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One-Pot Conversion of Amino Acids into 2,5-Disubstituted Oxazoles: No Metals Needed

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Abstract: 2,5-Disubstituted oxazoles with a variety of alkyl and aryl groups are efficiently formed from *N*-acylamino acids, by a one-pot radical decarboxylation–oxidation–enolization and iodine-promoted cyclization process. Remarkably, the reaction takes place under mild conditions, and no metal catalysis is needed. The process can be useful for the direct modification of small peptides.

Keywords: amino acids; cyclization; domino reactions; heterocycles; sustainable chemistry; synthetic methods

The oxazole ring can be found in many bioactive products, from natural compounds[1] such as the potent cytotoxic agents diazonamide[2] and telomestatin,[3] to synthetic agrochemicals[4] and synthetic drugs against cancer, microbial infections, arthritis, pain and diabetes.[5]

Besides, oxazoles are components of fluorescent dyes,[6] sensors,[7] receptors,[7] polymers[8] and ligands for catalysts.[9] Finally, they are useful synthetic intermediates.[10]

Therefore, the preparation[1–10] and functionalization[11] of oxazoles has attracted much interest. The synthetic methods vary from modification of other heterocycles, such as ring rearrangements[11] or oxazoline oxidation,[12] to the cyclization of acyclic precursors.[13] The classic methods, including the cyclodehydration of α-acylamino ketones (Robinson–Gabriel reaction),[14a,b] or the Hantzsch[15c] and Conforth cyclizations,[15d,e] among others, often have drawbacks such as harsh reaction conditions, long reaction times, or modest to poor yields. The introduction of new metal catalysts has enabled several efficient, mild synthesis of oxazoles.[16,17] However, the toxicity, price or scarcity of some metals has prompted the search for new metal-free methodologies.[18,19]

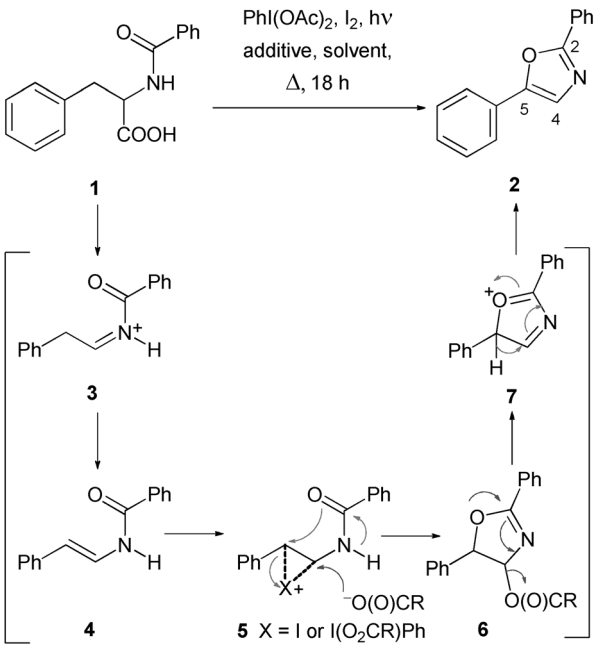
The combination of metal-free and cascade methods is particularly attractive for industry, since increasing environmental regulations have prompted the development of more sustainable chemical processes.[20] Metal-free cascade reactions are less toxic, and also save time, materials and purification of intermediates, and reduce the waste. Although few of these methods have yet been reported for the generation of oxazoles,[20] the development of new ones is an emerging area.

For these sustainable methods, the use of amino acids as substrates would be of interest, since amino acids are readily available, inexpensive, stable, and non-toxic compounds. Threonine and serine units have been used in biomimetic routes to produce 2,4-disubstituted oxazoles,[1] but to our surprise, the use of amino acid substrates to produce 2,5-disubstituted oxazoles (present in many drugs, polymers, sensors and dyes[1–10]) is unexplored.

We present herein a metal-free sequential process which efficiently transforms readily available amino acid derivatives (including a peptide model) into a diversity of 2,5-disubstituted oxazole rings (e.g., conversion **1**→**2**, Scheme 1 and Table 1), using low-toxicity hypervalent iodine reagents.

The first steps of the process (conversion **1**→**5**) were previously reported by our group.[21a] Thus, the decarboxylation of amino acids (such as compound **1**) using (diacetoxyiodo)benzene (DIB) and iodine under the irradiation of visible light, generated an iminium ion such as intermediate **3**. Under appropriate conditions the iminium ion isomerized to an enamide (e.g., compound **4**) which could undergo iodination.[21]

In our previous work, an iodinated intermediate **5** was trapped by external nucleophiles. In this work, we report a new process in which the addition of external nucleophiles is replaced by a multistep domino



Scheme 1. One-pot decarboxylation–cyclization.

Table 1. One-pot decarboxylation–cyclization.

Entry	**1**/DIB/I_2 (equiv.)	Additive (equiv.)[b]	Solvent	Yield [%]
1	1/2/1	–	DCE	55
2	1/2/1	–	CH_3CN	56
3	1/2/1	–	Tol	12
4	1/2/2	–	DCE	54
5	1/2/1	$BF_3{\cdot}OEt_2$ (1 equiv.)	DCE	43
6	1/2/1	$PhCO_2H$ (4 equiv.)	DCE	71
7	1/2/1[a]	$PhCO_2H$ (4 equiv)	DCE	74
8	1/2/1	$PhCO_2H$ (4 equiv.)	CH_3CN	59

[a] No irradiation with visible light; only heating at 80 °C.
[b] Yields obtained after purification by chromatography.

sequence where the intermediate **5** is trapped intramolecularly by the amido carbonyl group. A 4-substituted oxazoline **6** is formed,[22] which is converted into an oxycarbenium ion **7**, precursor of the desired oxazoles (such as product **2**).

The feasibility of this approach was studied using *N*-benzoylphenylalanine **1** as the substrate (Table 1). Different solvents (entries 1 and 2), amounts of iodine (entries 1 and 3) and additives (entries 4-6) were tried under irradiation with visible light and/or heating, affording 2,5-diphenyloxazole **2**.[18a] In the absence of iodine or DIB, oxazoles were not produced.

Interestingly, non-polar DCE and polar acetonitrile gave similar results, while the addition of excess iodine (2 equiv.) proved unnecessary. The use of a Lewis acid to favor conversion **6**→**2** (entry 4) resulted in decreased yields, but the addition of excess benzoic acid clearly improved the one-pot process (entry 5). This result could be due not only to Brønsted acid catalysis of the two last steps, but also to the initial *in situ* formation of (dibenzoyliodo)benzene. This reagent would generate more stable reaction intermediates (such as scission promoter BzOI instead of AcOI, and decarboxylation-resistant benzoate ions, instead of acetate ions, for the next steps, particularly the iodo substitution reaction. To ensure complete formation of (dibenzoyliodo)benzene from DIB, excess benzoic acid was needed (2 equiv. with respect to DIB, and 4 equiv. with respect to substrate **1**).

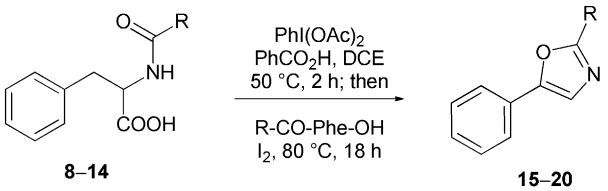
The influence of the reaction time was also studied, observing that with shorter times the reaction was not completed. In addition, heating was necessary for reasonable reaction times and yields.

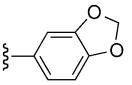
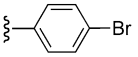
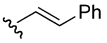
Remarkably, a similar result was obtained when light irradiation was replaced by heating at 80 °C (entry 6). The best conditions provided the oxazole **2** in 74% global yield. Since many steps are involved, each must proceed in excellent yields to account for the final result.

The optimized conditions were then tried with other *N*-acylphenylalanines **8**–**14**, in order to determine the role of the acyl substituent (Table 2).

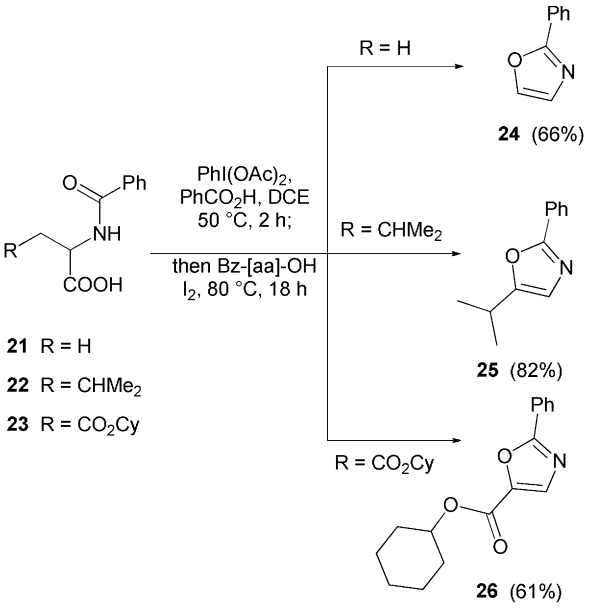
Thus, differently substituted benzamides **8** and **9** (entries 1 and 2), and the furan carboxamide **10**

Table 2. One-pot decarboxylation–cyclization.

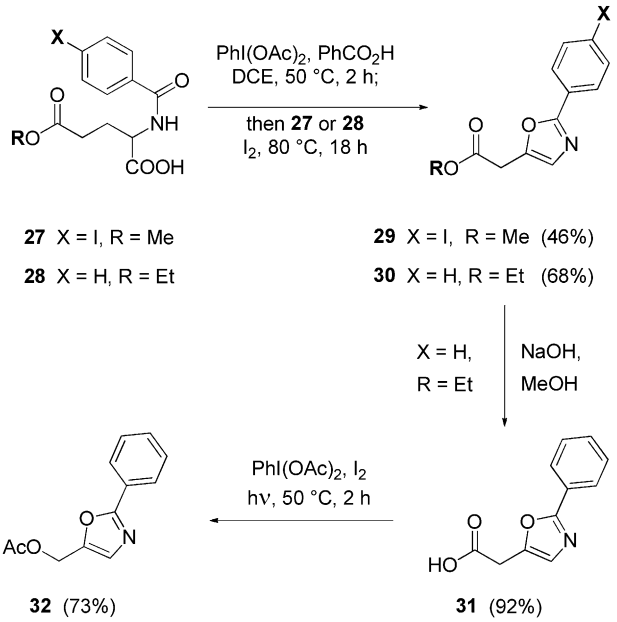


Entry	Substrate	R	Product [%][a]
1	**8**		**15** (59)
2	**9**		**16** (64)
3	**10**		**17** (52)
4	**11**		**18** (55)
5	**12**		**19** (51)
6	**13**		**20** (14)[b]
7	**14**	Me	–

[a] Yields obtained after purification by column chromatography.
[b] 22% without the additive $PhCO_2H$.



Scheme 2. Role of the lateral chain in the one-pot process.



Scheme 3. Derivatization of the oxazole rings.

(entry 3) were studied. With these aromatic rings, the process took place in satisfactory yields, affording compounds **15**–**20**. The formation of bromophenyl derivative **16**[18a] is interesting, since the bromo group allows the introduction of new chains by radical or sp^2–sp^2 couplings.[23] The furan ring in compound **17**[17a] can also be readily derivatized (e.g., reduction, Diels–Alder) into a variety of other chains.[24]

The aromatic rings were then replaced by vinyl and alkyl groups (entries 4–7). The use of vinyl (entry 4) and tertiary alkyl (*tert*-butyl, entry 5) groups afforded compounds **18** and **19**,[17a] respectively, in yields similar to those of the previous entries. The results suggest that these groups provide enough stabilization of the cationic intermediates. However, the use of secondary and primary alkyl groups gave inferior results. Thus, with the *sec*-butyl group (entry 6) the oxazole derivative **20** was formed in low yields (14% and 22% with and without the additive, respectively). The use of the methyl group (entry 7) resulted in complex reaction mixtures, probably by failure of the cyclization step after decarboxylation and decomposition of the enamide intermediate.

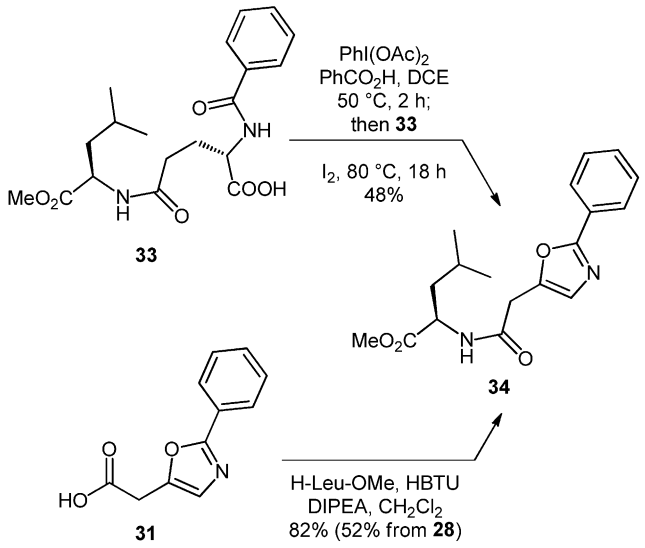
Fortunately, the reduction or functionalization of vinyl derivatives such as compound **18** can provide a variety of primary and secondary alkyl chains. The vinyl derivatives are interesting not only as synthetic intermediates but as components of many natural products[1,18a] and dyes.[6a]

The role of the amino acid chain substituents was explored next. Thus, alanine **21** (Scheme 2), leucine **22** and aspartic **23** benzamides underwent the scission–cyclization process to give the 2-phenyloxazoles **24**–**26**. Both the monosubstituted derivative **24**[25] and the 2,5-disubstituted compounds **25**[20b,26] and **26** were obtained in good yields. Compound **26** presents an ester functionality which allows introduction of new chains.

In a similar way, the glutamic acid derivatives **27** and **28** (Scheme 3) underwent the decarboxylation–cyclization reaction to give the oxazoles **29** and **30**, respectively. Oxazole **29** could be functionalized at both ends, for instance, using the iodophenyl ring for sp^2–sp^2 couplings, and by attachment of the carboxyl group to other chains. Besides, the acid can be manipulated to introduce other functions. For instance, saponification of the ester **30**[27] afforded the acid **31**. Its oxidative radical scission generated an intermediate cation which was trapped by acetate to give product **32**.[28] The introduction of other nucleophiles is currently under study.

An interesting application of the decarboxylation–cyclization process would be the selective modification of peptides, so that an oxazole ring could be introduced into a certain position of the peptide without affecting the others. Since many bioactive peptides contain oxazole rings in their structure, the possibility of increasing the diversity of a peptide library by introduction of oxazole rings was attractive. This approach was studied with the dipeptide **33**[21c] (Scheme 4), which underwent the one-pot decarboxylation–cyclization process, to give the oxazole derivative **34** in 48% yield.

To check that the leucine residue did not undergo epimerization during the process, compound **34** was prepared from the acid **31** and leucine methyl ester using conventional peptide coupling conditions. Both compounds displayed similar optical activities ($[\alpha]_D \approx$



Scheme 4. Derivatization of dipeptide **33**.

−27 in MeOH at $c = 0.35$), proving that no epimerization had taken place.

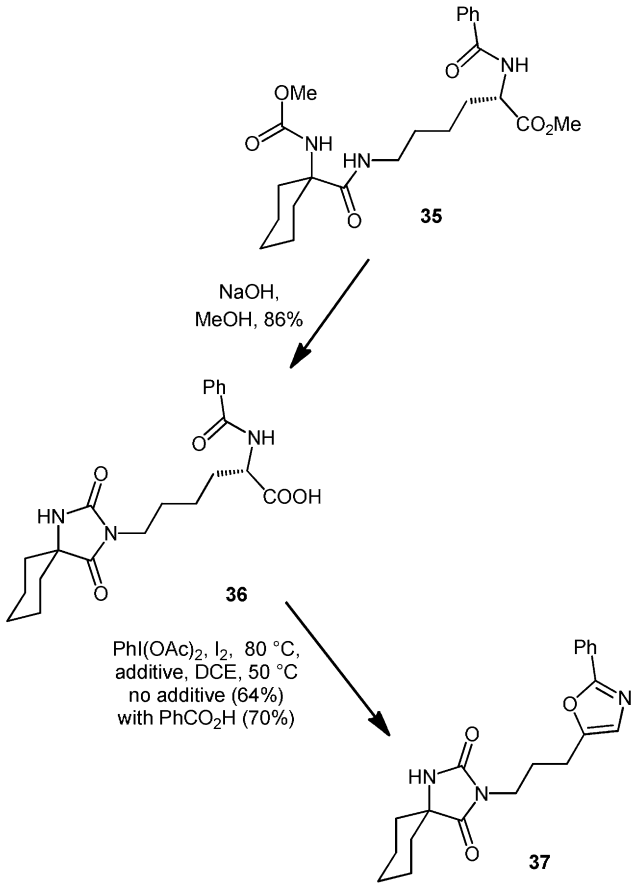
In another example, the Lys-Aib derivative **35** (Scheme 5) was converted into the acid **36**, which was transformed into the lysine-derived oxazole derivative **37** in good yield under two different sets of conditions, the standard decarboxylation–cyclization (70%) and the process without additive (64%).

The process was also studied with the Aib-Leu derivative **38** (Scheme 6). Interestingly, the acyl group involved in the cyclization step is an amino acid, and the resulting oxazole derivative **39** presents a chain with an amino group which allows extension of the peptidyl chain.

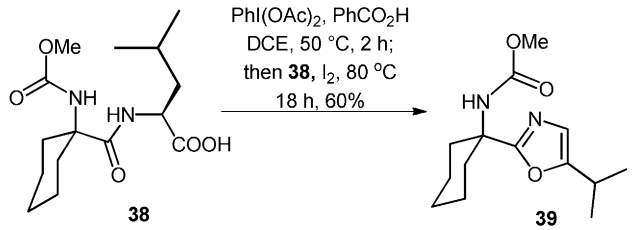
The optimization of this process for peptides, the use of non-proteinogenic units such as dehydroamino acids in the cyclization process, and its application to the generation of peptide libraries will be reported in due course.

In summary, *N*-acylamino acids can be converted into 2,5-disubstituted oxazoles using a one-pot process in which a radical decarboxylation–oxidation–isomerization reaction generates an enamide intermediate, which then undergoes an iodine-promoted cyclization. Remarkably, no metals are needed to promote this cyclization. The reaction proceeds with a variety of amino acids and acyl chains and, although many steps take place in this sequential process, the products are obtained in good global yields.

The one-pot process generates oxazoles in which both substituents can be manipulated independently. Besides, the mild conditions are suitable for the selective modification of peptides. The applications of this method to generate libraries of potentially antimicrobial and antitumoral oxazoles, including oxazole analogues of bioactive peptides, is currently underway and will be reported in due course.



Scheme 5. Derivatization of dipeptide **36**.



Scheme 6. Derivatization of dipeptide **33**.

Experimental Section

General Procedure for the Scission–Cyclization Process

A mixture of (diacetoxyiodo)benzene (258 mg, 0.8 mmol) and benzoic acid (195 mg, 1.6 mmol) in dry dichloroethane (4 mL) was heated at 50 °C for 2 h. Then the *N*-acylamino acid (0.4 mmol) and iodine (102 mg, 0.4 mmol) were added. The reaction mixture was heated under reflux for 18 h. Then the mixture was allowed to cool to room temperature (26 °C) and was poured into a 1:1 mixture of 10% aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The organic layer was dried over sodium sulfate and filtered, then the solvent was removed under

vacuum and the residue was purified by column chromatography (hexane/EtOAc), yielding the oxazole derivatives.

Ethyl 2-(2-phenyloxazol-5-yl)acetate (30): Obtained from δ-ethyl *N*-benzoylglutamate (**28**) (111 mg, 0.4 mmol) according to the general procedure above. The reaction mixture was purified by column chromatography on silica gel (hexane/EtOAc 90:10), affording compound (**30**) as a yellowish solid; yield: 63 mg (68%). Compound (**30**) has been previously reported.[27] ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.29$ (dd, $J = 7.1$ Hz, 3H), 3.79 (s, 2H), 4.22 (ddd, $J = 7.1$, 7.2, 7.2 Hz, 2H), 7.08 (s, 1H), 7.43–7.47 (m, 3H), 8.00–8.04 (m, 2H); ^{13}C NMR (125.7 MHz, $CDCl_3$, 26 °C): $\delta = 14.1$ (CH_3), 31.9 (CH_2), 61.5 (CH_2), 126.3 (2×CH), 127.4 (C), 128.7 (3×CH), 130.3 (CH), 145.0 (C), 161.5 (C), 168.3 (C).

2-(2-Phenyloxazol-5-yl)acetic acid (**31**): To a solution of the ester **30** (56 mg, 0.24 mmol) in methanol (9 mL) at 0 °C was added 2N aqueous NaOH (1 mL). The mixture was allowed to reach 26 °C and was stirred for 2 h; then was poured into 10% aqueous HCl and extracted with EtOAc. The organic layer was dried and evaporated in the usual way, affording acid **31** as a white amorphous solid; yield: 45 mg (92%). ^{1}H NMR (500 MHz, CD_3OD: $\delta = 3.86$ (s, 2H), 7.11 (s, 1H), 7.45–7.48 (m, 3H), 7.96–8.00 (m, 2H). ^{13}C NMR (125.7 MHz, CD_3OD): $\delta = 32.0$ (CH_2), 126.8 (CH), 127.2 (2×CH), 128.3 (C), 130.0 (2×CH), 131.7 (CH), 148.1 (C), 163.0 (C), 172.0 (C); HR-MS (EI): $m/z = 203.0579$, calcd. for $C_{11}H_9NO_3$ [M^+]: 203.0582; anal. calcd. for $C_{11}H_9NO_3$: C 65.02, H 4.46, N 6.89; found: C 64.87, H 4.80, N 6.89.

(2-Phenyloxazol-5-yl)methyl acetate (**32**): A solution of acid **31** (21 mg, 0.1 mmol) in dry dichloroethane (1.5 mL) was treated with (diacetoxyiodo)benzene (48 mg, 0.15 mmol) and iodine (13 mg, 0.05 mmol). The mixture was heated under reflux for 30 min, then was allowed to reach 26 °C and poured into saturated aqueous $Na_2S_2O_3$, and extracted with dichloromethane. The organic layer was dried and evaporated as usual, and the residue was purified by column chromatography (hexanes:EtOAc 90:10) affording compound **32** as a yellow syrup; yield: 16 mg (73%). The spectroscopic data of compound **32** have been previously reported.[28] ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.11$ (s, 3H), 5.18 (s, 2H), 7.28 (br s, 1H), 7.45–7.50 (m, 3H), 8.05–8.10 (m, 2H); ^{13}C NMR (125.7 MHz, $CDCl_3$, 26 °C): $\delta = 20.8$ (CH_3), 55.6 (CH_2), 126.7 (2×CH), 128.1 (CH), 128.9 (2×CH+C), 131.0 (CH), 146.8 (C), 162.5 (C), 170.4 (C); HR-MS (EI): $m/z = 218.0821$, calcd. for $C_{12}H_{12}NO_3$ [$M^+ + H$]; 218.0817; anal. calcd. for $C_{12}H_{11}NO_3$: C 66.35, H 5.10, N 6.45; found: C 62.60, H 5.34, N 6.13.

***N*-[2-(2-Phenyloxazol-5-yl)acetyl]leucine methyl ester** (**34**): Obtained from the dipeptide **33** (151 mg, 0.4 mmol) according to the general procedure. The reaction mixture was purified by column chromatography on silica gel (hexane/EtOAc 50:50), affording compound (**34**) as a as a yellowish syrup; yield: 63 mg (48%); $[\alpha]_D$: −27 (*c* 0.35, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.89$ (d, $J = 6.4$ Hz, 3H), 0.92 (d, $J = 6.3$ Hz, 3H), 1.53 (m, 1H), 1.60–1.68 (m, 2H), 3.71 (s, 3H), 3.74 (s, 2H), 4.66 (ddd, $J = 5.0$, 8.4, 8.8 Hz, 1H), 6.25 (br d, $J = 8.0$ Hz, 1H), 7.12 (brs, 1H), 7.44–7.47 (m, 3H), 8.01–8.05 (m, 2H); ^{13}C NMR (125.7 MHz, $CDCl_3$, 26 °C): $\delta = 21.9$ (CH_3), 22.7 (CH_3), 24.8 (CH), 33.8 (CH_2), 41.4 (CH_2), 51.0 (CH), 52.4 (CH_3), 126.3 (3×CH), 126.8 (C), 128.8 (2×CH), 130.6 (CH), 145.7 (C), 161.9 (C), 166.9 (C), 173.1 (C); IR ($CHCl_3$): $\nu = 3426$, 1741, 1684 cm^{-1}; HR-MS (EI): $m/z = 330.1591$, calcd. for $C_{18}H_{22}N_2O_4$ [M^+]: 330.1580; anal. calcd. for $C_{18}H_{22}N_2O_4$: C 65.44, H 6.71, N 8.48; found: C 65.58, H 6.86, N 8.36.

***N*-[2-(2-Phenyloxazol-5-yl)acetyl]leucine methyl ester** (**34**): To a solution of acid **31** (12 mg, 0.60 mmol) in CH_2Cl_2 (3 mL) was added H-Leu-OMe HCl (142 mg, 0.78 mmol), DIPEA (0.20 mL, 1.2 mmol) and HBTU (250 mg, 0.66 mmol). The reaction mixture was allowed to reach 26 °C and stirred for 3 h, then was poured into saturated aqueous $NaHCO_3$·and extracted with EtOAc. The organic layer was washed with 10% aqueous HCl, and then was dried and evaporated as usual. The residue was purified by column chromatography on silica gel (hexane/EtOAc 60:40) affording the compound **32** as a yellowish syrup; yield: 163 mg (82%); $[\alpha]_D$: −28 (*c* 0.35, MeOH).

Supporting Information

Experimental details, ^{1}H and ^{13}C NMR for all new products, and 2D-NMR spectra for compounds **15, 34** and **37** are available in the Supporting Information

Acknowledgements

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