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rsc.li/frontiers-organicCatalytic one-pot synthesis of 4-(hetero)aryl substituted 5-(2-oxoethyl) oxazol-2(3*H*)-ones by coupling–isomerization–elimination (CIE) sequence†‡Christina Görgen née Boersch,^a Kiril Lutsenko,^a Eugen Merkul,^a Walter Frank^b and Thomas J. J. Müller*^a*N*-Boc protected 1-aryl propargyl carbamates and acid chlorides can be readily transformed in a one-pot fashion by a coupling–isomerization–elimination (CIE) sequence into 4-substituted 5-(2-oxoethyl) oxazol-2(3*H*)-ones in moderate to good yield.

Introduction

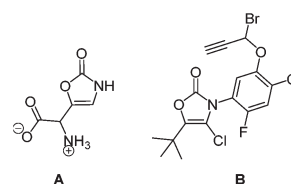
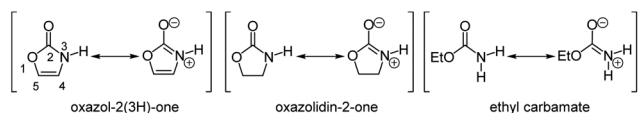
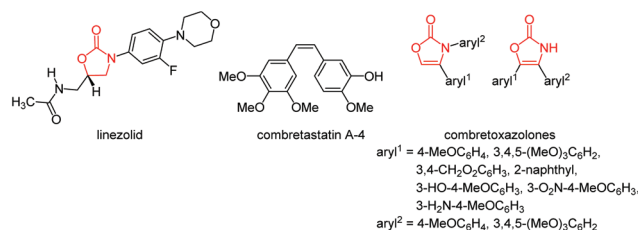
Oxazol-2(3*H*)-one is an interesting derivative of the parent oxazole. While the aromatic structure is formally negated by the presence of an amide carbonyl group, the amide resonance retains it (Fig. 1).¹ As a consequence, the *N*-proton is strongly acidified ($pK_a = 15.0$) in comparison to the saturated oxazolidin-2-one ($pK_a = 20.9$) or the structurally related open-chain ethyl carbamate ($pK_a = 24.6$).²The structural motif of oxazol-2(3*H*)-one is not only present in muscazone (A), a toxic, psychoactive ingredient of *amanita muscaria*,³ i.e. fly agaric, but also in highly active herbicides against broadleaf and narrowleaf weeds plaguing rice fields, such as compound B, which does not affect the growth of the crop (Fig. 2).⁴Fig. 2 Muscazone (A), an oxazol-2(3*H*)-one natural product, and a highly potent herbicide (B).Chiral oxazolidin-2-ones have found broad application as Evans' auxiliaries in enantioselective syntheses,⁵ such as asymmetric aldol additions, Diels–Alder reactions, 1,3-dipolar cycloadditions, and radical reactions,⁶ and as protected 1,2-amino alcohols in the synthesis of biologically active compounds.⁷ Furthermore they have reached particular attention as building blocks in natural product synthesis.⁸ Oxazolidinones and oxazolones can also be found in the core of a series of antimicrobial active ingredients.⁹ For instance, the antibiotic linezolid (zyvoxid® by Pfizer) was found to be active against multiresistant Gram positive bacteria (Fig. 3).¹⁰ Inter-Fig. 1 Oxazol-2(3*H*)-one, oxazolidin-2-one, and carbamate resonance structures.^aInstitut für Organische Chemie und Makromolekulare Chemie, Heinrich-Heine-Universität Düsseldorf, Universitätsstraße 1, 40225 Düsseldorf, Germany. E-mail: Thomas.J.Mueller@hhu.de^bInstitut für Anorganische Chemie und Strukturchemie, Heinrich-Heine-Universität Düsseldorf, Universitätsstraße 1, 40225 Düsseldorf, Germany† Dedicated to Professor Dr Barry M. Trost on the occasion of his 75th birthday.‡ Electronic supplementary information (ESI) available: ¹H and ¹³C NMR spectra and analytical data of compounds 2, and ¹H and ¹³C NMR spectra of compounds 3, cif file of the X-ray structure analysis of compound 3r. CCDC 1465496. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6qo00138f

Fig. 3 Oxazolidinone linezolid (left) and two cytotoxic combretoxazolones (right), analogues of anticancer active component combretastatin A-4 (middle).

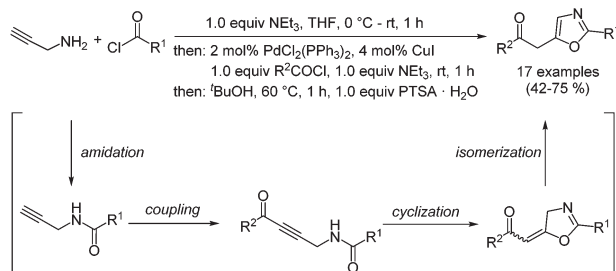


estingly, linezolid does not act as a classical peptide transferase inhibitor but rather binds to the 23S portion of the 50S subunit of tRNA and affects an early stage of translation.¹¹ Combretoxazolones are oxazolinones that were recognized as analogues of combretastatin A-4 (Fig. 3), a biologically active constituent of several anticancer agents. Similar activity found against the same cancer cell lines is attributed to the configurational fixation of the *Z*-configured double bond in the heterocyclic congeners (Fig. 3).¹²

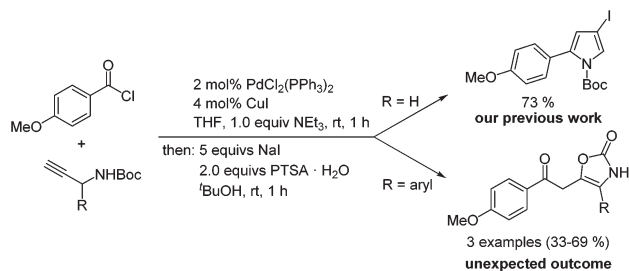
Finally, oxazol-2-ones in their own right have become valuable synthetic building blocks for multiple transformations.¹³ From *N*-acyl oxazol-2-ones¹⁴ over activation and displacements with oxygen, nitrogen, and carbon nucleophiles to give oxazoles,¹⁵ they span the range to Diels–Alder reactions with inverse electron demand, since oxazol-2-ones can be regarded as electron rich dienophiles.¹⁶

The classical syntheses of oxazoles predominantly rely on carbonyl condensation and some famous name reactions have paved the way to this important class of five-membered heterocycles.^{17,18} Recently, we reported an efficient three-component amidation–coupling–cyclization–isomerization (ACCI) of specifically 2,5-disubstituted oxazoles, which proceeds *via* an intramolecular Michael-type addition after the activating formation of an ynone by Sonogashira coupling (Scheme 1).¹⁹ By employing the heterocyclization concept and by addressing the methylene carbonyl functionality in the product for a Fischer indole synthesis a novel three-component synthesis of deep-blue luminescent 5-(3-indolyl)oxazoles could be successfully disclosed.²⁰ Later a related strategy was reported by Wachenfeldt and co-workers who took advantage of a solvent-free amidation of *N*-benzyl propargylamines under microwave irradiation furnishing trisubstituted oxazoles with concomitant, aromatizing cleavage of the benzyl group in good to excellent yield.²¹ Although classical syntheses²² and recent contributions on Au(I),^{23–26} Pd(II),²⁷ and Lewis acid²⁸ and ionic liquid²⁹ catalyzed cycloisomerization syntheses of structurally related oxazolidinones have been reported, the catalyzed, diversity-oriented formation of oxazol-2-ones has remained unexplored.

In the course of our studies on three-component coupling–addition–cyclocondensation synthesis³⁰ of *N*-Boc 2-substituted 4-iodopyrroles from acid chlorides and *N*-Boc protected propargyl carbamates,³¹ we discovered by serendipity that oxazol-



Scheme 1 One-pot amidation–coupling–cyclization–isomerization (ACCI) synthesis of 4-substituted 5-(2-oxoethyl) oxazol-2(3H)-ones.



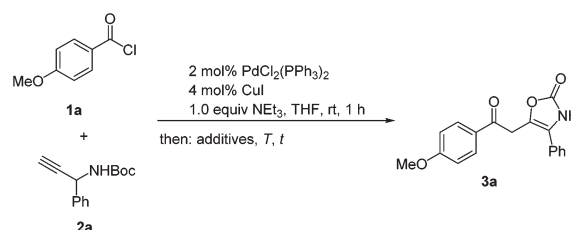
Scheme 2 Competing formation of oxazol-2-ones in the three-component coupling–addition–cyclocondensation synthesis of *N*-Boc 2-substituted 4-iodopyrroles.

2-ones were formed when 1-aryl substituted *N*-Boc protected propargyl carbamates were used as starting materials (Scheme 2). Important to notice is that oxazol-2-ones were already obtained upon aqueous workup of the ynone intermediate, indicating that sodium iodide was not involved in the cyclization. In addition, trifluoroacetic acid could also catalyze the cyclization–elimination reaction. Here, we report the optimization of this unprecedented formation of oxazol-2-ones and the methodological development of their synthesis by coupling–isomerization–elimination (CIE).

Results and discussion

Encouraged by the serendipitous finding of oxazol-2-ones (Scheme 2) we first set out to optimize the overall sequence with respect to catalytic acid, solvent, reaction temperature, and time. As a model reaction 4-methoxybenzoylchloride (**1a**) and *tert*-butyl(1-phenylprop-2-yn-1-yl) carbamate (**2a**) were chosen as reaction partners. For ynone formation the standard conditions were employed (Scheme 3).³² However, we were never able to isolate the corresponding ynone with this peculiar substitution pattern (*vide infra*). First, the effect of various Brønsted acids on the isomerization–elimination was investigated at room temperature for 1 h (Table 1).

It could be shown that the addition of *t*BuOH as a co-solvent as under 4-iodopyrrole formation conditions was not required for PTSA monohydrate ($pK_a \approx 0.7$) as an acid (Table 1, entries 1 and 2). A slightly increased acidity by changing the acid component to trifluoroacetic acid ($pK_a \approx 0.2$) did not increase the yield (Table 1, entry 3), whereas stronger



Scheme 3 Optimization of the coupling–isomerization–elimination synthesis (CIE) of the 2-oxoethyl oxazol-2(3H)-one **3a**.



Table 1 Optimization of the acid in the coupling–isomerization–elimination synthesis (CIE) of the 5-(2-oxoethyl) oxazol-2(3*H*)-one **3a**^a

| Entry | Acid ^b | Oxazol-2(3 <i>H</i>)-one 3a ^c |
|-------|--|--|
| 1 | PTSA-H ₂ O, ^t BuOH | 72% |
| 2 | PTSA-H ₂ O | 70% |
| 3 | CF ₃ CO ₂ H | 70% |
| 4 | CH ₃ SO ₃ H | 59% |
| 5 | HCl ^d | 37% |
| 6 | CH ₃ CO ₂ H | 40% ^e |
| 7 | H ₂ O | 33% |

^aAll reactions were performed on a 1.0 mmol scale at concentrations $c_0(\mathbf{1a}) = c_0(\mathbf{2a}) = 0.2$ m, the isomerization–elimination step was performed at room temp for 1 h. ^b2.0 equiv. of acid were added in the isomerization–elimination step. ^cIsolated yields after chromatography on silica gel. ^d37% aqueous solution. ^eImpure product.

acids, such as methane sulfonic acid ($pK_a \approx -1.9$) and concentrated hydrochloric acid, even diminished the yields of oxazolone **3a** (Table 1, entries 4 and 5). Weaker acetic acid and water were not efficient proton sources for the isomerization–elimination (Table 1, entries 6 and 7).

Further on, the solvent, reaction temperature, and reaction time were screened maintaining PTSA monohydrate as a catalyst for the product forming step (Table 2).

As a solvent best suitable for both the coupling and the isomerization–elimination steps THF gave higher yields (Table 2, entries 1–11) than 1,4-dioxane and dichloromethane (Table 2, entries 12 and 13). Performing the coupling step with carefully dried triethylamine (distillation from Na/benzophenone) as a

Table 2 Optimization of the solvent, reaction temperature, and reaction time in the coupling–isomerization–elimination synthesis (CIE) of the 4-substituted 5-(2-oxoethyl) oxazol-2(3*H*)-one **3a**^a

| Entry | Solvent | Temperature T [°C] | Time t [min] | Oxazol-2(3 <i>H</i>)-one 3a ^b |
|-----------------|---------------------------------|----------------------|----------------|--|
| 1 ^c | THF ^d | 23 | 60 | 66% |
| 2 ^c | THF | 0–4 | 60 | 68% |
| 3 ^c | THF ^d | 23 | 120 | 65% |
| 4 ^e | THF | 23 | 60 | 68% |
| 5 ^f | THF | 23 | 60 | 65% |
| 6 ^e | THF | 50 | 60 | 58% |
| 7 ^c | THF | 23 | 30 | 72% |
| 8 ^g | THF | 23 | 30 | 65% |
| 9 ^f | THF | 23 | 30 | 61% |
| 10 ^f | THF | 23 | 15 | 55% |
| 11 ^f | THF | 23 | 10 | 55% |
| 12 ^f | 1,4-dioxane | 23 | 30 | 52% |
| 13 ^c | CH ₂ Cl ₂ | 23 | 60 | 57% |

^aThe reactions were performed on a 1.0 mmol scale at concentrations $c_0(\mathbf{1a}) = c_0(\mathbf{2a}) = 0.2$ m, the coupling step was performed at room temp for 1 h and the isomerization–elimination step was performed at room temp for 1 h and 2.0 equiv. of PTSA-H₂O were added in the isomerization–elimination step. ^bIsolated yields after chromatography on silica gel. ^c $c_0(\mathbf{1a}) = c_0(\mathbf{2a}) = 0.4$ m. ^d1.0 equiv. of NEt₃ (99%), first dried with KOH pellets then distilled from Na/benzophenone. ^e1.0 equiv. of NEt₃ (99%), dried with KOH pellets. ^f2.0 equiv. of NEt₃ (99%), dried with KOH pellets. ^g2.0 equiv. of NEt₃ (99%), first dried with KOH pellets then distilled from Na/benzophenone and addition of 3.0 equiv. of PTSA-H₂O in the isomerization–elimination step.

base and thereby minimizing the water concentration gave comparable yields (Table 2, entries 1–3) to simply dried triethylamine (storage with KOH pellets) (Table 2, entries 4–6). For the sake of practicability the employment of peculiarly dried triethylamine is therefore not necessary. Complete conversion can be achieved after 30 min at room temperature (entry 7) whereas the addition of 2 equiv. of triethylamine does not improve the yield (entries 8 and 9). Further reduction of the reaction time results in lower yields (entries 10 and 11). Increasing the reaction temperature to 50 °C gave already lower yields (Table 2, entry 6). In summary, the optimal conditions of the coupling–isomerization–elimination sequence are given under entry 7. With these conditions in hand, the methodological scope and limitation study was performed with various acid chlorides **1** and 1-aryl substituted *N*-Boc protected propargyl carbamates **2**^{25,33,34} to give 4-substituted 5-(2-oxoethyl) oxazol-2(3*H*)-ones **3** in moderate to good yields (Scheme 4, Table 3).

The structures of the 5-substituted 2-oxoethyl oxazol-2(3*H*)-ones **3** were unambiguously assigned by ¹H and ¹³C NMR and IR spectroscopy, mass spectrometry, and combustion analysis or high resolution mass spectrometry. Most characteristically, the methylene protons between the ketone and the oxazol-2(3*H*)-one appear as singlets at δ 3.90–3.95 for aliphatic substituents R¹ and at δ 4.15–4.54 for (hetero)aryl substituents R¹ in the ¹H NMR spectra. The corresponding resonances of the methylene carbon nuclei can be found in the ¹³C NMR spectra between δ 35.0 and 40.3. The ketone carbon nuclei appear between δ 188.0 and 209.8 depending on the nature of the (hetero)aromatic or (cyclo)aliphatic substituent. The oxazolone carbonyl nuclei can be detected at higher field in a very narrow range around δ 155. In the proton spectra at lower field the heterocyclic NH-amide protons appear as broad signals between δ 11.0 and 11.3. In the IR spectra the two distinct carbonyl stretching vibrations can be assigned for the methylene ketones appearing between 1694 and 1661 cm⁻¹ and for the oxazol-2-ones in a range from 1753 to 1736 cm⁻¹ typical for oxazol-2(3*H*)-one.³⁵ The structure was additionally corroborated by an X-ray structure analysis of 5-substituted 2-oxoethyl oxazol-2(3*H*)-one **3r** indicating the formation of unsymmetrical dimers by amide hydrogen bonding in the solid state (Fig. 4).³⁶

The presented one-pot coupling–isomerization–elimination (CIE) synthesis of 4-substituted 5-(2-oxoethyl) oxazol-2(3*H*)-ones **3** can be performed with a broad range of (hetero)aryl chlorides ranging from electron rich (Table 3, entries 1, 3, 4, 6, 7, 18–22) over electroneutral (Table 3, entries 5 and 8) to electron deficient (Table 3, entries 2, 9–13), heterocyclic (Table 3,

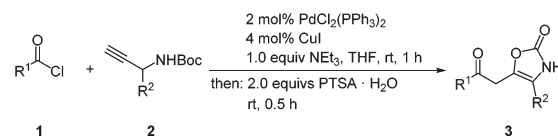
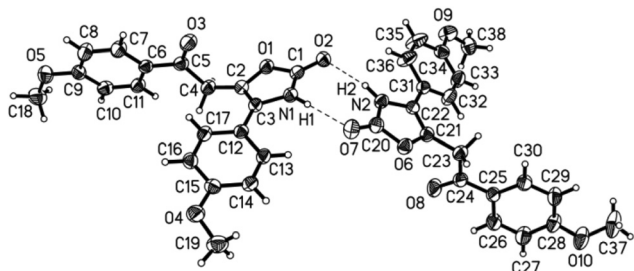
**Scheme 4** General procedure for the coupling–isomerization–elimination synthesis of oxazole-2(3*H*)-ones **3**.

Table 3 One-pot coupling–isomerization–elimination (CIE) synthesis of 4-substituted 5-(2-oxoethyl) oxazol-2(3*H*)-ones **3**^a

| Entry | Acid chloride 1 | <i>N</i> -Boc 1-aryl-propargyl carbamate 2 | 4-Substituted 5-(2-oxoethyl) oxazol-2(3 <i>H</i>)-one 3 (yield) ^b |
|-------------------|---|---|--|
| 1 | R ¹ = <i>p</i> -MeOC ₆ H ₄ (1a) | R ² = Ph (2a) | 3a (73%) |
| 2 | R ¹ = <i>m</i> -MeOC ₆ H ₄ (1b) | 2a | 3b (70%) |
| 3 ^{c,d} | R ¹ = <i>o</i> -MeOC ₆ H ₄ (1c) | 2a | 3c (81%) |
| 4 | R ¹ = <i>p</i> -MeC ₆ H ₄ (1d) | 2a | 3d (47%) |
| 5 | R ¹ = <i>m</i> -MeC ₆ H ₄ (1e) | 2a | 3e (49%) |
| 6 ^{c,e} | R ¹ = <i>o</i> -MeC ₆ H ₄ (1f) | 2a | 3f (55%) |
| 7 | R ¹ = <i>p</i> -PhC ₆ H ₄ (1g) | 2a | 3g (61%) |
| 8 | R ¹ = Ph (1h) | 2a | 3h (46%) |
| 9 | R ¹ = <i>p</i> -FC ₆ H ₄ (1i) | 2a | 3i (55%) |
| 10 | R ¹ = <i>m</i> -FC ₆ H ₄ (1j) | 2a | 3j (71%) |
| 11 | R ¹ = <i>o</i> -FC ₆ H ₄ (1k) | 2a | 3k (57%) |
| 12 ^f | R ¹ = 3,5-F ₂ C ₆ H ₃ (1l) | 2a | 3l (30%) |
| 13 ^c | R ¹ = <i>p</i> -BrC ₆ H ₄ (1m) | 2a | 3m (66%) |
| 14 | R ¹ = 2-thienyl (1n) | 2a | 3n (62%) |
| 15 ^{c,g} | R ¹ = ⁱ Pr (1o) | 2a | 3o (54%) |
| 16 ^{c,h} | R ¹ = cyclopropyl (1p) | 2a | 3p (24%) |
| 17 | R ¹ = 1-adamantyl (1q) | 2a | 3q (27%) |
| 18 ^c | 1a | R ² = <i>p</i> -MeOC ₆ H ₄ (2b) | 3r (41%) |
| 19 | 1a | R ² = <i>p</i> -MeC ₆ H ₄ (2c) | 3s (37%) |
| 20 | 1a | R ² = <i>p</i> -ClC ₆ H ₄ (2d) | 3t (55%) |
| 21 ^g | 1a | R ² = <i>o</i> -ClC ₆ H ₄ (2e) | 3u (10%) |
| 22 | 1a | R ² = 2-thienyl (2f) | 3v (43%) |
| 23 | 1n | 2c | 3w (60%) |

^a The reactions were performed at a 1 mmol scale with concentrations $c_0(\mathbf{1a}) = c_0(\mathbf{2a}) = 0.4$ m, the coupling step was performed at room temp for 1 h and the isomerization–elimination step was performed at room temp for 0.5 h. ^b Isolated yields after chromatography on silica gel. ^c The reaction was performed at 0.5 mmol scale. ^d The coupling was performed for 1.5 h (monitored by TLC). ^e The coupling was performed in 3.5 h (monitored by TLC). ^f The coupling was performed for 2.0 h (monitored by TLC). ^g The isomerization–elimination step was performed for 1 h (monitored by TLC). ^h The coupling was performed for 24 h (monitored by TLC).

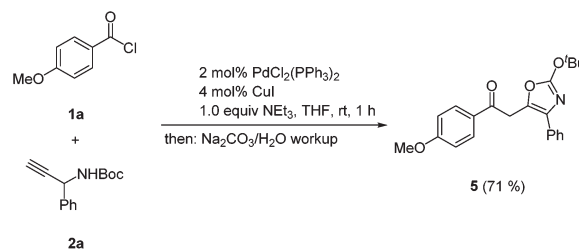
**Fig. 4** ORTEP plot of the molecular structure of the 4-substituted 5-(2-oxoethyl) oxazol-2(3*H*)-one **3r**.

entries 14 and 23) and even certain (cyclo)aliphatic acid chlorides (Table 3, entries 15–17). The substitution pattern of *N*-Boc protected 1-(hetero)aryl propargyl carbamates **2** also allows for the implementation of electron releasing and withdrawing substituents as well as heteroaromatic substituents, however, an *ortho*-substituent apparently hampers the cycloisomerization (Table 3, entry 21).

As a consequence of the elusiveness of the ynone coupling product and the subsequent acid mediated isomerization–elimination to furnish 4-substituted 5-(2-oxoethyl) oxazol-2(3*H*)-ones **3** we reasoned that in case of a strict absence of an acid the *tert*-butyl group will be kept intact and thereby the corresponding 2-*tert*-butoxy oxazole derivative should be accessible. Indeed, upon reacting *p*-methoxy benzoyl chloride (**1a**) and *N*-Boc protected 1-phenyl propargyl carbamate (**2a**) under

modified Sonogashira coupling conditions³² and upon basic aqueous workup and chromatography on silica gel the 2-*tert*-butoxy oxazole **5** was obtained in 71% yield (Scheme 5).

Mechanistically, this observation can be interpreted as a consequence of a steric interaction of the *tert*-butyl carbamate with the 1-aryl moiety which is present in the *N*-Boc substituted 1-aryl substituted propargyl carbamate. Thus, the oxygen atom of the carbamate immediately undergoes a Michael-type on the triple bond of the ynone that is formed by the cross-coupling reaction, resulting in the observed cyclization. In the absence of 1-aryl substitution the ynone becomes persistent to spontaneous Michael addition, as supported by the consecutive transformation to 4-iodo pyrroles.³¹ Hence, the acid in this novel one-pot CIE synthesis of 4-substituted 5-(2-oxoethyl) oxazol-2(3*H*)-ones cannot be attributed to the cycloisomerization, but rather to induce *tert*-butyl cleavage.

**Scheme 5** Coupling-cycloisomerization synthesis of the 4-substituted 5-(2-oxoethyl) 2-*tert*-butoxy oxazole **5**.

Conclusion

Here, we have unraveled and developed an unusual coupling–isomerization–elimination synthesis of 4-substituted 5-(2-oxoethyl) oxazol-2(3*H*)-ones, a subclass of side-chain functionalized oxazol-2(3*H*)-one derivatives. The substitution pattern at the two diversity points, *i.e.* the acid chloride and the *N*-Boc protected 1-aryl substituted propargyl carbamate is fairly broad and allows electronically diverse decoration of the title compound class by a straightforward one-pot protocol. The isolation of a 5-substituted 2-oxoethyl 2-*tert*-butoxy oxazole product as a consequence of strict absence of acid not only elucidates the overall mechanistic rationale but also sets the stage for further developing one-pot methodologies with this intermediate. Further studies directed to develop propargyl amide and carbamate based one-pot sequences initiated by cross-coupling are currently underway.

Experimental

Synthetic procedures

General procedure (GP) of the coupling–isomerization–elimination synthesis of 4-substituted 5-(2-oxoethyl) oxazol-2(3*H*)-ones 3. In an oven-dried Schlenk tube with stir bar and screw cap PdCl₂(PPh₃)₂ (14 mg, 0.02 mmol, 2 mol%) and CuI (8 mg, 0.04 mmol, 4 mol%) were placed under nitrogen. Then, dry THF (2.5 mL) was added and mixture was degassed with nitrogen for 5 min. The acid chloride **1** (1.00 mmol), the *N*-Boc 1-aryl propargyl carbamate **2**^{25,33} (1.00 mmol), and dry triethylamine (0.14 mL, 1.00 mmol) were successively added and the mixture was stirred at room temp (water bath) for 1 h (for experimental details see Table 4). The conversion was monitored by TLC. Then, PTSA-H₂O was added (388 mg, 2.00 mmol) and the mixture was stirred at room temp (water bath) for 0.5 h. Then, deionized water (2.5 mL) was added and the mixture was extracted several times with dichloromethane (monitored by TLC). The combined organic phases were dried with anhydrous sodium sulfate and the solvents were removed under reduced pressure. The crude product was adsorbed on Celite[®] and purified by chromatography on silica gel (petroleum ether/ethyl acetate) to give the analytically pure 4-substituted 5-(2-oxoethyl) oxazol-2(3*H*)-ones **3**.

5-(2-(4-Methoxyphenyl)-2-oxoethyl)-4-phenyloxazol-2(3*H*)-one (3a). According to the GP compound **3a** was obtained after chromatography on silica gel (petroleum ether/ethyl acetate 1 : 1) as a pale brown solid.

*R*_f (petroleum ether/ethyl acetate 1 : 1) = 0.32, Mp 161–166 °C. ¹H NMR (DMSO-*d*₆, 300 MHz), δ = 3.85 (s, 3 H), 4.41 (s, 2 H), 7.02–7.12 (m, 2 H), 7.32–7.50 (m, 5 H), 7.97–8.08 (m, 2 H), 11.15 (s, 1 H). ¹³C NMR (DMSO-*d*₆, 75 MHz), δ = 35.5 (CH₂), 55.7 (CH₃), 114.1 (CH), 123.9 (C_{quat}), 126.0 (CH), 127.2 (C_{quat}), 128.4 (CH), 128.7 (C_{quat}), 129.0 (CH), 130.5 (C_{quat}), 130.9 (CH), 155.0 (C_{quat}), 163.7 (C_{quat}), 193.3 (C_{quat}). MS (EI), *m/z*: 309 (M⁺, 2), 135 (C₈H₇O₂⁺, 100), 107 (C₇H₇O⁺, 8), 92 (C₆H₄O⁺, 5), 77 (C₆H₅⁺, 13). IR (ATR), $\tilde{\nu}$ [cm⁻¹]: 1736 (s),

Table 4 Experimental details of the coupling–isomerization–elimination synthesis of 4-substituted 5-(2-oxoethyl) oxazol-2(3*H*)-ones **3**

| Entry | Acid chloride 1 [mg] (mmol) | <i>N</i> -Boc 1-arylpropargyl carbamate 2 [mg] (mmol) | 4-Substituted 5-(2-oxoethyl) oxazol-2(3 <i>H</i>)-one 3 [mg] (%) |
|-----------------|---------------------------------------|---|---|
| 1 | 176 (1.00) of 1a | 232 (1.00) of 2a | 224 (73) of 3a |
| 2 | 173 (1.00) of 1b | 232 (1.00) of 2a | 215 (70) of 3b |
| 3 ^a | 88 (0.5) of 1c | 116 (0.50) of 2a | 125 (81) of 3c |
| 4 | 158 (1.00) of 1d | 232 (1.00) of 2a | 136 (47) of 3d |
| 5 | 158 (1.00) of 1e | 232 (1.00) of 2a | 145 (49) of 3e |
| 6 ^b | 79 (0.50) of 1f | 116 (0.50) of 2a | 81 (55) of 3f |
| 7 | 216 (1.00) of 1g | 232 (1.00) of 2a | 217 (61) of 3g |
| 8 | 142 (1.00) of 1h | 232 (1.00) of 2a | 130 (46) of 3h |
| 9 | 165 (1.00) of 1i | 232 (1.00) of 2a | 163 (55) of 3i |
| 10 | 162 (1.00) of 1j | 232 (1.00) of 2a | 210 (71) of 3j |
| 11 | 162 (1.00) of 1k | 232 (1.00) of 2a | 169 (57) of 3k |
| 12 ^c | 181 (1.00) of 1l | 232 (1.00) of 2a | 95 (30) of 3l |
| 13 | 112 (0.50) of 1m | 116 (0.50) of 2a | 118 (66) of 3m |
| 14 | 150 (1.00) of 1n | 232 (1.00) of 2a | 178 (62) of 3n |
| 15 ^d | 54 (0.50) of 1o | 116 (0.50) of 2a | 67 (54) of 3o |
| 16 ^d | 52 (0.50) of 1p | 116 (0.50) of 2a | 30 (24) of 3p |
| 17 | 203 (1.00) of 1q | 232 (1.00) of 2a | 93 (27) of 3q |
| 18 | 88 (0.50) of 1a | 131 (0.50) of 2b | 69 (41) of 3r |
| 19 | 176 (1.00) of 1a | 246 (1.00) of 2c | 119 (37) of 3s |
| 20 | 176 (1.00) of 1a | 266 (1.00) of 2d | 190 (55) of 3t |
| 21 ^e | 176 (1.00) of 1a | 266 (1.00) of 2e | 34 (10) of 3u |
| 22 | 176 (1.00) of 1a | 237 (1.00) of 2f | 135 (43) of 3v |
| 23 | 150 (1.00) of 1n | 246 (1.00) of 2c | 179 (60) of 3w |

^a The coupling was performed for 1.5 h (monitored by TLC). ^b The coupling was performed for 3.5 h (monitored by TLC). ^c The coupling was performed for 2.0 h (monitored by TLC). ^d The coupling was performed for 24 h (monitored by TLC). ^e The isomerization was performed for 1.0 h (monitored by TLC).

1676 (m). Anal. calcd for C₁₈H₁₅NO₄ (309.3): C 69.89, H 4.89, N 4.53; Found: C 69.73, H 4.84, N 4.44.

5-(2-(3-Methoxyphenyl)-2-oxoethyl)-4-phenyloxazol-2(3*H*)-one (3b). According to the GP compound **3b** was obtained after chromatography on silica gel (petroleum ether/ethyl acetate 2 : 1 to 1 : 1) as a light brown solid.

*R*_f (petroleum ether/ethyl acetate 2 : 1) = 0.12, Mp 151–154 °C. ¹H NMR (DMSO-*d*₆, 300 MHz), δ = 3.80 (s, 3 H), 4.49 (s, 2 H), 7.16–7.30 (m, 1 H), 7.32–7.57 (m, 7 H), 7.58–7.69 (m, 1 H), 11.17 (s, 1 H). ¹³C NMR (DMSO-*d*₆, 75 MHz), δ = 36.1 (CH₂), 55.4 (CH₃), 113.0 (CH), 119.9 (CH), 120.9 (CH), 124.1 (C_{quat}), 126.0 (CH), 127.1 (C_{quat}), 128.5 (CH), 129.0 (CH), 130.0 (CH), 130.2 (C_{quat}), 137.2 (C_{quat}), 155.0 (C_{quat}), 159.5 (C_{quat}), 194.9 (C_{quat}). MS (EI), *m/z*: 309 (M⁺, 11), 174 ((M – C₈H₇O₂)⁺, 4), 135 (C₈H₇O₂⁺, 100), 107 (C₇H₇O⁺, 15), 103 (11), 92 (C₆H₄O⁺, 6), 77 (C₆H₅⁺, 13). IR (ATR), $\tilde{\nu}$ [cm⁻¹]: 1751 (s), 1684 (m). Anal. calcd for C₁₈H₁₅NO₄ (309.3): C 69.89, H 4.89, N 4.53; Found: C 69.81, H 5.13, N 4.31.

5-(2-(2-Methoxyphenyl)-2-oxoethyl)-4-phenyloxazol-2(3*H*)-one (3c). According to the GP compound **3c** was obtained after chromatography on silica gel (petroleum ether/ethyl acetate 1 : 1) as a colorless solid.

*R*_f (petroleum ether/ethyl acetate 1 : 1) = 0.32, Mp 177–181 °C. ¹H NMR (DMSO-*d*₆, 300 MHz), δ = 3.79 (s, 3 H), 4.33 (s, 2 H), 7.04 (dt, *J* = 7.4 Hz, *J* = 0.7 Hz, 1 H), 7.17 (d, *J* =



8.1 Hz, 1 H), 7.30–7.50 (m, 5 H), 7.52–7.64 (m, 2 H), 11.12 (s, 1 H). ^{13}C NMR (DMSO- d_6 , 75 MHz), δ = 40.3 (CH₂), 55.8 (CH₃), 112.5 (CH), 120.6 (CH), 123.8 (C_{quat}), 126.0 (CH), 126.8 (C_{quat}), 127.2 (C_{quat}), 128.4 (CH), 129.0 (CH), 129.8 (CH), 130.4 (C_{quat}), 134.4 (CH), 155.0 (C_{quat}), 158.3 (C_{quat}), 196.6 (C_{quat}). MS (EI), m/z : 309 (M⁺, 2), 149 (10), 135 (C₈H₇O₂⁺, 100), 105 (12), 77 (C₆H₅⁺, 23), 44 (12), 43 (25), 40 (60). IR (ATR), $\tilde{\nu}$ [cm⁻¹]: 1744 (s), 1668 (m). Anal. calcd for C₁₈H₁₅NO₄ (309.3): C 69.89, H 4.89, N 4.53; Found: C 69.88, H 4.87, N 4.32.

5-(2-Oxo-2-(4-tolyl)ethyl)-4-phenyloxazol-2(3H)-one (3d)

According to the GP compound **3d** was obtained after chromatography on silica gel (petroleum ether/ethyl acetate 2 : 1) as a light brown solid.

R_f (petroleum ether/ethyl acetate 2 : 1) = 0.14, Mp 187–193 °C. ^1H NMR (DMSO- d_6 , 300 MHz), δ = 2.39 (s, 3 H), 4.45 (s, 2 H), 7.30–7.50 (m, 7 H), 7.89–7.99 (m, 2 H), 11.15 (s, 1 H). ^{13}C NMR (DMSO- d_6 , 75 MHz), δ = 21.2 (CH₃), 35.7 (CH₂), 124.0 (C_{quat}), 126.0 (CH), 127.1 (C_{quat}), 128.4 (CH), 128.6 (CH), 129.0 (CH), 129.4 (CH), 130.4 (C_{quat}), 133.3 (C_{quat}), 144.4 (C_{quat}), 155.0 (C_{quat}), 194.5 (C_{quat}). MS (EI), m/z : 293 (M⁺, 6), 174 ((M - C₈H₇O)⁺, 2), 119 (C₈H₇O⁺, 100), 91 (C₇H₇⁺, 18), 77 (C₆H₅⁺, 4). IR (ATR), $\tilde{\nu}$ [cm⁻¹]: 1742 (s), 1684 (m). HRMS (ESI): m/z calcd for C₁₈H₁₆NO₃ ((M + H)⁺): 294.1125; Found: 294.1119.

5-(2-Oxo-2-(3-tolyl)ethyl)-4-phenyloxazol-2(3H)-one (3e)

According to the GP compound **3e** was obtained after chromatography on silica gel (petroleum ether/ethyl acetate 2 : 1) as a light brown solid.

R_f (petroleum ether/ethyl acetate 2 : 1) = 0.16, Mp 149–160 °C. ^1H NMR (DMSO- d_6 , 300 MHz), δ = 2.39 (s, 3 H), 4.45 (s, 2 H), 7.30–7.50 (m, 7 H), 7.89–7.99 (m, 2 H), 11.15 (s, 1 H). ^{13}C NMR (DMSO- d_6 , 75 MHz), δ = 20.9 (CH₃), 35.9 (CH₂), 124.0 (C_{quat}), 125.7 (CH), 126.0 (CH), 127.1 (C_{quat}), 128.4 (CH), 128.7 (CH), 128.8 (CH), 129.0 (CH), 130.3 (C_{quat}), 134.4 (CH), 135.8 (C_{quat}), 138.3 (C_{quat}), 155.0 (C_{quat}), 195.1 (C_{quat}). MS (EI), m/z : 293 (M⁺, 8), 174 ((M - C₈H₇O)⁺, 4), 119 (C₈H₇O⁺, 100), 103 (10), 91 (C₇H₇⁺, 21), 77 (C₆H₅⁺, 5). IR (ATR), $\tilde{\nu}$ [cm⁻¹]: 1748 (s), 1686 (m). HRMS (ESI): m/z calcd for C₁₈H₁₆NO₃ ((M + H)⁺): 294.1125; Found: 294.1124.

5-(2-Oxo-2-(2-tolyl)ethyl)-4-phenyloxazol-2(3H)-one (3f)

According to the GP compound **3f** was obtained after chromatography on silica gel (petroleum ether/ethyl acetate 2 : 1) as a colorless solid.

R_f (petroleum ether/ethyl acetate 2 : 1) = 0.43, Mp 169–172 °C. ^1H NMR (DMSO- d_6 , 300 MHz), δ = 2.38 (s, 3 H), 4.40 (s, 2 H), 7.20–7.58 (m, 8 H), 7.80–7.98 (m, 1 H), 11.15 (s, 1 H). ^{13}C NMR (DMSO- d_6 , 75 MHz), δ = 20.8 (CH₃), 38.5 (CH₂), 124.1 (C_{quat}), 125.8 (CH), 126.0 (CH), 127.1 (C_{quat}), 128.4 (CH), 129.0 (CH), 129.2 (CH), 130.3 (C_{quat}), 131.8 (CH), 131.9 (CH), 136.5 (C_{quat}), 137.7 (C_{quat}), 154.9 (C_{quat}), 198.5 (C_{quat}). MS (EI), m/z : 293 (M⁺, 3), 174 ((M - C₈H₇O)⁺, 2), 119 (C₈H₇O⁺, 100), 116 (23), 115 (11), 105 (C₇H₅O⁺, 10), 103 (11), 91 (C₇H₇⁺, 30), 77 (C₆H₅⁺, 9), 43 (20), 40 (36). IR (ATR), $\tilde{\nu}$ [cm⁻¹]: 1737 (s), 1692 (m), 1680 (m). Anal. calcd for C₁₈H₁₅NO₃ (293.3): C 73.71, H 5.15, N 4.78; Found: C 73.49, H 5.28, N 4.64.

5-(2-([1,1'-Biphenyl]-4-yl)-2-oxoethyl)-4-phenyloxazol-2(3H)-one (3g). According to the GP compound **3g** was obtained after chromatography on silica gel (petroleum ether/ethyl acetate 2 : 1) as a light brown solid.

R_f (petroleum ether/ethyl acetate 2 : 1) = 0.14, Mp 189–201 °C. ^1H NMR (DMSO- d_6 , 300 MHz), δ = 4.54 (s, 2 H), 7.30–7.59 (m, 8 H), 7.71–7.81 (m, 2 H), 7.81–7.92 (m, 2 H), 8.04–8.20 (m, 2 H), 11.18 (s, 1 H). ^{13}C NMR (DMSO- d_6 , 75 MHz), δ = 35.9 (CH₂), 124.1 (C_{quat}), 126.0 (CH), 127.0 (CH), 127.07 (CH), 127.10 (C_{quat}), 128.4 (CH), 128.5 (CH), 129.0 (CH), 129.1 (CH), 129.2 (CH), 130.2 (C_{quat}), 134.6 (C_{quat}), 138.8 (C_{quat}), 145.1 (C_{quat}), 155.0 (C_{quat}), 194.6 (C_{quat}). MS (EI), m/z : 355 (M⁺, 3), 182 (14), 181 (C₁₃H₉O⁺, 100), 174 ((M - C₁₃H₉O)⁺, 1), 153 (C₁₂H₉⁺, 13), 152 (21), 77 (C₆H₅⁺, 3). IR (ATR), $\tilde{\nu}$ [cm⁻¹]: 1746 (s), 1674 (m). Anal. calcd for C₂₃H₁₇NO₃ (355.4): C 77.73, H 4.82, N 3.94; Found: C 77.53, H 4.87, N 3.91.

5-(2-Oxo-2-phenylethyl)-4-phenyloxazol-2(3H)-one (3h)

According to the GP compound **3h** was obtained after chromatography on silica gel (petroleum ether/ethyl acetate 2 : 1) as a colorless solid.

R_f (petroleum ether/ethyl acetate 2 : 1) = 0.16, Mp 189–194 °C. ^1H NMR (DMSO- d_6 , 300 MHz), δ = 4.51 (s, 2 H), 7.32–7.48 (m, 5 H), 7.51–7.61 (m, 2 H), 7.64–7.74 (m, 1 H), 7.97–8.10 (m, 2 H), 11.16 (s, 1 H). ^{13}C NMR (DMSO- d_6 , 75 MHz), δ = 35.9 (CH₂), 124.1 (C_{quat}), 126.0 (CH), 127.1 (C_{quat}), 128.41 (CH), 128.44 (CH), 128.8 (CH), 129.0 (CH), 130.2 (C_{quat}), 133.8 (CH), 135.8 (C_{quat}), 155.0 (C_{quat}), 195.0 (C_{quat}). MS (EI), m/z : 279 (M⁺, 9), 174 ((M - C₇H₅O)⁺, 9), 105 (C₇H₅O⁺, 100), 103 (17), 77 (C₆H₅⁺, 25). IR (ATR), $\tilde{\nu}$ [cm⁻¹]: 1742 (s), 1690 (s). Anal. calcd for C₁₇H₁₃NO₃ (279.3): C 73.11, H 4.69, N 5.02; Found: C 72.95, H 4.80, N 4.89.

5-(2-(4-Fluorophenyl)-2-oxoethyl)-4-phenyloxazol-2(3H)-one (3i). According to the GP compound **3i** was obtained after chromatography on silica gel (petroleum ether/ethyl acetate 2 : 1) as a light brown solid.

R_f (petroleum ether/ethyl acetate 2 : 1) = 0.16, Mp 164–172 °C. ^1H NMR (DMSO- d_6 , 300 MHz), δ = 4.50 (s, 2 H), 7.26–7.55 (m, 7 H), 8.02–8.23 (m, 2 H), 11.16 (s, 1 H). ^{13}C NMR (DMSO- d_6 , 75 MHz), δ = 35.9 (CH₂), 115.9 (d, J = 22 Hz, CH), 124.1 (C_{quat}), 126.0 (CH), 127.1 (C_{quat}), 128.4 (CH), 129.0 (CH), 130.1 (C_{quat}), 131.5 (d, J = 10 Hz, CH), 132.6 (d, J = 3 Hz, C_{quat}), 155.0 (C_{quat}), 165.4 (d, J = 253 Hz, C_{quat}), 193.7 (C_{quat}). MS (EI), m/z : 297 (M⁺, 8), 174 ((M - C₇H₄FO)⁺, 19), 123 (C₇H₄FO⁺, 100), 104 (C₇H₄O⁺, 9), 103 (18), 95 (C₆H₄F⁺, 16), 77 (C₆H₅⁺, 10). IR (ATR), $\tilde{\nu}$ [cm⁻¹]: 1748 (s), 1688 (m). Anal. calcd for C₁₇H₁₂FNO₃ (297.3): C 68.68, H 4.07, N 4.71; Found: C 68.65, H 4.21, N 4.57.

5-(2-(3-Fluorophenyl)-2-oxoethyl)-4-phenyloxazol-2(3H)-one (3j). According to the GP compound **3j** was obtained after chromatography on silica gel (petroleum ether/ethyl acetate 2 : 1 to 1 : 1) as a light brown solid.

R_f (petroleum ether/ethyl acetate 2 : 1) = 0.15, Mp 185–192 °C. ^1H NMR (DMSO- d_6 , 300 MHz), δ = 4.53 (s, 2 H), 7.28–7.49 (m, 5 H), 7.49–7.68 (m, 2 H), 7.75–7.96 (m, 2 H), 11.17 (s, 1 H). ^{13}C NMR (DMSO- d_6 , 75 MHz), δ = 36.1 (CH₂), 115.1 (d, J = 22 Hz, CH), 120.7 (d, J = 21 Hz, CH), 124.2 (C_{quat}),



124.6 (d, $J = 3$ Hz, CH), 126.1 (CH), 127.0 (C_{quat}), 128.5 (CH), 129.0 (CH), 129.9 (C_{quat}), 131.1 (d, $J = 8$ Hz, CH), 137.9 (d, $J = 6$ Hz, C_{quat}), 155.0 (C_{quat}), 162.2 (d, $J = 245$ Hz, C_{quat}), 194.2 (d, $J = 2$ Hz, C_{quat}). MS (EI), m/z : 297 (M⁺, 19), 175 (11), 174 ((M - C₇H₄FO)⁺, 100), 123 (C₇H₄FO⁺, 88), 104 (C₇H₄O⁺, 12), 103 (48), 95 (C₆H₄F⁺, 21), 77 (C₆H₅⁺, 12), 43 (10). IR (ATR), $\tilde{\nu}$ [cm⁻¹]: 1753 (s), 1692 (m). Anal. calcd for C₁₇H₁₂FNO₃ (297.3): C 68.68, H 4.07, N 4.71; Found: C 68.53, H 4.33, N 4.51.

5-(2-(2-Fluorophenyl)-2-oxoethyl)-4-phenyloxazol-2(3H)-one (3k). According to the GP compound **3k** was obtained after chromatography on silica gel (petroleum ether/ethyl acetate 2 : 1) as a light brown solid.

R_f (petroleum ether/ethyl acetate 2 : 1) = 0.16, Mp 162–176 °C. ¹H NMR (DMSO-d₆, 300 MHz), $\delta = 4.39$ (d, $J = 1.6$ Hz, 2 H), 7.14–7.58 (m, 7 H), 7.64–7.79 (m, 1 H), 7.88 (td, $J = 7.7$ Hz, $J = 1.7$ Hz, 1 H), 11.17 (s, 1 H). ¹³C NMR (DMSO-d₆, 75 MHz), $\delta = 39.6$ (d, $J = 7$ Hz, CH₂), 117.0 (d, $J = 23$ Hz, CH), 124.2 (C_{quat}), 124.7 (d, $J = 12$ Hz, C_{quat}), 124.9 (d, $J = 3$ Hz, CH), 126.1 (CH), 127.0 (C_{quat}), 128.5 (CH), 129.0 (CH), 129.7 (d, $J = 2$ Hz, C_{quat}), 130.5 (d, $J = 2$ Hz, CH), 135.6 (d, $J = 9$ Hz, CH), 155.0 (C_{quat}), 161.1 (d, $J = 255$ Hz, C_{quat}), 193.1 (d, $J = 4$ Hz, C_{quat}). MS (EI), m/z : 297 (M⁺, 13), 174 ((M - C₇H₄FO)⁺, 40), 123 (C₇H₄FO⁺, 100), 104 (C₇H₄O⁺, 10), 103 (27), 95 (C₆H₄F⁺, 11), 77 (C₆H₅⁺, 9). IR (ATR), $\tilde{\nu}$ [cm⁻¹]: 1744 (s), 1686 (s). Anal. calcd for C₁₇H₁₂FNO₃ (297.3): C 68.68, H 4.07, N 4.71; Found: C 68.47, H 4.28, N 4.47.

5-(2-(3,5-Difluorophenyl)-2-oxoethyl)-4-phenyloxazol-2(3H)-one (3l). According to the GP compound **3l** was obtained after chromatography on silica gel (petroleum ether/ethyl acetate 2 : 1 to 1 : 1) as a light brown solid.

R_f (petroleum ether/ethyl acetate 2 : 1) = 0.21, Mp 185–197 °C. ¹H NMR (DMSO-d₆, 300 MHz), $\delta = 4.56$ (s, 2 H), 7.31–7.48 (m, 5 H), 7.62 (tt, $J = 9.0$ Hz, $J = 2.3$ Hz, 1 H), 7.68–7.79 (m, 2 H), 11.18 (s, 1 H). ¹³C NMR (DMSO-d₆, 75 MHz), $\delta = 36.2$ (CH₂), 109.1 (t, $J = 26$ Hz, CH), 111.8 (dd, $J = 18$ Hz, $J = 8$ Hz, CH), 124.4 (C_{quat}), 126.1 (CH), 127.0 (C_{quat}), 128.5 (CH), 129.0 (CH), 129.5 (C_{quat}), 138.9 (t, $J = 8$ Hz, C_{quat}), 155.0 (C_{quat}), 162.5 (dd, $J = 248$ Hz, $J = 12$ Hz, C_{quat}), 193.2 (t, $J = 2$ Hz, C_{quat}). MS (EI), m/z : 315 (M⁺, 14), 277 ((M - F₂)⁺, 11), 183 (11), 175 (14), 174 ((M - C₇H₃F₂O)⁺, 100), 141 (C₇H₃F₂O⁺, 69), 149 (12), 138 (20), 125 (16), 113 (40), 111 (25), 109 (13), 105 (C₇H₅O⁺, 45), 104 (26), 103 (59), 99 (14), 97 (30), 95 (17), 85 (26), 83 (24), 81 (15), 77 (C₆H₅⁺, 30), 71 (33), 69 (23), 57 (44), 55 (20), 43 (43). IR (ATR), $\tilde{\nu}$ [cm⁻¹]: 1749 (s), 1726 (m), 1694 (m). Anal. calcd for C₁₇H₁₁F₂NO₃ (315.3): C 64.76, H 3.52, N 4.44; Found: C 64.47, H 3.78, N 4.23.

5-(2-(4-Bromophenyl)-2-oxoethyl)-4-phenyloxazol-2(3H)-one (3m). According to the GP compound **3m** was obtained after chromatography on silica gel (petroleum ether/ethyl acetate 2 : 1) as a light brown solid.

R_f (petroleum ether/ethyl acetate 2 : 1) = 0.16, Mp 198–201 °C. ¹H NMR (DMSO-d₆, 300 MHz), $\delta = 4.50$ (s, 2 H), 7.31–7.41 (m, 1 H), 7.41–7.49 (m, 4 H), 7.73–7.83 (m, 2 H), 7.92–8.02 (m, 2 H), 11.17 (s, 1 H). ¹³C NMR (DMSO-d₆, 75 MHz), $\delta = 35.9$ (CH₂), 124.2 (C_{quat}), 126.0 (CH), 127.0 (C_{quat}), 128.0 (CH), 128.4 (C_{quat}), 129.0 (CH), 129.9 (C_{quat}), 130.4 (CH),

131.9 (CH), 134.8 (C_{quat}), 155.0 (C_{quat}), 194.4 (C_{quat}). MS (EI), m/z : 359 (M(⁸¹Br)⁺, 6), 357 (M(⁷⁹Br)⁺, 6), 277 ((M - HBr)⁺, 15), 185 (C₇H₄⁸¹BrO⁺, 97), 183 (C₇H₄⁷⁹BrO⁺, 100), 174 ((M - C₇H₄BrO)⁺, 37), 172 (30), 157 (C₆H₄⁸¹Br⁺, 18), 155 (C₆H₄⁷⁹Br⁺, 18), 131 (10), 121 (19), 105 (33), 104 (24), 103 (48), 77 (C₆H₅⁺, 32), 76 (13), 69 (11), 43 (25). IR (ATR), $\tilde{\nu}$ [cm⁻¹]: 1744 (s), 1690 (m). Anal. calcd for C₁₇H₁₂BrNO₃ (358.2): C 57.00, H 3.38, N 3.91; Found: C 57.13, H 3.49, N 3.84.

5-(2-Oxo-2-(thiophen-2-yl)ethyl)-4-phenyloxazol-2(3H)-one (3n). According to the GP compound **3n** was obtained after chromatography on silica gel (petroleum ether/ethyl acetate 2 : 1) as a light brown solid.

R_f (petroleum ether/ethyl acetate 2 : 1) = 0.13, Mp 188–190 °C. ¹H NMR (DMSO-d₆, 300 MHz), $\delta = 4.42$ (s, 2 H), 7.05–7.32 (m, 1 H), 7.33–7.66 (m, 5 H), 7.88–8.44 (m, 2 H), 11.19 (s, 1 H). ¹³C NMR (DMSO-d₆, 75 MHz), $\delta = 36.0$ (CH₂), 124.3 (C_{quat}), 126.1 (CH), 127.0 (C_{quat}), 128.6 (CH), 129.0 (CH), 129.1 (CH), 129.9 (C_{quat}), 134.8 (CH), 136.1 (CH), 142.6 (C_{quat}), 154.9 (C_{quat}), 188.0 (C_{quat}). MS (EI), m/z : 285 (M⁺, 15), 174 ((M - C₅H₃OS)⁺, 25), 111 (C₅H₃OS⁺, 100), 103 (24), 83 (C₄H₃S⁺, 4), 77 (C₆H₅⁺, 11). IR (ATR), $\tilde{\nu}$ [cm⁻¹]: 1753 (s), 1661 (m). Anal. calcd for C₁₅H₁₁NO₃S (285.3): C 63.14, H 3.89, N 4.91; Found: C 63.29, H 3.95, N 4.66.

5-(3-Methyl-2-oxobutyl)-4-phenyloxazol-2(3H)-one (3o). According to the GP compound **3o** was obtained after chromatography on silica gel (petroleum ether/ethyl acetate 2 : 1) as a light brown solid.

R_f (petroleum ether/ethyl acetate 2 : 1) = 0.17, Mp 102–105 °C. ¹H NMR (DMSO-d₆, 300 MHz), $\delta = 1.05$ (d, $J = 6.9$ Hz, 6 H), 2.76 (sept, $J = 6.9$ Hz, 1 H), 3.91 (s, 2 H), 7.28–7.55 (m, 5 H), 11.11 (s, 1 H). ¹³C NMR (DMSO-d₆, 75 MHz), $\delta = 17.8$ (CH₃), 37.2 (CH₂), 39.8 (CH), 123.7 (C_{quat}), 125.9 (CH), 127.1 (C_{quat}), 128.4 (CH), 129.0 (CH), 130.3 (C_{quat}), 154.9 (C_{quat}), 209.2 (C_{quat}). MS (EI), m/z : 245 (M⁺, 23), 175 (39), 174 ((M - C₄H₇O)⁺, 88), 149 (29), 131 (15), 105 (13), 104 (35), 103 (100), 77 (C₆H₅⁺, 31), 71 (C₄H₇O⁺, 66), 69 (12), 57 (18), 55 (12), 44 (17), 43 (C₃H₇⁺, 81), 41 (18), 40 (68). IR (ATR), $\tilde{\nu}$ [cm⁻¹]: 1748 (s), 1709 (m), 1682 (w). Anal. calcd for C₁₄H₁₅NO₃ (245.3): C 68.56, H 6.16, N 5.71; Found: C 68.80, H 6.44, N 5.51.

5-(2-Cyclopropyl-2-oxoethyl)-4-phenyloxazol-2(3H)-one (3p). According to the GP compound **3p** was obtained after chromatography on silica gel (petroleum ether/ethyl acetate 2 : 1) as a brown solid.

R_f (petroleum ether/ethyl acetate 2 : 1) = 0.13, Mp 144–148 °C. ¹H NMR (DMSO-d₆, 300 MHz), $\delta = 0.77$ –1.04 (m, 4 H), 2.05–2.21 (m, 1 H), 3.95 (s, 2 H), 7.29–7.57 (m, 5 H), 11.14 (s, 1 H). ¹³C NMR (DMSO-d₆, 75 MHz), $\delta = 10.9$ (CH₂), 20.1 (CH), 39.6 (CH₂), 123.8 (C_{quat}), 126.0 (CH), 127.0 (C_{quat}), 128.4 (CH), 129.0 (CH), 130.1 (C_{quat}), 154.9 (C_{quat}), 205.4 (C_{quat}). MS (EI), m/z : 243 (M⁺, 17), 174 ((M - C₄H₅O)⁺, 36), 105 (31), 104 (16), 103 (46), 77 (C₆H₅⁺, 27), 69 (C₄H₅O⁺, 100), 57 (11), 43 (15), 41 (C₃H₅⁺, 25). IR (ATR), $\tilde{\nu}$ [cm⁻¹]: 1744 (s), 1701 (s), 1687 (w). Anal. calcd for C₁₄H₁₃NO₃ (243.3): C 69.12, H 5.39, N 5.76; Found: C 69.20, H 5.64, N 5.48.

5-(2-(Adamantan-1-yl)-2-oxoethyl)-4-phenyloxazol-2(3H)-one (3q). According to the GP compound **3q** was obtained after



chromatography on silica gel (petroleum ether/ethyl acetate 2 : 1) as a light brown solid.

R_f (petroleum ether/ethyl acetate 2 : 1) = 0.21, Mp 182–194 °C. ^1H NMR (DMSO- d_6 , 300 MHz), δ = 1.59–1.75 (m, 6 H), 1.76–1.88 (m, 6 H), 1.94–2.06 (m, 3 H), 3.90 (s, 2 H), 7.22–7.55 (m, 5 H), 11.07 (s, 1 H). ^{13}C NMR (DMSO- d_6 , 75 MHz), δ = 27.3 (CH), 33.4 (CH₂), 35.9 (CH₂), 37.2 (CH₂), 46.0 (C_{quat}), 123.8 (C_{quat}), 125.8 (CH), 127.2 (C_{quat}), 128.3 (CH), 128.9 (CH), 130.7 (C_{quat}), 154.9 (C_{quat}), 209.8 (C_{quat}). MS (EI), m/z : 337 (M⁺, 4), 163 (C₁₁H₁₅O⁺, 4), 136 (11), 135 (C₁₀H₁₅⁺, 100), 77 (C₆H₅⁺, 5). IR (ATR), $\tilde{\nu}$ [cm⁻¹]: 1755 (s), 1705 (m). HRMS (ESI): m/z calcd For C₂₁H₂₄NO₃ ((M + H)⁺): 338.1756; Found: 338.1753.

4-(4-Methoxyphenyl)-5-(2-(4-methoxyphenyl)-2-oxoethyl)oxazol-2(3H)-one (3r). According to the GP compound 3r was obtained after chromatography on silica gel (petroleum ether/ethyl acetate 1 : 1) as a light brown solid.

R_f (petroleum ether/ethyl acetate 1 : 1) = 0.26, Mp 162–169 °C. ^1H NMR (DMSO- d_6 , 300 MHz), δ = 3.76 (s, 3 H), 3.85 (s, 3 H), 4.35 (s, 2 H), 6.90–7.03 (m, 2 H), 7.03–7.12 (m, 2 H), 7.30–7.44 (m, 2 H), 7.94–8.09 (m, 2 H), 11.04 (s, 1 H). ^{13}C NMR (DMSO- d_6 , 75 MHz), δ = 35.4 (CH₂), 55.3 (CH₃), 55.6 (CH₃), 114.0 (CH), 114.5 (CH), 119.5 (C_{quat}), 123.7 (C_{quat}), 127.5 (CH), 128.7 (C_{quat}), 129.3 (C_{quat}), 130.9 (CH), 155.0 (C_{quat}), 159.3 (C_{quat}), 163.6 (C_{quat}), 193.4 (C_{quat}). MS (EI), m/z : 339 (M⁺, 4), 204 ((M – C₈H₇O₂)⁺, 3), 135 (C₈H₇O₂⁺, 100), 107 (C₇H₇O⁺, 6), 92 (C₆H₄O⁺, 4), 77 (C₆H₅⁺, 7). IR (ATR), $\tilde{\nu}$ [cm⁻¹]: 1748 (s), 1683 (m). Anal. calcd for C₁₉H₁₇NO₅ (339.3): C 67.25, H 5.05, N 4.13; Found: C 67.49, H 5.34, N 3.84.

5-(2-(4-Methoxyphenyl)-2-oxoethyl)-4-(4-tolyl)oxazol-2(3H)-one (3s). According to the GP compound 3s was obtained after chromatography on silica gel (petroleum ether/ethyl acetate 2 : 1) as a light brown solid.

R_f (petroleum ether/ethyl acetate 2 : 1) = 0.09, Mp 167–175 °C. ^1H NMR (DMSO- d_6 , 300 MHz), δ = 2.30 (s, 3 H), 3.85 (s, 3 H), 4.38 (s, 2 H), 6.99–7.15 (m, 2 H), 7.16–7.29 (m, 2 H), 7.29–7.40 (m, 2 H), 7.93–8.10 (m, 2 H), 11.08 (s, 1 H). ^{13}C NMR (DMSO- d_6 , 75 MHz), δ = 20.8 (CH₃), 35.5 (CH₂), 55.6 (CH₃), 114.1 (CH), 123.9 (C_{quat}), 124.3 (C_{quat}), 125.9 (CH), 128.7 (C_{quat}), 129.5 (CH), 130.0 (C_{quat}), 130.9 (CH), 138.0 (C_{quat}), 155.0 (C_{quat}), 163.6 (C_{quat}), 193.4 (C_{quat}). MS (EI), m/z : 323 (M⁺, 4), 188 ((M – C₈H₇O₂)⁺, 1), 136 (10), 135 (C₈H₇O₂⁺, 100), 119 (10), 107 (C₇H₇O⁺, 4), 92 (C₆H₄O⁺, 4), 91 (5), 77 (C₆H₅⁺, 7). IR (ATR), $\tilde{\nu}$ [cm⁻¹]: 1759 (s), 1670 (m). Anal. calcd for C₁₉H₁₇NO₄ (323.3): C 70.58, H 5.30, N 4.33; Found: C 70.27, H 5.47, N 4.27.

4-(4-Chlorophenyl)-5-(2-(4-methoxyphenyl)-2-oxoethyl)oxazol-2(3H)-one (3t). According to the GP compound 3t was obtained after chromatography on silica gel (petroleum ether/ethyl acetate 2 : 1) as a light yellow solid.

R_f (petroleum ether/ethyl acetate 2 : 1) = 0.10, Mp 186–195 °C. ^1H NMR (DMSO- d_6 , 300 MHz), δ = 3.85 (s, 3 H), 4.42 (s, 2 H), 7.07 (d, J = 8.9 Hz, 2 H), 7.28–7.67 (m, 4 H), 8.01 (d, J = 8.8 Hz, 2 H), 11.20 (s, 1 H). ^{13}C NMR (DMSO- d_6 , 75 MHz), δ = 35.4 (CH₂), 55.7 (CH₃), 114.1 (CH), 123.1 (C_{quat}), 126.0 (C_{quat}), 127.7 (CH), 128.7 (C_{quat}), 129.0 (CH), 130.9 (CH), 131.1 (C_{quat}), 133.0 (C_{quat}), 154.8 (C_{quat}), 163.7 (C_{quat}), 193.2 (C_{quat}). MS (EI), m/z : 343

(M(³⁵Cl)⁺, 1), 208 ((M(³⁵Cl) – C₈H₇O)⁺, 1), 135 (C₈H₇O⁺, 100), 107 (C₇H₇O⁺, 4), 92 (C₆H₄O⁺, 4), 77 (C₆H₅⁺, 6). IR (ATR), $\tilde{\nu}$ [cm⁻¹]: 1742 (s), 1682 (m). Anal. calcd for C₁₈H₁₄ClNO₄ (343.8): C 62.89, H 4.10, N 4.07; Found: C 62.83, H 4.27, N 3.84.

4-(2-Chlorophenyl)-5-(2-(4-methoxyphenyl)-2-oxoethyl)oxazol-2(3H)-one (3u). According to the GP compound 3u was obtained after chromatography on silica gel (petroleum ether/ethyl acetate 1 : 1) as a yellow solid.

R_f (petroleum ether/ethyl acetate 1 : 1) = 0.18, Mp 102–106 °C. ^1H NMR (DMSO- d_6 , 300 MHz), δ = 3.84 (s, 3 H), 4.15 (s, 2 H), 6.94–7.14 (m, 2 H), 7.36–7.55 (m, 3 H), 7.55–7.66 (m, 1 H), 7.85–8.03 (m, 2 H), 10.99 (s, 1 H). ^{13}C NMR (DMSO- d_6 , 75 MHz), δ = 35.0 (CH₂), 55.6 (CH₃), 114.0 (CH), 121.3 (C_{quat}), 126.1 (C_{quat}), 127.6 (CH), 128.6 (C_{quat}), 130.0 (CH), 130.7 (CH), 131.2 (CH), 131.8 (CH), 132.0 (C_{quat}), 132.9 (C_{quat}), 154.9 (C_{quat}), 163.5 (C_{quat}), 193.0 (C_{quat}). MS (EI), m/z : 343 (M(³⁵Cl)⁺, 1), 135 (C₈H₇O⁺, 100), 107 (C₇H₇O⁺, 6), 92 (C₆H₄O⁺, 6), 77 (C₆H₅⁺, 9), 58 (10). IR (ATR), $\tilde{\nu}$ [cm⁻¹]: 1751 (s), 1684 (m). Anal. calcd for C₁₈H₁₄ClNO₄ (343.8): C 62.89, H 4.10, N 4.07; Found: C 62.74, H 4.38, N 3.78.

5-(2-(4-Methoxyphenyl)-2-oxoethyl)-4-(thiophen-2-yl)oxazol-2(3H)-one (3v). According to the GP compound 3v was obtained after chromatography on silica gel (petroleum ether/ethyl acetate 2 : 1 to 1 : 1) as a light brown solid.

R_f (petroleum ether/ethyl acetate 2 : 1) = 0.10, Mp 176–186 °C. ^1H NMR (DMSO- d_6 , 300 MHz), δ = 3.86 (s, 3 H), 4.44 (s, 2 H), 6.52–7.23 (m, 3 H), 7.30 (d, J = 2.4 Hz, 1 H), 7.57 (d, J = 4.6 Hz, 1 H), 8.03 (d, J = 8.5 Hz, 2 H), 11.32 (s, 1 H). ^{13}C NMR (DMSO- d_6 , 75 MHz), δ = 35.7 (CH₂), 55.7 (CH₃), 114.1 (CH), 119.3 (C_{quat}), 125.6 (CH), 126.5 (CH), 127.8 (CH), 128.0 (C_{quat}), 128.6 (C_{quat}), 130.1 (C_{quat}), 130.8 (CH), 154.6 (C_{quat}), 163.7 (C_{quat}), 192.7 (C_{quat}). MS (EI), m/z : 315 (M⁺, 3), 180 ((M – C₈H₇O)⁺, 1), 135 (C₈H₇O⁺, 100), 107 (C₇H₇O⁺, 5), 92 (C₆H₄O⁺, 4), 77 (C₆H₅⁺, 8). IR (ATR), $\tilde{\nu}$ [cm⁻¹]: 1751 (m), 1667 (w). Anal. calcd for C₁₆H₁₃NO₄S (315.3): C 60.94, H 4.16, N 4.44; Found: C 60.95, H 4.37, N 4.29.

5-(2-Oxo-2-(thiophen-2-yl)ethyl)-4-(4-tolyl)oxazol-2(3H)-one (3w). According to the GP compound 3w was obtained after chromatography on silica gel (petroleum ether/ethyl acetate 2 : 1 to 1 : 1) as a light brown solid.

R_f (petroleum ether/ethyl acetate 2 : 1) = 0.14, Mp 178–192 °C. ^1H NMR (DMSO- d_6 , 300 MHz), δ = 2.31 (s, 3 H), 4.39 (s, 2 H), 7.17–7.32 (m, 3 H), 7.32–7.42 (m, 2 H), 8.08 (d, J = 4.4 Hz, 2 H), 11.12 (s, 1 H). ^{13}C NMR (DMSO- d_6 , 75 MHz), δ = 20.8 (CH₃), 36.0 (CH₂), 124.1 (C_{quat}), 124.2 (C_{quat}), 126.0 (CH), 129.0 (CH), 129.3 (C_{quat}), 129.5 (CH), 134.7 (CH), 136.0 (CH), 138.1 (C_{quat}), 142.6 (C_{quat}), 154.9 (C_{quat}), 188.0 (C_{quat}). MS (EI), m/z : 299 (M⁺, 31), 189 (13), 188 ((M – C₅H₃OS)⁺, 100), 119 (15), 118 (14), 117 (45), 115 (13), 111 (C₅H₃OS⁺, 100), 91 (C₇H₇⁺, 14). IR (ATR), $\tilde{\nu}$ [cm⁻¹]: 1736 (s), 1657 (m). Anal. calcd for C₁₆H₁₃NO₃S (299.3): C 64.20, H 4.38, N 4.68; Found: C 64.03, H 4.49, N 4.55.

Coupling-cycloisomerization synthesis of 2-oxoethyl 2-*tert*-butoxy oxazole 5 under basic conditions

In an oven-dried Schlenk tube with stir bar and screw cap PdCl₂(PPh₃)₂ (14 mg, 0.02 mmol, 2 mol%) and CuI (8 mg,



0.04 mmol, 4 mol%) were placed under nitrogen. Then, dry THF (2.5(5.5 mL)) was added and the mixture was degassed with nitrogen for 5 min. The 4-methoxy benzoylchloride (**4b**) (176 mg, 1.00 mmol), *N*-Boc 1-phenylpropargyl carbamate (**2a**) (232 mg, 1.00 mmol), and dry triethylamine (0.14 mL, 1.00 mmol) were successively added and the mixture was stirred at room temp (water bath) for 1 h. The conversion was monitored by TLC. Then, aqueous saturated Na₂CO₃ solution (5 mL) was added and the aqueous layer was extracted with dichloromethane (3 × 5 mL). The combined organic phases were dried with anhydrous sodium sulfate and the solvents were removed under reduced pressure. The crude product was adsorbed on Celite[®] and chromatographed on silica gel (petroleum ether/ethyl acetate/triethylamine 100:10:1) to give 259 mg (71%) of analytically pure 2-(2-(*tert*-butoxy)-4-phenyl-oxazol-5-yl)-1-(4-methoxyphenyl)-ethanone (**5**) as an orange red solid.

R_f (petroleum ether/ethyl acetate 10:1) = 0.18. ¹H NMR (CDCl₃, 300 MHz), δ = 1.59 (s, 9 H), 3.87 (s, 3 H), 4.35 (s, 2 H), 6.88–7.00 (m, 2 H), 7.26–7.42 (m, 3 H), 7.61–7.71 (m, 2 H), 7.95–8.06 (m, 2 H). ¹³C NMR (CDCl₃, 75 MHz), δ = 28.2 (CH₃), 36.4 (CH₂), 55.9 (CH₃), 85.1 (C_{quat}), 114.3 (CH), 127.1 (CH), 127.9 (CH), 128.9 (CH), 129.5 (C_{quat}), 131.3 (CH), 132.6 (C_{quat}), 135.0 (C_{quat}), 136.7 (C_{quat}), 159.1 (C_{quat}), 164.2 (C_{quat}), 193.4 (C_{quat}). MS (EI), m/z : 365 (M⁺, 0.2), 350 ((M – CH₃)⁺, 0.3), 309 ((M – C₄H₉ + H)⁺, 7), 136 (9), 135 (C₈H₇O₂⁺, 100), 105 (C₇H₅O⁺, 6), 77 (C₆H₅⁺, 9), 57 (C₄H₉⁺, 14), 41 (16).

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