After the consumption of the reagents (4–10 h, by TLC), the removal of DMF and the chromatographic purification of the crude products, interesting 2-(2-ethoxy-2-oxoethyl)-1*H*-imidazole derivatives **5a**–**i** were obtained in good yields (53–75%) (Scheme 1, Table 1). A plausible mechanism of the reaction is outlined in Scheme 1. As we postulated, isoxazol-5-one **2** affords conjugate addition at the terminal carbon of the conjugated azo-ene system through its NH tautomeric form producing the hydrazone intermediate **3**. Subsequent internal aza-Michael reaction leads to the heterobicyclic structure **4**. Upon spontaneous ring-opening and decarboxylation, **4** gives rise to 2-(2-ethoxy-2-oxoethyl)-1*H*-imidazole derivative **5**. The occasional isolation of the heterobicyclic imidazoisoxazole system **4a** from the reaction between **1a** and **2**, supports the proposed reaction pathway in which the driving force of the ring-opening is probably due to both the aromatization of imidazole ring and the good carboxylate leaving group.



Scheme 1. Proposed mechanism for the synthesis of (imidazol-2-yl)acetate derivatives **5a**–**i**.

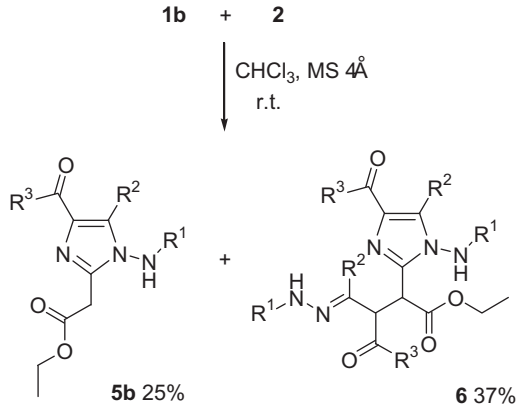
Although *N*-substituted derivatives of **2** are known for their propensity to extrude carbon dioxide by photochemical or pyrolytic conditions giving iminocarbenes that cyclize into imidazoles[10b,c] our results represent the first example in which *N*-substituted derivatives of **2** directly affords the imidazole ring by way of two sequential aza-Michael reactions with carbon dioxide extrusion, preserving the acetate functionality that can be used as a convenient handle for further transformation due to the presence of active methylene and carboxylate groups.

Table 1
Results of the synthesis of (imidazol-2-yl)acetate derivatives **5a**–**i**

Entry	DD **1**				Imidazole **5**		
		R^1	R^2	R^3		Mp (°C)	Yield[a](%)
1	**1a**	CONHPh	Me	$N(Me)_2$	**5a**	98–100	68
2	**1b**	CO_2t-Bu	Me	OMe	**5b**	122–124	75
3	**1c**	CO_2Me	Me	OMe	**5c**	118–120	59
4	**1d**	CO_2Bn	Me	OMe	**5d**	121–123	61
5	**1e**	$CONH_2$	Me	OEt	**5e**	195–198	63
6	**1f**	CO_2t-Bu	Me	OBn	**5f**	118–119	64
7	**1g**	CONHPh	Me	OMe	**5g**	178–179	53
8	**1h**	CO_2Bn	Et	OMe	**5h**	114–115	56
9	**1i**	CO_2t-Bu	Et	OMe	**5i**	132–133	57

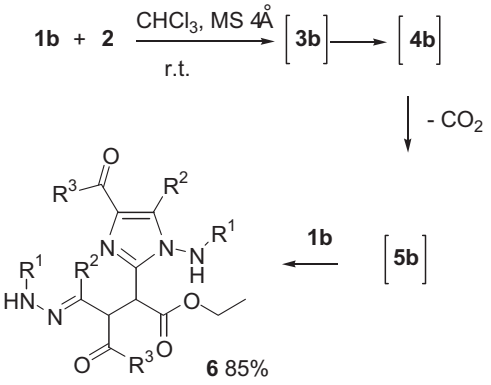
[a] Yield of pure isolated product.

When the reaction in equimolar ratio between **1b** and **2** was carried out at room temperature in $CHCl_3$, the TLC check displayed the formation of **5b**, **6** together with not completely reacted **2**. As showed in the Scheme 2, the formation of **6** can be explained by the nucleophilic attack of the methylene function of the 2-acetate appendage of **5b** to another molecule of **1b**.



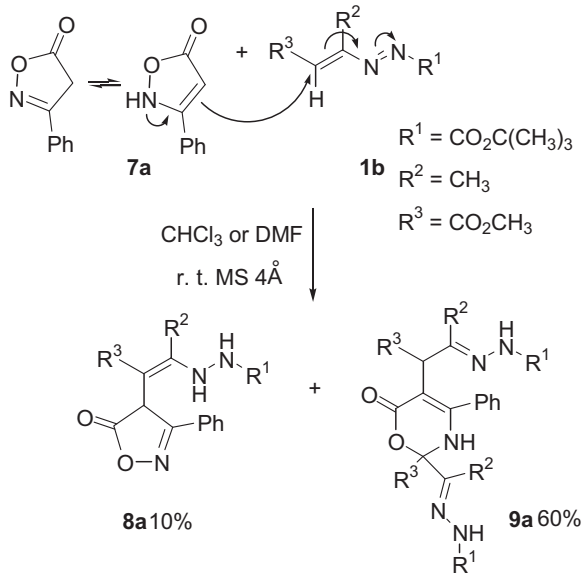
Scheme 2. Results of the reaction pathway between **1b** and **2** (1:1) in $CHCl_3$.

Confirmation of this reaction pathway derived from the result of the reaction between **1b** (2 equiv) and **2** (1 equiv), carried out in the same conditions, that afforded **6** as a diastereomeric mixture in 85% yield (Scheme 3). Contrary to what was observed from the reactivity of **2** and propiolate esters, in any case none *C*-addition of the isoxazol-5-one **2** to the α,β-unsaturated system of DD **1b** was observed.[13]



Scheme 3. Results of the reaction pathway between **1b** and **2** in 2:1 ratio.

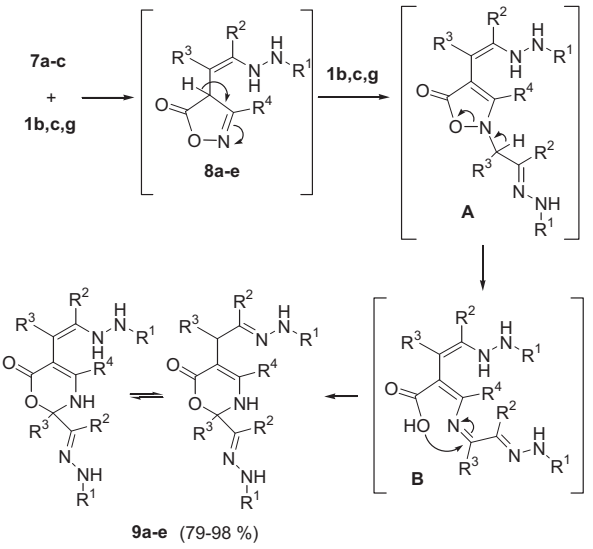
Next, we turned our attention to the nucleophilic behaviour of 3-phenylisoxazol-5-one (**7a**) towards DD **1b** carrying out the reaction in equimolar ratio both in DMF and in $CHCl_3$ and obtained the same results: unreacted **7a** in spite of the complete disappearance of **1b**. The incomplete consumption of **7a** can be explained by a second and faster nucleophilic attack of **8a** to another **1b** molecule as recognized by NMR spectroscopy. In fact, in the ^1H and ^{13}C NMR spectra of **9a**, a double set of signals attributable to the skeleton of **1b** was observed (Scheme 4).



Scheme 4. Results of the reaction pathway between **1b** and **7a** in equimolar ratio.

We postulated that in this case the reaction takes place, at first, via *C*-nucleophilic addition of **7a** at the terminal carbon of the heterodiene system of **1b** leading to Michael monoadduct[9c] **8a** (10%) followed by a further nucleophilic addition of **8a** to another molecule of **1b** providing **9a** (60%) even in neutral conditions. Furthermore, in a separate experiment, the isolated monoadduct **8a** has proven to react with **1b** providing derivative **9a** in nearly quantitative yield (95%). The structural characterization of **8a** was based on spectral data. The presence in the ^1H NMR of three exchangeable protons at 5.16, 9.07 and 10.52 ppm, the presence of diagnostic doublet at 86.4 ppm and of a C-sp^2 at 91.7 ppm in ^{13}C NMR together with a NOE experiment, confirmed the mono *C*-adduct in *E*-configuration. The structure of **9a** was tentatively assigned on the base of spectroscopic evidences hypothesizing a complete rearrangement of the starting heterocycle. In fact, the detection of a doublet at 51.3 ppm, attributable to a CH signal, together with two singlets at 91.0 and 95.7 ppm due to sp^2 and sp^3 carbons in ^{13}C NMR spectra, suggested an analogous behaviour to that observed from the reactivity of disubstituted isoxazolin-5-one systems on DMAD.[9a]

As shown in Scheme 5, the NH tautomeric form of the isoxazolone ring in **8** can add a second molecule of **1** to give the intermediate **A**. The shift of the acidic proton of the hydrazone chain bonded at N-2 of the heterocycle in **A** allows the N–O bond cleavage of the isoxazole ring even in neutral condition, producing the α,β,γ,δ-unsaturated carboxylic acid derivative **B**. Subsequent intramolecular nucleophilic attack by the carboxylate function at the β-carbon of the conjugated diimine framework causes an insertion of a carbon unit, which concludes with a ring enlargement of the heterocycle providing the 1,3-oxazin-6-one derivatives **9**. Hence, when the reactions between **1b**,**c**,**g** and **7a**–**c** were carried



Scheme 5. Proposed mechanism for the formation of the 1,3-oxazin-6-one derivatives **9a**–**e**.

out directly in a 2:1 ratio (**1**:**7**), no trace of **7a**–**c** was observed (TLC check) and **9a**–**e** were obtained as diastereomeric mixtures in good yields (Scheme 5, Table 2).

Table 2
Results of the reactions between **1b**,**c**,**g** and **7a**–**c** in 2:1 ratio to afford **9a**–**e**

Entry	9	R^1	R^2	R^3	R^4	Yield[a]
1	**9a**	CO_2t-Bu	Me	CO_2Me	Ph	98
2	**9b**	CO_2Me	Me	CO_2Me	Ph	81
3	**9c**	CO_2Me	Me	CO_2Me	Me	79
4	**9d**	CONHPh	Me	CO_2Me	Ph	82
5	**9e**	CO_2Me	Me	CO_2Me	*p*-$NO_2C_6H_4$	88

[a] Yield of the diastereomeric mixture.

3. Conclusions

In summary, an investigation of the chemistry of monosubstituted isoxazol-5-ones applied to conjugated azo-ene systems under mild conditions was assessed. Under appropriate solvent conditions, uncatalyzed reactions of DDs with isoxazol-5-one bearing a carboxylate group in 4-position, offer a useful entry to (imidazol-2-yl)acetate by domino sequential aza-Michael/ring-closing/ring-opening reactions. The availability of the proton in 3-position of the heterocycle seems to be a prerequisite for the proposed mechanism and our results represent the first example in which the decarboxylation of the isoxazol-5-one derivative **2** is driven by the aromatization process. Moreover, this protocol conveniently achieves the assembly, in one-pot and under mild conditions, of the imidazole skeleton bearing the acetate appendage in 2-position, as useful building block for the synthesis of biologically active compounds[14]and supplements the known protocols based to 1,3-dipolar cycloaddition of 2-unsubstituted imidazole 3-oxide to DMAD[15]or to condensation reaction of imidates with α-amino ketals.[16] On the contrary, when 3-substituted isoxazol-5-one **7a**–**c** react with DDs under neutral conditions, the active methylene of the heterocycle affords, at first, *C*-Michael addition at a DD molecule and then *N*-Michael attack to another unit of DD leading to 2,3,4-trisubstituted isoxazol-5-one derivative that upon ring-opening/ring-closing processes affords ring enlargement of the starting heterocycle to produce 2,2,4,5-tetrasubstituted 1,3-oxazin-6-one derivative.

4. Experimental

4.1. General experimental section

All chemicals and solvents were purchased from commercial suppliers and used as received. 1,2-Diaza-1,3-dienes were prepared as reported[6,17] and used as *EE*/*EZ* isomer mixtures. Melting points were determined in open capillary tubes and are uncorrected. FTIR spectra were obtained as Nujol mulls. Mass spectra (MS) were carried out by electron ionization (EI, 70 eV) and electrospray. ^{1}H (400 MHz) and ^{13}C (100 MHz) spectra were recorded in DMSO-d_6. Chemical shifts (δ_H) are reported in parts per million (ppm), relative to TMS as internal standard. All coupling constant (*J* values) are given in hertz (Hz). Chemical shifts (δ_C) are reported in parts per million (ppm), relative to the central peak of DMSO-d_6 as internal standard. The abbreviations used are as follows: s, singlet; d, doublet; dd, double-doublet; t, triplet; q, quartet; m, multiplet; br, broad; ArH, aromatic hydrogen. All the NH exchanged with D_2O. Precoated silica gel plates 0.25 mm were employed for analytical thin layer chromatography and silica gel 35–70 μm for column chromatography. All new compounds showed satisfactory elemental analysis (C+0.35; H+0.30; N+0.30). The nomenclature was generated using ACD/IUPAC Name (version 3.50, 5 Apr. 1998), Advanced Chemistry Development Inc., Toronto, ON (Canada).

4.2. General one-pot procedure for the synthesis of 2-(2-ethoxy-2-oxoethyl)-1-*H*-imidazole derivatives 5a–i

To a stirred solution of ethyl 5-oxo-4,5-dihydroisoxazole-4-carboxylate (**2**) (0.157 g, 1 mmol) in DMF (2 mL) containing suspended molecular sieves 4 Å, the corresponding DD 1 (1 mmol) was added at room temperature. After the disappearance of the reagents (3.5–25 h) (TLC check) and partial evaporation of DMF in vacuo, the crude was extracted with EtOAc (20 mL) and washed with brine (5×5 mL). The organic layer was dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, cyclohexane/EtOAc or EtOAc/MeOH) to give **5a**–**i** that were crystallized from the appropriate solvent.

*4.2.1. Ethyl 1-[(anilinocarbonyl)amino]-3-[(dimethylamino)carbonyl]-2-methyl-6-oxo-1,6,7,7a-tetrahydroimidazo[1,2-b]isoxazole-7-carboxylate (**4a**).* Yield: 0.0125 g (3%). Beige powder; mp: 155–157 °C (from THF/*n*-pentane). IR (Nujol) ν_{max} 3335, 3194, 1745, 1699, 1649, 1601, 1540 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.16 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 1.83 (3H, s, CH_3), 2.88 (3H, s, CH_3), 3.12 (3H, s, CH_3), 4.16 (2H, q, *J*=7.2 Hz, OCH_2CH_3), 4.50 (1H, d, *J*=7.2 Hz, CH), 4.85 (1H, d, *J*=7.2 Hz, CH), 7.01 (1H, t, *J*=7.2 Hz, ArH), 7.30 (2H, t, *J*=7.2 Hz, ArH), 7.59 (2H, d, *J*=7.2 Hz, ArH), 8.67 (1H, s, NH), 9.96 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 13.8 (q), 14.8 (q), 35.5 (q), 37.4 (q), 48.9 (d), 50.1 (d), 62.7 (t), 116.8 (s), 119.1 (d), 122.7 (d), 128.9 (d), 139.0 (s), 143.9 (s), 153.3 (s), 165.7 (s), 167.2 (s), 167.6 (s). MS (EI): *m*/*z* (%) 373 [M$^+$–CO_2, (33)], 328 (31), 301 (41), 281 (24), 235 (49), 210 (80), 182 (100). Anal. Calcd for $C_{19}H_{23}N_5O_6$ (417.41): C, 54.67; H, 5.55; N, 16.78. Found: C, 54.49; H, 5.62; N, 16.93.

*4.2.2. Ethyl {1-[(anilinocarbonyl)amino]-4-[(dimethylamino)carbonyl]-5-methyl-1H-imidazol-2-yl}acetate (**5a**).* Yield: 0.2539 g (68%). Pale yellow solid, mp: 98–100 °C (from EtOAc). IR (Nujol) ν_{max} 3276, 3220, 1742, 1700, 1618, 1602, 1546 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.14 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 2.19 (3H, s, CH_3), 2.92 (3H, s, CH_3), 3.27 (3H, s, CH_3), 3.69 (2H, s, CH_2), 4.06 (2H, q, *J*=7.2 Hz, OCH_2CH_3), 7.00 (1H, t, *J*=7.8 Hz, ArH), 7.28 (2H, t, *J*=7.8 Hz, ArH), 7.45 (2H, d, *J*=7.8 Hz, ArH), 9.37 (1H, s, NH), 9.51 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 9.0 (q), 13.9 (q), 32.6 (t), 35.3 (q), 38.3 (q), 60.8 (t), 118.8 (d), 122.6 (d), 128.7 (s), 128.8 (d), 133.9 (s), 139.0 (s), 139.7 (s), 153.4 (s), 164.4 (s), 168.3 (s). MS (EI): *m*/*z* (%) 373 (M$^+$, 40), 345 (1), 330 (15), 302 (80), 183 (84), 168 (44), 119 (100). Anal. Calcd for $C_{18}H_{23}N_5O_4$ (373.41): C, 57.90; H, 6.21; N, 18.76. Found: C, 58.20; H, 6.10; N, 18.96.

*4.2.3. Methyl 1-[(tert-butoxycarbonyl)amino]-2-(2-ethoxy-2-oxoethyl)-5-methyl-1H-imidazole-4-carboxylate (**5b**).* Yield: 0.2560 g (75%). White solid, mp: 122–124 °C (from THF/*n*-pentane). IR (Nujol) ν_{max} 3126, 1733, 1685, 1558, 1537 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.18 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 1.44 (9H, s, O^{t}Bu), 2.28 (3H, s, CH_3), 3.61 (1H, d, *J*=16.0 Hz, CH_aH_b), 3.71 (1H, d, *J*=16.0 Hz, CH_aH_b), 3.74 (3H, s, OCH_3), 4.07 (2H, q, *J*=7.2 Hz, OCH_2CH_3), 10.61 (1H, s, NH). ^{13}C NMR (100 MHz DMSO-d_6) δ: 9.0 (q), 13.9 (q), 27.7 (q), 32.4 (t), 50.9 (q), 60.8 (t), 81.5 (s), 124.8 (s), 136.9 (s), 141.5 (s), 153.6 (s), 163.2 (s), 167.8 (s). MS (EI): *m*/*z* (%) 341 (M$^+$, 21), 285 (100), 253 (41), 241 (37), 209 (53), 181 (31), 153 (27), 137 (67), 121 (35). Anal. Calcd for $C_{15}H_{23}N_3O_6$ (341.36): C, 52.78; H, 6.79; N, 12.31. Found: C, 52.93; H, 6.61; N, 12.28.

*4.2.4. Methyl 2-(2-ethoxy-2-oxoethyl)-1-[(methoxycarbonyl)amino]-5-methyl-1H-imidazole-4-carboxylate (**5c**).* Yield: 0.1766 g (59%). White solid, mp: 118–120 °C (from EtOAc/light petroleum ether). IR (Nujol) ν_{max} 3065, 1752, 1735, 1723, 1594, 1555 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.17 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 2.29 (3H, s, CH_3), 3.69–3.74 (8H, m, CH_2 and 2 OCH_3), 4.05 (2H, q, *J*=7.2 Hz, OCH_2CH_3), 10.85 (1H, br s, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 9.1 (q), 13.9 (q), 32.4 (t), 51.7 (q), 53.1 (q), 60.9 (t), 124.9 (s), 136.9 (s), 141.5 (s), 153.6 (s), 163.1 (s), 167.9 (s). MS (EI): *m*/*z* (%) 299 (M$^+$, 71), 267 (100), 239 (23), 226 (44), 194 (29), 167 (15), 152 (14), 137 (20), 121 (13). Anal. Calcd for $C_{12}H_{17}N_3O_6$ (299.28): C, 48.16; H, 5.73; N, 14.04. Found: C, 48.27; H, 5.62; N, 13.93.

*4.2.5. Methyl 1-{[(benzyloxy)carbonyl]amino}-2-(2-ethoxy-2-oxoethyl)-5-methyl-1H-imidazole-4-carboxylate (**5d**).* Yield: 0.2289 g (61%). White solid, mp: 121–123 °C (from EtOAc/*n*-pentane). IR (Nujol) ν_{max} 3125, 1740, 1716, 1559 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.15 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 2.28 (3H, s, CH_3), 3.63–3.77 (5H, m, CH_2 and OCH_3), 4.05 (2H, q, *J*=7.2 Hz, OCH_2CH_3), 5.20 (2H, s, OCH_2Ph), 7.40 (5H, br s, ArH), 11.08 (1H, br s, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 9.1 (q), 13.9 (q), 32.4 (t), 51.0 (q), 60.9 (t), 67.2 (t), 124.9 (s), 128.0 (d), 128.3 (d), 128.5 (d), 135.8 (s), 136.9 (s), 141.5 (s), 154.6 (s), 163.1 (s), 167.9 (s). MS (EI): *m*/*z* (%) 375 (M$^+$, 100), 302 (8), 284 (17), 252 (26), 226 (18), 194 (39), 137 (6), 121 (15). Anal. Calcd for $C_{18}H_{21}N_3O_6$ (375.38): C, 57.59; H, 5.64; N, 11.19. Found: C, 57.70; H, 5.51; N, 10.98.

*4.2.6. Ethyl 1-[(aminocarbonyl)amino]-2-(2-ethoxy-2-oxoethyl)-5-methyl-1H-imidazole-4-carboxylate (**5e**).* Yield: 0.1879 g (63%). White solid, mp: 195–198 °C (from EtOAc). IR (Nujol) ν_{max} 3372, 3269, 3156, 1744, 1719, 1690, 1596, 1547 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.17 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 1.24 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 2.28 (3H, s, CH_3), 3.57 (1H, d, *J*=16.8 Hz, CH_aH_b), 3.71 (1H, d, *J*=16.8 Hz, CH_aH_b), 4.08 (2H, q, *J*=7.2 Hz, OCH_2CH_3), 4.20 (2H, q, *J*=7.2 Hz, OCH_2CH_3), 6.44 (2H, s, NH_2), 9.45 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 9.3 (q), 14.0 (q), 14.3 (q), 32.4 (t), 59.3 (t), 60.8 (t), 124.7 (s), 137.5 (s), 142.5 (s), 156.4 (s), 162.9 (s), 168.2 (s). MS (EI): *m*/*z* (%) 298 (M$^+$, 83), 252 (100), 224 (33), 209 (44), 180 (34), 163 (25), 137 (48), 121 (27). Anal. Calcd for $C_{12}H_{18}N_4O_5$ (298.30): C, 48.32; H, 6.08; N, 18.78. Found: C, 48.37; H, 6.15; N, 18.65.

*4.2.7. Benzyl 1-[(tert-butoxycarbonyl)amino]-2-(2-ethoxy-2-oxoethyl)-5-methyl-1H-imidazole-4-carboxylate (**5f**).* Yield: 0.2672 g (64%). White solid, mp: 118–119 °C (from THF/*n*-pentane). IR (Nujol) ν_{max} 3119, 1735, 1716, 1686, 1563 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.17 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 1.45 (9H, s, O^{t}Bu), 2.29 (3H, s, CH_3), 3.62 (1H, d, *J*=16.8 Hz, CH_aH_b), 3.73 (1H, d, *J*=16.8 Hz, CH_aH_b), 4.07 (2H, q, *J*=7.2 Hz, OCH_2CH_3), 5.25 (2H, s, OCH_2Ph), 7.34–7.44 (5H, m,

ArH), 10.63 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 9.1 (q), 13.9 (q), 27.7 (q), 32.4 (t), 60.8 (t), 65.1 (t), 81.6 (s), 124.7 (s), 128.0 (d), 128.1 (d), 128.4 (d), 136.4 (s), 137.3 (s), 141.7 (s), 153.6 (s), 162.5 (s), 167.8 (s). MS (EI): m/z (%) 417 (M^+, 9), 317 (11), 311 (14), 283 (23), 255 (25), 227 (100), 211 (15), 183 (46), 168 (12). Anal. Calcd for $C_{21}H_{27}N_3O_6$ (417.46): C, 60.42; H, 6.52; N, 10.07. Found: C, 60.24; H, 6.67; N, 10.16.

*4.2.8. Methyl 1-[(anilinocarbonyl)amino]-2-(2-ethoxy-2-oxoethyl)-5-methyl-1H-imidazole-4-carboxylate (**5g**).* Yield: 0.1910 g (53%). White solid, mp: 178–179 °C (from DCM/*n*-pentane). IR (Nujol) ν_{max} 3340, 3298, 1745, 1730, 1703, 1608, 1561 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.12 (3H, t, J=7.2 Hz, OCH_2CH_3), 2.33 (3H, s, CH_3), 3.68–3.75 (5H, m, CH_2 and OCH_3), 4.06 (2H, q, J=7.2 Hz, OCH_2CH_3), 7.00 (1H, t, J=7.2 Hz, ArH), 7.28 (2H, t, J=7.2 Hz, ArH), 7.45 (2H, d, J=7.2 Hz, ArH), 9.39 (1H, s, NH), 9.65 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 9.4 (q), 13.9 (q), 32.5 (t), 50.9 (q), 60.8 (t), 118.8 (d), 122.6 (d), 124.7 (s), 128.8 (d), 137.9 (s), 138.9 (s), 142.1 (s), 153.2 (s), 163.3 (s), 168.1 (s). MS (EI): m/z (%) 360 (M^+, 100), 328 (16), 268 (38), 241 (85), 236 (55), 209 (67), 181 (20), 137 (60), 121 (49), 119 (71). Anal. Calcd for $C_{17}H_{20}N_4O_5$ (360.36): C, 56.66; H, 5.59; N, 15.55. Found: C, 56.45; H, 5.77; N, 15.72.

*4.2.9. Methyl 1-{[(benzyloxy)carbonyl]amino}-2-(2-ethoxy-2-oxoethyl)-5-ethyl-1H-imidazole-4-carboxylate (**5h**).* Yield: 0.2180 g (56%). White solid, mp: 115–116 °C (from EtOAc/Et_2O). IR (Nujol) ν_{max} 3153, 1751, 1714, 1564 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.02 (3H, t, J=6.8 Hz, CH_2CH_3), 1.15 (3H, t, J=7.2 Hz, OCH_2CH_3), 2.61–2.78 (2H, m, CH_2CH_3), 3.62 (1H, d, J=16.8 Hz, CH_aH_b), 3.70–3.74 (4H, m, CH_aH_b and OCH_3), 4.06 (2H, q, J=7.2 Hz, OCH_2CH_3), 5.21 (2H, br s, OCH_2Ph), 7.36–7.41 (5H, m, ArH), 11.12 (1H, br s, NH). ^{13}C NMR (100 MHz DMSO-d_6) δ: 12.9 (q), 13.9 (q), 16.6 (t), 32.4 (t), 50.9 (q), 60.9 (t), 67.2 (t), 124.3 (s), 127.9 (d), 128.3 (d), 128.5 (d), 135.8 (s), 141.5 (s), 142.2 (s), 154.8 (s), 162.9 (s), 167.8 (s). MS (EI): m/z (%) 389 (M^+, 83), 357 (100), 329 (9), 266 (42), 238 (10), 222 (25), 208 (29). Anal. Calcd for $C_{19}H_{23}N_3O_6$ (389.40): C, 58.60; H, 5.95; N, 10.79. Found: C, 58.52; H, 6.12; N, 10.90.

*4.2.10. Methyl 1-[(tert-butoxycarbonyl)amino]-2-(2-ethoxy-2-oxoethyl)-5-ethyl-1H-imidazole-4-carboxylate (**5i**).* Yield: 0.2025 g (57%). White solid, mp: 132–133 °C (from EtOAc/*n*-pentane). IR (Nujol) ν_{max} 3116, 1737, 1715, 1685, 1545 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.06 (3H, t, J=7.2 Hz, CH_2CH_3), 1.18 (3H, t, J=7.2 Hz, OCH_2CH_3), 1.45 (9H, s, O^tBu), 2.65–2.76 (2H, m, CH_2CH_3), 3.59 (1H, d, J=16.0 Hz, CH_aH_b), 3.70 (1H, d, J=16.0 Hz, CH_aH_b), 3.74 (3H, s, OCH_3), 4.05–4.11 (2H, m, OCH_2CH_3), 10.72 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 12.9 (q), 14.0 (q), 16.6 (t), 27.7 (q), 32.4 (t), 50.9 (q), 60.8 (t), 81.5 (s), 124.2 (s), 141.6 (s), 142.3 (s), 153.7 (s), 163.0 (s), 167.7 (s). MS (EI): m/z (%) 355 (M^+, 14), 299 (76), 267 (100), 255 (9), 223 (38), 195 (27). Anal. Calcd for $C_{16}H_{25}N_3O_6$ (355.39): C, 54.07; H, 7.09; N, 11.82. Found: C, 54.19; H, 6.87; N, 11.90.

4.3. General one-pot procedure for the synthesis of 6

To a stirred solution of DD **1b** (0.456 g, 2 mmol) in $CHCl_3$ (6 mL) containing molecular sieves 4 Å, ethyl 5-oxo-4,5-dihydroisoxazole-4-carboxylate (**2**) (0.157 g, 1 mmol) was added portionwise within 3 h at room temperature. After the disappearance of **2** (2 h) the reaction mixture showed the presence of predominant **5b** over **6** (TLC check) and was left under magnetic stirring until **1b** was completely consumed (16 h) (TLC monitoring). Then, the solvent was removed and the residue was chromatographed yielding **6** as mixture of diastereoisomers in 85%. Analytically pure diastereomer was obtained by recrystallization from EtOAc/Et_2O.

*4.3.1. 1-Ethyl 4-methyl 2-{1-[(tert-butoxycarbonyl)amino]-4-(methoxycarbonyl)-5-methyl-1H-imidazol-2-yl}-3-[N-(tert-butoxycarbonyl)ethanehydrazonoyl]succinate (**6**).* Major diastereomer. Light pink solid, mp: 117–121 °C (from EtOAc/Et_2O). IR (Nujol) ν_{max} 3226, 3168, 1744, 1711, 1589, 1531 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.05 (3H, t, J=6.8 Hz, OCH_2CH_3), 1.45 (9H, s, O^tBu), 1.50 (9H, s, O^tBu), 1.80 (3H, s, CH_3), 2.24 (3H, s, CH_3), 3.68 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 3.87–3.91 (1H, m, $OCH_aH_bCH_3$), 3.99–4.07 (2H, m, $OCH_aH_bCH_3$ and CH), 4.58 (1H, d, J=11.6 Hz, CH), 10.12 (1H, s, NH), 10.58 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 9.0 (q), 13.6 (q), 16.8 (q), 27.7 (q), 27.8 (q), 40.4 (d), 50.9 (q), 52.7 (q), 54.6 (d), 61.1 (t), 81.0 (s), 81.2 (s), 125.0 (s), 136.9 (s), 143.7 (s), 147.2 (s), 152.9 (s), 154.9 (s), 163.0 (s), 168.6 (s), 170.1 (s). MS (EI): m/z (%) 569 (M^+, 36), 469 (18), 397 (55), 338 (99), 306 (52), 278 (100). Anal. Calcd for $C_{25}H_{39}N_5O_{10}$ (569.60): C, 52.72; H, 6.90; N, 12.30. Found: C, 52.84; H, 6.69; N, 12.22.

4.4. General one-pot procedure for the synthesis of 2,2,4,5-tetrasubstituted 1,3-oxazin-6-one derivatives 9a–e

To a stirred solution of DD **1b**,**c**,**g** (2 mmol) in $CHCl_3$ (4 mL) containing molecular sieves 4 Å, isoxazol-5-one derivative **7a**–**c** (1 mmol) was added portionwise within 2–3 h at room temperature. After the disappearance of **7a**–**c** (2 h) the reaction mixture was left at room temperature until the consumption of **1b**,**c**,**g** was complete (3–5 h, TLC check). The solvent was removed in vacuo and **9a**–**d** were obtained by crystallization from appropriate solvents after a chromatographic separation, whereas **9e** was collected by crystallization from the crude reaction mixture.

*4.4.1. tert-Butyl 2-[(1E)-3-methoxy-1-methyl-3-oxo-2-(5-oxo-3-phenyl-4,5-dihydroisoxazol-4-yl)prop-1-en-1-yl]hydrazinecarboxylate (**8a**).* White powder, mp: 95–98 °C, (EtOAc/Et_2O). IR (Nujol) ν_{max} 3257, 3195, 1755, 1720, 1707, 1701, 1656, 1596 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.45 (9H, s, O^tBu), 1.97 (3H, s CH_3), 3.71 (3H, s, OCH_3), 5.16 (1H, s, CH), 7.51–7.58 (3H, m, ArH), 7.71 (2H, d, J=7.2 Hz, ArH), 9.03 (1H, s, NH), 10.19 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 12.4 (q), 28.0 (q), 52.9 (q), 79.9 (s), 86.3 (d), 91.8 (s), 127.3 (d), 128.8 (d), 131.7 (d), 132.0 (s), 145.3 (s), 152.6 (s), 158.7 (s), 162.2 (s), 169.1 (s). MS (EI): m/z (%) 389 (M^+, 2), 345 (5), 289 (9), 274 (100), 229 (44), 170 (24), 103 (44). Anal. Calcd for $C_{19}H_{23}N_3O_6$ (389.40): C, 58.60; H, 5.95; N, 10.79. Found: C, 58.78; H, 6.07; N, 10.62.

*4.4.2. Methyl 2-[N-(tert-butoxycarbonyl)ethanehydrazonoyl]-5-{2-[2-(tert-butoxycarbonyl)hydrazono]-1-(methoxycarbonyl)propyl}-6-oxo-4-phenyl-3,6-dihydro-2H-1,3-oxazine-2-carboxylate (**9a**).* Major diastereomer. Light yellow powder from Et_2O. IR (Nujol) ν_{max} 3405, 3229, 3183, 1752, 1709, 1703, 1689, 1600, 1564, 1528 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.37 (9H, s, O^tBu), 1.45 (9H, s, O^tBu), 1.69 (3H, s CH_3), 1.95 (3H, s, CH_3), 3.56 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 4.03 (1H, s, CH), 7.37–7.54 (5H, m, ArH), 9.24 (1H, s, NH), 9.39 (1H, s, NH), 10.16 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 12.4 (q), 13.7 (q), 27.9 (q), 28.0 (q), 51.3 (d), 51.9 (q), 53.0 (q), 78.9 (s), 80.0 (s), 91.0 (s), 95.7 (s), 128.8 (d), 129.3 (d), 130.7 (d), 132.0 (s), 143.6 (s), 152.5 (s), 152.8 (s), 159.1 (s), 162.5 (s), 169.3 (s), 171.5 (s). MS (ESI): m/z 618 $[M+H]^+$, 640 $[M+Na]^+$. Anal. Calcd for $C_{29}H_{39}N_5O_{10}$ (617.64): C, 56.39; H, 6.36; N, 11.34. Found: C, 56.45; H, 6.18; N, 11.43.

*4.4.3. Methyl 2-[N-(methoxycarbonyl)ethanehydrazonoyl]-5-{1-[methoxycarbonyl]-2-[2-(methoxycarbonyl)hydrazino]-prop-1-en-1-yl}-6-oxo-4-phenyl-3,6-dihydro-2H-1,3-oxazine-2-carboxylate (**9b**).* Beige powder from Et_2O. IR (Nujol) ν_{max}, 3290, 3244, 3201, 1768, 1755, 1736, 1681, 1671, 1641, 1588, 1567 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.36 and 1.70 (3H, 2s, CH_3), 1.96 and 1.98 (3H, 2s, CH_3), 3.52, 3.57, 3.69, 3.75 and 3.78 (12H, 5s, 4 OCH_3), 7.35–7.43 (5H, m, ArH), 8.77 and 8.88 (1H, 2s, NH), 9.19 and 9.34

(1H, 2br s, NH), 9.87 and 9.92 (1H, 2s, NH), 10.42 and 10.49 (1H, 2s, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 12.5 (q), 14.1 (q), 15.5 (q), 50.3 (q), 50.6 (q), 52.1 (q), 52.2 (q), 52.9 (q), 53.0 (q), 88.3 (s), 89.0 (s), 90.7 (s), 91.1 (s), 96.5 (s), 96.9 (s), 127.9 (d), 128.0 (d), 128.1 (d), 129.9 (d), 130.2 (d), 133.9 (s), 134.2 (s), 145.3 (s), 154.2 (s), 156.6 (s), 157.7 (s), 158.5 (s), 162.0 (s), 162.4 (s), 162.6 (s), 168.9 (s), 169.3 (s), 169.7 (s), 170.4 (s). MS (ESI): *m*/*z* 534 $[M+H]^+$, 556 $[M+Na]^+$. Anal. Calcd for $C_{23}H_{27}N_5O_{10}$ (533.48): C, 51.78; H, 5.10; N, 13.13. Found: C, 51.98; H, 5.02; N, 13.09.

*4.4.4. Methyl 2-[N-(methoxycarbonyl)ethanehydrazonoyl]-5-{1-[methoxycarbonyl]-2-[2-(methoxycarbonyl)hydrazino]-prop-1-en-1-yl}-6-oxo-4-methyl-3,6-dihydro-2H-1,3-oxazine-2-carboxylate (**9c**).* White powder from DCM/*n*-pentane. IR (Nujol) ν_{max}, 3470, 3267, 3206, 1751, 1721, 1674, 1605, 1586 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.57 and 1.65 (3H, 2s, CH_3), 1.75 (3H, s, CH_3), 1.94 and 1.96 (3H, 2s, CH_3), 3.45, 3.49, 3.61, 3.67, 3.68 and 3.71 (12H, 6s, 4 OCH_3), 8.69 and 8.85 (1H, 2s, NH), 9.39 (1H, br s, NH), 10.04 and 10.07 (1H, 2s, NH), 10.42 and 10.48 (1H, 2s, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 12.2 (q), 14.2 (q), 14.7 (q), 17.0 (q), 17.1 (q), 50.6 (q), 52.2 (q), 52.7 (q), 52.9 (q), 88.0 (s), 88.6 (s), 90.5 (s), 90.6 (s), 96.3 (s), 96.6 (s), 145.5 (s), 154.2 (s), 156.8 (s), 159.2 (s), 159.5 (s), 161.6 (s), 162.9 (s), 163.5 (s), 169.3 (s), 169.5 (s), 169.6 (s), 170.4 (s). MS (ESI): *m*/*z* 472 $[M+H]^+$, 494 $[M+Na]^+$. Anal. Calcd for $C_{18}H_{25}N_5O_{10}$ (471.41): C, 45.86; H, 5.35; N, 14.86. Found: C, 45.98; H, 5.18; N, 14.65.

*4.4.5. Methyl 2-[N-(anilinocarbonyl)ethanehydrazonoyl]-5-{2-[2-(anilinocarbonyl)hydrazono]-1-(methoxycarbonyl)-propyl}-6-oxo-4-phenyl-3,6-dihydro-2H-1,3-oxazine-2-carboxylate (**9d**).* Light yellow powder from EtOAc/Et_2O. IR (Nujol) ν_{max} 3353, 3323, 3192, 1746, 1708, 1686, 1596, 1534 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.76 and 1.78 (3H, 2s, CH_3), 1.98 and 2.04 (3H, 2s, CH_3), 3.57 and 3.62 (3H, 2s, OCH_3), 3.73 and 3.87 (3H, 2s, OCH_3), 3.96 and 4.14 (1H, 2s, CH), 6.97–7.05 (2H, m, ArH), 7.28–7.32 (4H, m, ArH), 7.43–7.60 (9H, m, ArH), 8.16 and 8.19 (1H, 2s, NH), 8.69 (1H, s, NH), 9.24 and 9.37 (1H, 2s, NH), 9.59 and 9.65 (1H, 2s, NH), 10.22 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 12.2 (q), 12.3 (q), 14.9 (q), 15.5 (q), 51.2 (d), 51.8 (d), 51.9 (q), 52.0 (q), 53.6 (q), 53.7 (q), 89.9 (s), 97.1 (s), 118.2 (d), 118.5 (d), 119.3 (d), 119.5 (d), 122.3 (d), 123.0 (d), 128.3 (d), 128.7 (d), 128.8 (d), 128.9 (d), 130.9 (d), 132.1 (s), 138.3 (s), 138.4 (s), 138.8 (s), 140.9 (s), 141.2 (s), 147.1 (s), 147.5 (s), 152.6 (s), 153.0 (s), 158.4 (s), 158.5 (s), 162.5 (s), 162.8 (s), 169.3 (s), 169.5 (s), 171.2 (s). MS (ESI): *m*/*z* 656 $[M+H]^+$, 678 $[M+Na]^+$. Anal. Calcd for $C_{33}H_{33}N_7O_8$ (655.65): C, 60.45; H, 5.07; N, 14.95. Found: C, 60.62; H, 5.12; N, 14.76.

*4.4.6. Methyl 2-[N-(methoxycarbonyl)ethanehydrazonoyl]-5-{1-[methoxycarbonyl]-2-[2-(methoxycarbonyl)hydrazino]-prop-1-en-1-yl}-4-(4-nitrophenyl)-6-oxo-3,6-dihydro-2H-1,3-oxazine-2-carboxylate (**9e**).* Orange powder from $CHCl_3$/*n*-pentane. IR (Nujol) ν_{max}, 3413, 3373, 3297, 3188, 1758, 1744, 1717, 1686, 1670, 1604, 1560 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.40 and 1.67 (3H, 2s, CH_3), 1.98 and 2.00 (3H, 2s, CH_3), 3.39 and 3.51 (3H, 2s, OCH_3), 3.57 (3H, s, OCH_3), 3.69 and 3.70 (3H, 2s, OCH_3), 3.77 and 3.80 (3H, 2s, OCH_3), 7.58–7.63 (2H, m, ArH), 8.23–8.30 (2H, m, ArH), 9.02 and 9.21 (1H, s and br s, NH), 9.16 (1H, s, NH), 9.84 and 9.91 (1H, 2s, NH), 10.45 and 10.52 (1H, 2s, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 12.4 (q), 14.3 (q), 15.4 (q), 50.4 (q), 50.7 (q), 52.0 (q), 52.1 (q), 52.2 (q), 53.0 (q), 53.1 (q), 87.6 (s), 88.4 (s), 90.9 (s), 91.3 (s), 98.0 (s), 98.3 (s), 123.0 (d), 123.3 (d), 123.6 (d), 129.5 (d), 129.6 (d), 140.1 (s), 140.5 (s), 145.0 (s), 148.0 (s), 148.1 (s), 154.3 (s), 155.9 (s), 156.5 (s), 162.0 (s), 162.1 (s), 162.4 (s), 168.5 (s), 168.9 (s), 169.2 (s), 170.1 (s). MS (ESI): *m*/*z* 579 $[M+H]^+$, 601 $[M+Na]^+$. Anal. Calcd for $C_{23}H_{26}N_6O_{12}$ (578.48): C, 47.75; H, 4.53; N, 14.53. Found: C, 47.91; H, 4.43; N, 14.36.

Acknowledgements

Financial support from the Ministero dell'Istruzione, dell'Università e della Ricerca (MIUR)-Roma and from the University of Urbino 'Carlo Bo' is gratefully acknowledged.

Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2011.10.118.

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