Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 62 (2006) 4698–4704
Tetrahedron

Convenient preparation of substituted 5-aminooxazoles via a microwave-assisted Cornforth rearrangement

M. Brad Nolt,* Mark A. Smiley,† Sandor L. Varga, Ray T. McClain, Scott E. Wolkenberg and Craig W. Lindsley

Department of Medicinal Chemistry, Technology Enabled Synthesis Group, Merck Research Laboratories, Merck & Co. Inc., PO Box 4, West Point, PA 19486, USA

Received 1 December 2005; revised 14 December 2005; accepted 16 December 2005
Available online 31 March 2006

Abstract—The preparation of oxazole-4-carboxamides and their subsequent thermal rearrangement to 5-aminooxazole-4-carboxylates is optimized in a high-speed microwave-assisted procedure. The reaction sequence is effective with a variety of substituted oxazoles, and produces products in good yield and high purity.

1. Introduction

The biological activity and therapeutic potential of 5-aminooxazole containing structures is demonstrated in the pseudomonic acid derived antibiotic **1**,[1a] oxazolo-[5,4-*d*]pyrimidine **2** an inhibitor of ricin and shiga toxins,[1b] and peptidomimetics with oxazole-incorporated amino acids **3**.[1c] Additionally, 5-(*p*-tolyl)urea-oxazole **4** is shown to have in vitro activity as a Raf kinase inhibitor with the possibility of use as a treatment for cancers (Fig. 1).[1d]

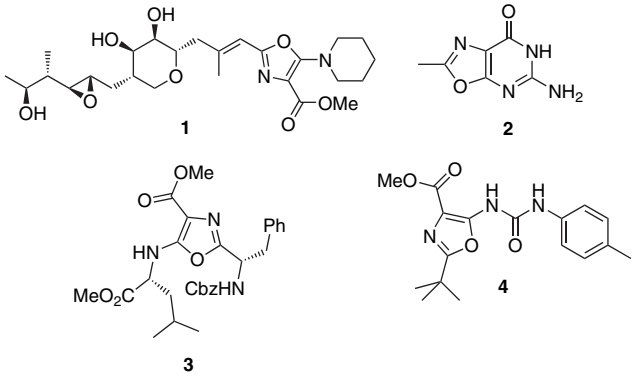
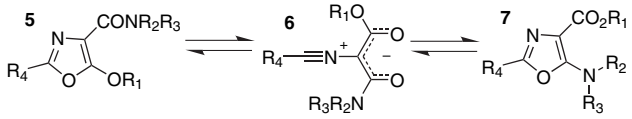


Figure 1. Biologically active 5-aminooxazoles.

A number of synthetic routes have been described for the preparation of 5-aminooxazoles.[1–3] While they are adequate for the generation of individual compounds, the typical procedures do not lend themselves to the rapid generation of a large number of diverse products. Although novel, efficient methodology has been developed, these reactions do not make use of readily available starting materials and hence, are not easily applied in a parallel format. A particularly attractive alternative presents itself in the Cornforth rearrangement (Scheme 1). This formal rearrangement occurs upon heating 5-alkoxyoxazole-4-carboxamides at $\geq$100 °C for 17 h and is believed to proceed via an intermediate nitrile ylide such as **6**. Originally discovered by Cornforth during studies related to penicillin, the reaction was studied in detail by Dewar[3] whose mechanistic and computational work defined the intermediate as a delocalized zwitterion.[4] Intermediate **6** exhibits a psuedo-symmetrical dicarbonyl structure, which can cyclize either to reform **5** or proceed to **7**. Because the formation of **6** is reversible, the final product distribution (**5**:**7**) is wholly determined by the relative thermodynamic stabilities of the 5-alkoxy-oxazole-4-carboxamide and 5-amino-oxazole-4-carboxylate. Despite its intriguing mechanism and synthetic potential, the reaction has received relatively little attention since these pioneering studies.

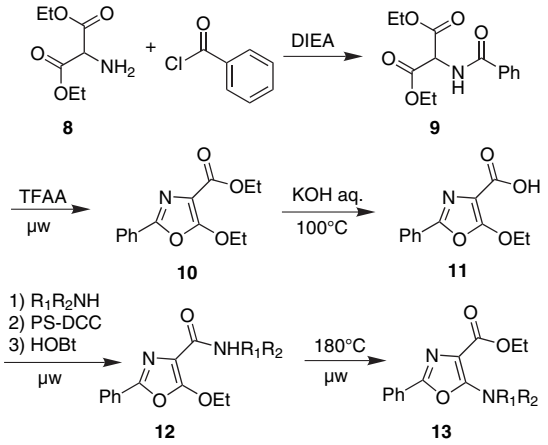


Scheme 1. Cornforth rearrangement.

* Corresponding author. Tel.: +1 215 652 1485; fax: +1 215 652 6345; e-mail: brad_nolt@merck.com
† UNCF/Merck undergraduate fellow, 2005–2006.

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.12.065

Based on this precedent, we envisioned a synthesis such as that shown in Scheme 2.[2f] Acylation of 2-amino diethylmalonate followed by cyclodehydration would afford oxazole **10**, which after saponification and amide coupling would generate the Cornforth substrate **12**. Thermal rearrangement then produces the 5-amino-oxazole-4-carboxylate **13**.



Scheme 2. General synthesis of 5-amino-oxazole-4-carboxylates.

This route enables the incorporation of diverse substituents at all positions of the oxazole and importantly does so via the use of readily available carboxylic acid chloride and amine building blocks. This affords the opportunity to generate fully substituted oxazoles with a diverse array of functionality.

A secondary goal was to generate these structures rapidly and therefore microwave-assisted conditions were investigated. Microwave-assisted organic synthesis (MAOS) has been widely utilized recently as it is typically associated with dramatic reductions in reaction times, a diminution in side product formation, and increased yields.[5]

In this paper we describe the microwave-assisted formation of several 5-aminooxazole compounds and apply this methodology to the formal synthesis of a biologically active target (Fig. 1), 4-(methoxycarbonyl)-2-(1-normon-2-yl)-5-piperidin-1-yloxazole (**1**).[1a]

2. Results and discussion

Preparation of rearrangement substrate **12** proceeded with straightforward acylation of 2-amino diethylmalonate (DIEA, benzoyl chloride, 94%). Cyclodehydration to form oxazoles has been performed using a number of dehydrating reagents under thermal conditions. For example, the generation of 5-amino-oxazole-4-carboxylates from 2-amidomalonates has been reported, in only moderate yield, using 1 equiv PCl_5 in toluene and heating for 30 min to 14 h at reflux.[2f,6] Other reagents such as triphenylphosphine/iodine or trichloroacetyl chloride, in conjunction with conventional heating, have been used as well.[1a,7]

In an effort to accelerate the cyclodehydration step a range of solvents, dehydrating reagents, microwave irradiation times, and temperatures were surveyed. Optimal conditions for the transformation of **9** to **10** were identified as a 2:1 mixture of trifluorotoluene/trifluoroacetic anhydride (TFAA) and heating at 160 °C for 10 min. A dramatic reduction in reaction time was observed (5 min vs 0.5–14 h) and good yields of the oxazole **10** were obtained (79%). This reaction was successfully scaled up from 0.03 g to 3.00 g without reoptimization of the microwave conditions. The solvent/substrate ratio, the duration, and temperature of the microwave heating was maintained and afforded 2-aryloxazoles in multigram quantities.

Basic hydrolysis of the cyclization product with 15% aq potassium hydroxide, heated at 100 °C, cleanly gives the carboxylic acid **11**.[3] Amide bond formation under a variety of conditions (PS-DCC, HOBt; EDCI, HOBt) was sluggish, and therefore the recently disclosed microwave procedure using polymer bound carbodiimide was employed.[8] PS-carbodiimide amide coupling was accelerated by microwave heating (100 °C, 10 min) and after filtration of the solid-phase reagent(s), the 5-ethoxy-2-phenyloxazolamides **12** were obtained in excellent yields. Although formed at 100 °C, these amides had clearly not undergone a Cornforth rearrangement (^{1}H NMR, see below). Excess HOBt can be removed from the products prior to the rearrangement step by treatment with MP-carbonate. However, we observed that the presence of HOBt does not alter the success of the rearrangement step and it is likely that the reagent is thermally decomposed to volatile and gaseous byproducts when targeted rearrangement temperatures are reached.[9]

Cornforth rearrangement products were produced by heating 5-alkoxy-oxazole-4-carboxamides **12** using microwave irradiation (Table 1). The reaction requires temperatures >170 °C for complete conversion to the thermodynamically more stable products **13**. As can be seen in Table 1, small changes in temperature have a large impact on conversion at these short reaction times. While excellent conversions (by LC–MS) were realized in acetonitrile and trifluorotoluene, isolated yields were much higher in trifluorotoluene. Optimized microwave heating at 180 °C for 5 min in trifluorotoluene gave compounds in 23–99% yield and of purity greater than 93% by ^{1}H NMR (Table 2); entry 11 required chromatographic purification to obtain product **13k**. A range of functional groups are tolerated in the reaction including acetals, thioethers, sulfonamides, and Boc-protected amines. Primary and secondary amines perform equally well in the amide formation rearrangement sequence.

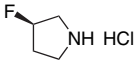
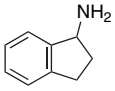
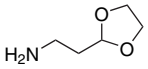
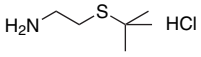
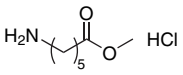
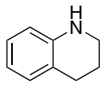
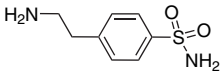
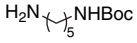
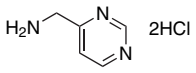
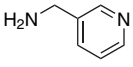
Three characteristic observations allowed us to distinguish the starting materials from products in the final step of the synthesis. First, HPLC retention times differed for

Table 1. Cornforth rearrangement temperature optimization study

Entry	Solvent	Rearrangement conditions	Product/starting material[a]
1	Acetonitrile	150 °C, 10 min	1:99
2	Acetonitrile	160 °C, 10 min	31:69
3	Acetonitrile	170 °C, 10 min	42:58
4	Acetonitrile	180 °C, 10 min	99:1
5	$PhCF_3$	180 °C, 5 min	99:1

[a] Determined by UV HPLC.

Table 2. Microwave-assisted amide formation and Cornforth rearrangement

Entry	Amine	Coupling conditions	Product	Rearrangement conditions	Yield (%)
1		100 °C, 5 min	**13a**	180 °C, 5 min.	76
2		100 °C, 5 min	**13b**	180 °C, 5 min	98
3		100 °C, 5 min, PS-DIEA (1 equiv)	**13c**	180 °C, 5 min	47
4		100 °C, 5 min	(±)-**13d**	180 °C, 5 min	99
5		100 °C, 5 min	**13e**	180 °C, 5 min	99
6		100 °C, 5 min	**13f**	180 °C, 5 min	23
7		100 °C, 5 min, PS-DIEA (1 equiv)	**13g**	180 °C, 5 min	51
8		100 °C, 5 min, PS-DIEA (1 equiv)	**132h**	180 °C, 5 min	76
9		100 °C, 5 min	**13i**	180 °C, 5 min	85
10		100 °C, 5 min	**13j**	180 °C, 5 min	19
11		100 °C, 5 min	**13k**	180 °C, 5 min	99
12		100 °C, 5 min, PS-DIEA (2 equiv)	**13l**	180 °C, 5 min	23[a]
13		100 °C, 5 min	**13m**	180 °C, 5 min	82
14		100 °C, 5 min	**13n**	180 °C, 5 min	97

[a] After flash chromatography.

compounds **12** and **13**. Second, HMBC NMR studies of compound **12b** and its Cornforth product **13b** showed a partial carbonyl shielding effect on the 2- and 5-position methylene protons of the pyrrolidine amide. This with a change in carbon shifts for the ethyl group in both molecules suggested that the rearrangement had successfully occurred. And third, the diisobutyl aluminohydride reduction of **13e** to the corresponding alcohol **14** unequivocally confirmed the rearrangement of **12e** (Fig. 2).

The formal synthesis of **1** began with N-acylation of 2-amino-dimethylmalonate to form the amide **15** (Scheme 3).

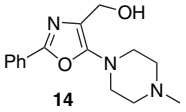
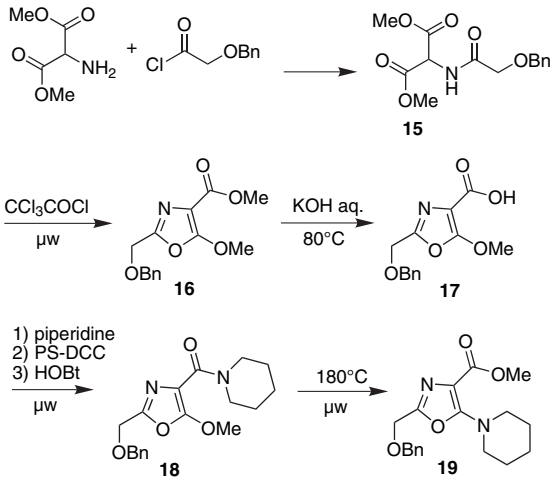


Figure 2. (5-(4-Methylpiperazin-1-yl)-2-phenyloxazol-4-yl)methanol.



Scheme 3. Formal synthesis of 4-(methoxycarbonyl)-2-(1-normon-2-yl)-5-piperidin-1-yloxazole (**1**).

The established cyclodehydration procedure was then applied, however microwave heating at 160 °C for 10 min with TFAA resulted only in 50% conversion (^{1}H NMR) of the starting material to oxazole **16**. Increased temperatures (≥160 °C) caused noticeable decomposition and did little to facilitate the conversion to the oxazole. Longer heating times were also unsuccessful. After trying several dehydrating reagents, it was discovered that trichloroacetyl chloride provided an improved product ratio and virtually no degredation was observed. While increased heating times and temperatures did not give the desired product, five successive heat cycles at 160 °C for 20 min resulted in 97% conversion (^{1}H NMR) to the cyclodehydration product.[10]

Hydrolysis of the oxzaole-4-carboxylate **17** was accomplished by heating at 80 °C for 15 min in KOH (15% aq). Amide formation, and the thermal rearrangement were then conducted under the usual conditions to give the benzyl protected compound **19**. Hydrogenation to deprotect the 2-hydroxymethyl oxazole, followed by halogenation and phosphorylation would prepare the right-hand piece for connection with the ozonolyzed psuedomonic acid substrate.[11]

3. Conclusion

The incorporation of microwave heating dramatically decreases the time required for the polymer-assisted formation of 5-alkoxyoxazole-4-carboxamides and their subsequent rearrangement to 5-aminooxazoles. A range of 5-aminooxazoles can be obtained using the methodology we describe. To further illustrate the utility of our synthetic procedure, we have successfully carried out a formal synthesis of 4-(methoxycarbonyl)-2-(1-normon-2-yl)-5-piperidin-1-yloxazole (**1**).

4. Experimental

4.1. Ethyl-5-ethoxy-2-phenyloxazole-4-carboxylate (10)

In a 10–20 mL microwave vial (Biotage) with stir bar was placed diethyl-2-(benzamido)malonate (3.0 g, 10.7 mmol) and trifluoroacetic anhydride (5.0 mL, 40.7 mmol) in trifluorotoluene (10 mL). The vial was sealed and heated at 160 °C for 10 min in the microwave (Biotage Emrys Optimizer). The desired temperature was reached in approximately 1 min at 300 W power. The crude material was concentrated and purified by flash chromatography (0–25% EtOAc/*n*-hexanes) to give 2.2 g (79%) of **10**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97–8.00 (m, 2H), 7.43–7.46 (m, 3H), 4.60 (q, J=6.9 Hz, 2H), 4.41 (q, J=7.2 Hz, 2H), 1.54 (t, J=7.2 Hz, 3H), 1.40 (t, J=6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.9, 161.6, 151.3, 130.6, 128.9, 126.8, 126.2, 108.9, 70.3, 61.0, 15.2, 14.7. HRMS calcd for $C_{14}H_{16}NO_4$ (M+H) 262.1074, found 262.1079.

4.2. 5-Ethoxy-2-phenyloxazole-4-carboxylic acid (11)

To ethyl 5-ethoxy-2-phenyloxazole-4-carboxylate (1.0 g, 3.83 mmol) was added a solution of 15% aq KOH (2.15 mL, 5.75 mmol). The reaction was heated at 100 °C in an oil bath for 30 min then cooled to 0 °C and acidified with 10% aq H_2SO_4 until a pH of around three was obtained. The resulting suspension was filtered and the solid was collected and dried in vacuo to give 0.424 g (48%) of pure product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.954–7.97 (m, 2H), 7.45–7.47 (m, 3H), 4.68 (q, J=7.2 Hz, 2H), 1.56 (t, J=7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.3, 161.9, 151.1, 130.6, 128.8, 126.2, 126.0, 107.4, 70.4, 15.0. HRMS calcd for $C_{12}H_{12}NO_4$ (M+H) 234.0761, found 234.0774.

4.3. General procedure for the preparation of compounds 12a–m

In a 2–5 mL microwave vial with stir bar was placed 5-ethoxy-2-phenyloxazole-4-carboxylic acid (**11**) 0.028 g, (0.12 mmol), PS-DCC (0.093 g, 0.12 mmol), HOBt (0.016 g, 0.12 mmol), and amine (0.12 mmol) in trifluorotoluene (3 mL). The vial was sealed and heated at 100 °C for 5 min using the microwave. The desired temperature was reached in approximately 30 s at 300 W power. The reaction mixture was filtered to remove the solid-phase reagents and the resin was rinsed with an additional milliliter of trifluorotoluene. The filtered solution was then transferred to a clean 2–5 mL microwave vial and used directly in the next step of the synthesis.

4.4. General procedure for the preparation of compounds 13a–m

The crude products **12** were heated at 180 °C in the microwave for 5 min. The desired temperature was reached in approximately 2 min at 300 W power. Removal of the trifluorotoluene solvent under reduced pressure left products that were ≥93% pure by ^{1}H NMR analysis.

4.4.1. Ethyl 2-phenyl-5-(piperidin-1-yl)oxazole-4-carboxylate (13a). Purified by silica gel flash chromatography (*n*-hexanes/EtOAc, 3–10% gradient over 20 min). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94–7.95 (m, 2H), 7.36–7.42 (m, 3H), 4.38 (q, J=14, 7.2 Hz, 2H), 3.63–3.64 (m, 4H), 1.70–1.74 (m, 6H), 1.41 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 160.0, 150.7, 129.9, 128.7, 127.1, 126.0, 108.1, 60.6, 49.8, 25.8, 24.3, 14.8. HRMS calcd for $C_{17}H_{21}N_2O_3$ (M+H) 301.1547, found 301.1550.

4.4.2. Ethyl 2-phenyl-5-(pyrrolidin-1-yl)oxazole-4-carboxylate (13b). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91–7.94 (m, 2H), 7.34–7.43 (m, 3H), 4.35 (q, J=14, 6.8 Hz, 2H), 3.75–3.79 (m, 2H), 1.98–2.04 (m, 2H), 1.40 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 158.1, 149.9, 129.6, 128.7, 127.2, 125.8, 60.3, 50.2, 25.7, 14.8. HRMS calcd for $C_{16}H_{19}N_2O_3$ (M+H) 287.1390, found 287.1377.

4.4.3. Ethyl 5-(3-fluoropyrrolidin-1-yl)-2-phenyloxazole-4-carboxylate (13c). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93–7.96 (m, 2H), 7.39–7.45 (m, 3H), 5.36 (d, J=52.8 Hz, 1H), 4.37 (q, J=6.9 Hz, 2H), 3.88–4.20 (m, 5H), 2.34–2.46 (m, 1H), 2.01–2.28 (m, 1H), 1.42 (t, J=6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.7, 157.5, 150.2, 129.7, 128.6, 126.8, 125.7, 106.3, 92.3 (d, J=176.6 Hz), 60.3, 56.7 (d, J=23.0), 47.4, 32.1 (d, J=21.2), 14.6. HRMS calcd for $C_{16}H_{18}FN_2O_3$ (M+H) 305.1296, found 305.1285.

4.4.4. (±)-Ethyl 5-(2,3-dihydro-1*H*-inden-1-ylamino)-2-phenyloxazole-4-carboxylate (13d). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94–7.97 (m, 2H), 7.22–7.44 (m, 7H), 6.55 (d, J=8.4 Hz, 1H), 5.38 (q, J=15.6, 7.6 Hz, 1H), 4.37 (q, J=14.4, 7.2 Hz, 2H), 3.07–3.14 (m, 1H), 2.91–2.99 (m, 1H), 2.68–2.77 (m, 1H), 2.02–2.11 (m, 1H), 1.39 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 160.3, 150.4, 143.3, 142.4, 129.9, 128.9, 128.7, 127.2, 127.1, 125.9, 125.2, 124.2, 60.4, 59.0, 34.8, 30.4, 14.9. HRMS calcd for $C_{21}H_{21}N_2O_3$ (M+H) 349.1547, found 349.1539.

4.4.5. Ethyl 5-(4-methylpiperazin-1-yl)-2-phenyloxazole-4-carboxylate (13e). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93–7.96 (m, 2H), 7.40–7.43 (m, 3H), 4.38 (q, J=14.4, 7.2 Hz, 2H), 3.77 (t, J=4.8 Hz, 4H), 2.65 (t, J=4.8 Hz, 4H), 2.40 (s, 3H), 1.41 (t, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 159.4, 151.2, 130.1, 128.8, 126.9, 126.1, 108.9, 60.8, 54.6, 48.1, 46.1, 14.8. HRMS calcd for $C_{17}H_{22}N_3O_3$ (M+H) 316.1656, found 316.1647.

4.4.6. Ethyl 5-(2-(1,3-dioxolan-2-yl)ethylamino)-2-phenyloxazole-4-carboxylate (13f). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93–7.96 (m, 2H), 7.36–7.44 (m, 3H), 6.75–6.79 (m, 1H), 5.05 (t, J=4.2 Hz, 1H), 4.38 (q, J=7.2 Hz, 2H), 3.99–4.07 (m, 2H), 3.88–3.96 (m, 2H), 3.67 (q, J=6.3 Hz, 2H), 2.07–2.13 (m, 2H), 1.39 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 160.4, 150.2, 129.7, 128.8, 127.1, 125.8, 103.2, 65.3, 60.3, 38.5, 33.2, 14.8. HRMS calcd for $C_{17}H_{21}N_2O_5$ (M+H) 333.1445, found 333.1439.

4.4.7. Ethyl 5-(2-(*tert*-butylthio)ethylamino)-2-phenyloxazole-4-carboxylate (13g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93–7.96 (m, 2H), 7.36–7.44 (m, 3H), 6.60 (t, J=5.6 Hz, 1H), 4.39 (q, J=14.4, 7.2 Hz, 2H), 3.68 (q, J=13.6, 6.8 Hz, 2H), 2.84 (t, J=7.2 Hz, 2H), 1.41 (t, J=7.2, 3H), 1.36 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.0, 160.1, 150.2, 129.7, 128.6, 126.8, 125.6, 104.8, 76.8, 60.3, 43.4, 42.73, 42.72, 31.1, 28.3, 14.7. HRMS calcd for $C_{18}H_{25}N_2O_3S$ (M+H) 349.1581, found 349.1577.

4.4.8. Ethyl 5-(5-(methoxycarbonyl)pentylamino)-2-phenyloxazole-4-carboxylate (13h). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92–7.95 (m, 2H), 7.36–7.44 (m, 3), 6.34 (s, 1H), 4.38 (q, J=14.4, 7.2 Hz, 2H), 3.67 (s, 3H), 3.50 (q, J=6.4 Hz, 2H), 2.35 (t, J=7.6 Hz, 2H), 1.67–1.76 (m, 4H), 1.44–1.50 (m, 2H), 1.41 (t, J=8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 160.9, 150.2, 129.8, 128.8, 127.1, 125.8, 104.6, 76.9, 60.4, 51.7, 43.2, 34.0, 30.0, 26.4, 24.7, 14.9. HRMS calcd for $C_{19}H_{25}N_2O_5$ (M+H) 361.1758, found 361.1750.

4.4.9. Ethyl 5-(3,4-dihydroquinolin-1(2*H*)-yl)-2-phenyloxazole-4-carboxylate (13i). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94–7.97 (m, 2H), 7.22–7.44 (m, 7H), 6.55 (d, J=8.4 Hz, 1H), 5.38 (q, J=15.6, 7.6 Hz, 1H), 4.37 (q, J=14.4, 7.2 Hz, 2H), 3.07–3.14 (m, 1H), 2.91–2.99 (m, 1H), 2.68–2.77 (m, 1H), 2.02–2.11 (m, 1H), 1.39 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 160.3, 150.4, 143.3, 142.4, 129.9, 128.9, 128.7, 127.2, 127.1, 125.9, 125.2, 124.2, 60.4, 59.0, 34.8, 30.4, 14.9. HRMS calcd for $C_{21}H_{21}N_2O_3$ (M+H) 349.1547, found 349.1544.

4.4.10. Ethyl 5-({2-[4-(aminosulfonyl)phenyl]ethyl}-amino)-2-phenyl-1,3-oxazole-4-carboxylate (13j). ^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ 7.72–7.73 (m, 4H), 7.43–7.50 (m, 5H), 7.26 (s, 2H), 4.20 (q, J=6.9 Hz, 2H), 3.67 (br s, 2H), 3.01 (t, J=6.6 Hz, 2H), 1.25 (t, J=6.9 Hz, 3H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ 163.1, 160.5, 149.2, 143.8, 142.9, 130.2, 129.9, 129.7, 127.2, 126.4, 125.6, 103.8, 59.7, 44.4, 36.1, 15.3. HRMS calcd for $C_{20}H_{22}N_3O_5S$ (M+H) 416.1275, found 416.1271.

4.4.11. *tert*-Butyl 3-(4-(ethoxycarbonyl)-2-phenyloxazol-5-ylamino)propylcarbamate (13k). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93–7.99 (m, 2H), 7.36–7.43 (m, 3H), 6.60 (s, 1H), 4.66 (s, 1H), 4.39 (q, J=6.8 Hz, 2H), 3.55 (q, J=6.8, 2H), 3.27 (q, J=6.4 Hz, 2H), 1.86 (apparent quintet, J=6.6, 2H), 1.46 (s, 9H), 1.41 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0, 160.4, 156.3, 150.0, 129.6, 128.6, 126.9, 125.6, 104.5, 60.2, 40.5, 37.6, 30.9, 28.4, 14.7. HRMS calcd for $C_{20}H_{28}N_3O_5$ (M+H) 390.2024, found 390.2023.

4.4.12. Ethyl 5-((pyrimidin-4-yl)methylamino)-2-phenyloxazole-4-carboxylate (13l). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.23–9.24 (m, 1H), 8.74 (d, J=5.4 Hz, 1H), 7.88–7.91 (m, 2H), 7.38–7.44 (m, 4H), 7.23–7.27 (m, 1H), 4.81 (d, J=5.7 Hz, 2H), 4.43 (q, J=7.2 Hz, 2H), 1.44 (t, J=6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 164.1, 159.9, 159.0, 157.7, 150.8, 130.0, 128.9, 126.8, 125.9, 118.6, 105.7, 60.7, 47.4, 14.8. HRMS calcd for $C_{17}H_{17}N_4O_3$ (M+H) 325.1222, found 325.1294.

4.4.13. Ethyl 5-((pyridin-3-yl)methylamino)-2-phenyloxazole-4-carboxylate (13m). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.58–8.59 (m, 1H), 7.89–7.92 (m, 2H), 7.71–7.74 (m, 1H), 7.39–7.41 (m, 3H), 7.31–7.34 (m, 1H), 6.72–6.75 (m, 1H), 4.69 (d, J=6.4 Hz, 2H), 4.39 (q, J=7.2 Hz, 2H), 1.41 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 160.2, 150.7, 149.7, 149.3, 135.3, 133.3, 130.0, 128.9, 126.8, 128.9, 124.0, 105.4, 76.9, 60.6, 45.0, 14.8. HRMS calcd for $C_{18}H_{18}N_3O_3$ (M+H) 324.1343, found 324.1332.

4.4.14. Ethyl 5-(cyclopropylamino)-2-phenyloxazole-4-carboxylate (13n). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97–7.99 (m, 2H), 7.37–7.45 (m, 3H), 6.50 (s, 1H), 4.37 (q, J=7.2 Hz, 2H), 2.81–2.87 (m, 1H), 1.41 (t, J=3.6 Hz, 3H), 0.87–0.91 (m, 2H), 0.73–0.77 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 161.5, 150.8, 129.8, 128.9, 128.8, 127.1, 125.9, 60.5, 24.6, 14.9, 7.4. HRMS calcd for $C_{15}H_{17}N_2O_3$ (M+H) 295.1053, found 295.1052.

4.4.15. (5-(4-Methylpiperazin-1-yl)-2-phenyloxazol-4-yl)methanol (14). In a clean, dry 40 mL sample vial was placed ethyl 5-(4-methylpiperazin-1-yl)-2-phenyloxazole-4-carboxylate (0.089 g, 0.28 mmol) in dry dichloromethane under N_2. The stirred solution was cooled to −78 °C and Dibal-H (0.84 mL, 0.84 mmol) was added via syringe. After 10 min, the reaction was complete by LC–MS and quenched with H_2O. After warming to rt the crude reaction mixture was filtered through packed Celite and extracted with EtOAc

(3×10 mL). Purification by flash chromatography (5–10% MeOH/DCM) gave 0.070 g (91%) of **14**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89–7.92 (m, 2H), 7.37–7.44 (m, 3H), 4.62 (s, 2H), 3.31 (t, J=4.8 Hz, 2H), 2.55 (t, J=4.8 Hz), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 129.8, 128.9, 127.8, 127.3, 125.7, 122.4, 57.1, 54.9, 50.1, 46.5. HRMS calcd for $C_{15}H_{20}N_3O_2$ (M+H) 274.1550, found 274.1541.

4.4.16. Dimethyl 2-(2-(benzyloxy)acetamido)malonate (15). To a stirred suspension of 2-amino-dimethylmalonate hydrochloride (1.0 g, 5.45 mmol) in dichloromethane (20 mL) was added diisopropylethylamine (1.8 mL, 10.9 mmol) and the reaction was stirred at rt for 10 min. To the resulting clear slightly yellow solution was added benzoylacetoxychloride (0.87 mL, 5.45 mmol) and the reaction was stirred at rt for 15 min. The mixture was diluted with dichloromethane, washed with 1 N HCl then satd aq $NaHCO_3$. The aqueous layer was extracted with dichloromethane (2×10 mL), the organic extracts were washed with brine and dried over Na_2SO_4. Filtration and removal of solvent under reduced pressure gave 1.56 g (97%) of a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.64 (m, 1H), 7.30–7.41 (m, 4H), 5.27 (d, J=7.2 Hz, 1H), 4.63 (s, 2H), 4.04 (s, 2H), 3.83 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 166.7, 136.8, 128.8, 128.5, 128.2, 73.9, 69.3, 55.6, 53.7. HRMS calcd for $C_{14}H_{18}NO_6$ (M+H) 296.1129, found 296.1126.

4.4.17. Methyl 2-((benzyloxy)methyl)-5-methoxyoxazole-4-carboxylate (16). In a 2–5 mL microwave vial with stir bar were placed dimethyl 2-(2-(benzyloxy)acetamido)malonate (**15**) (0.020 g, 0.07 mmol), trichloroacetyl chloride (1 mL), and trifluorotoluene (3 mL). The vial was heated at 160 °C for 20 min then cooled to rt, and this heating cycle was repeated five times. The desired temperature was reached in approximately 1 min at 300 W power. Flash chromatography of the concentrated crude product (30–60% EtOAc/*n*-hexanes) yielded 0.170 g (31%) of **16**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.38 (m, 5H), 4.60 (s, 2H), 4.52 (s, 2H), 4.18 (s, 3H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 161.9, 150.0, 137.2, 128.72, 128.71, 128.3, 128.2, 73.1, 64.2, 60.0, 52.0. HRMS calcd for $C_{14}H_{16}NO_5$ (M+H) 278.1017, found 278.1023.

4.4.18. 2-((Benzyloxy)methyl)-5-methoxyoxazole-4-carboxylic acid (17). In a 40 mL sample vial with stir bar was placed **16** (0.120 g, 0.43 mmol) and KOH (3 mL of a 15% aq solution). The vial was heated at 80 °C for 15 min in an oil bath, then cooled to 0 °C and neutralized with H_2SO_4 (10% aq solution). The mixture was diluted and extracted with EtOAc (2×10 mL), and the organic extracts washed with brine, and dried over Na_2SO_4. The solution was filtered, concentrated, and dried under reduced pressure to give 0.118 g (99%) of analytically pure **17** as an off-white solid. HRMS calcd for $C_{13}H_{14}NO_5$ (M+H) 264.0867, found 264.0867.

4.4.19. (5-Ethoxy-2-phenyloxazol-4-yl)(piperidin-1-yl)-methanone (18). In a 0.5–2 mL microwave vial with spin van were placed **17** (0.038 g, 0.14 mmol), piperidine (0.014 mL, 0.14 mmol), PS-DCC (0.107 g, 0.14 mmol), and HOBt (0.019 g, 0.14 mmol) in $PhCF_3$ (2 mL). The vial was sealed and heated at 100 °C for 5 min in the microwave. The desired temperature was reached in approximately 30 s at 300 W power. Filtration and removal of the solid-phase reagent gave the crude product **18**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29–7.36 (m, 5H), 4.60 (s, 2H), 4.47 (s, 2H), 4.07 (s, 3H), 3.59–3.75 (m, 4H), 1.55–1.69 (m, 5H); ^{13}C NMR δ 161.5, 149.2, 137.3, 128.7, 128.23, 128.21, 73.0, 64.1, 60.0, 24.9. HRMS calcd for $C_{18}H_{23}N_2O_4$ (M+H) 331.1658, found 331.1658.

4.4.20. Methyl 2-((benzyloxy)methyl)-5-(piperidin-1-yl)oxazole-4-carboxylate (19). In a 0.5–2 mL microwave vial with spin vane was placed **18** (0.030 g, 0.09 mmol) in $PhCF_3$ (2 mL). The vial was sealed and heated at 180 °C for 5 min. The desired temperature was reached in approximately 2 min at 300 W power. The contents were concentrated and dried under reduced pressure to give 0.030 g (99%) of analytically pure **19**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.34 (m, 5H), 4.58 (s, 2H), 4.48 (s, 2H), 3.85 (s, 3H), 3.57–3.61 (m, 4H), 1.66–1.71 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 160.5, 149.3, 137.5, 128.6, 128.13, 128.12, 73.0, 64.2, 51.7, 49.5, 25.8, 24.2. HRMS calcd for $C_{18}H_{23}N_2O_4$ (M+H) 331.1653, found 331.1656.

Acknowledgments

We are grateful to Joan S. Murphy, Vincent van Nostrand, and Charles W. Ross, III for their assistance with HRMS analyses.

References and notes

1. (a) Brown, P.; Davies, D. T.; O'Hanlon, P. J.; Wilson, J. M. *J. Med. Chem.* **1996**, *39*, 446; (b) Miller, D. J.; Ravikumar, K.; Shen, H.; Suh, J.-K.; Kerwin, S. M.; Robertus, J. D. *J. Med. Chem.* **2002**, *45*, 90; (c) Falorni, M.; Giacomelli, G.; Porcheddu, A.; Dettori, G. *Eur. J. Org. Chem.* **2000**, 3217; (d) Smith, R. A.; Barbosa, J.; Blum, C. L.; Bobko, M. A.; Caringal, Y. V.; Dally, R.; Johnson, J. S.; Katz, M. E.; Kennure, N.; Kingery-Wood, J.; Lee, W.; Lowinger, T. B.; Lyons, J.; Marsh, V.; Rogers, D. H.; Swartz, S.; Walling, T.; Wild, H. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2775.
2. (a) Connell, R.; Scavo, F.; Helquist, P. *Tetrahedron Lett.* **1986**, *27*, 5559; (b) Wang, Q.; Xia, Q.; Ganem, B. *Tetrahedron Lett.* **2003**, *44*, 6825; (c) Sun, X.; Janvier, P.; Zhao, G.; Bienaymé, H.; Zhu, J. *Org. Lett.* **2001**, *3*, 877; (d) Yoo, S.-K. *Tetrahedron Lett.* **1992**, *33*, 2159; (e) Schregenberger, C.; Seebach, D. *Liebigs Ann. Chem.* **1986**, 2081; (f) Dewar, M. J. S.; Turchi, I. *J. Org. Chem.* **1975**, *40*, 1521; (g) Clerin, D.; Kille, G.; Fleury, J.-P. *Tetrahedron* **1974**, *30*, 469; (h) Falco, E. A.; Elion, G. B.; Burgi, E.; Hitchings, G. H. *J. Am. Chem. Soc.* **1952**, *74*, 4897.
3. For a review see: Turchi, I. J.; Dewar, M. J. S. *Chem. Rev.* **1975**, *75*, 389.
4. (a) Dewar, M. J. S.; Turchi, I. J. *J. Am. Chem. Soc.* **1974**, *19*, 6148; (b) Dewar, M. J. S.; Spanninger, P. A.; Turchi, I. J. *J. Chem. Soc., Chem. Commun.* **1973**, 925.
5. For a comprehensive review of microwave-assisted organic synthesis, see: (a) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250 and references therein; (b) Wolkenberg, S. E.; Shipe, W. D.; Lindsley, C. W.; Guare, J. P.; Pawluczyk, J. *Curr. Opin. Drug Discov. Dev.* **2005**, *8*, 701.

6. Ramage, G. R.; Waring, W. S. G.B. Patent 591,656, 1947.
7. (a) Falorni, M.; Dettori, G.; Giacomelli, G. *Tetrahedron: Asymmetry* **1998**, *9*, 1419; (b) Crimmin, M. J.; O'Hanlon, P. J.; Rogers, N. H.; Sime, F. M.; Walker, G. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2059.
8. Sauer, D. R.; Kalvin, D.; Phelan, K. M. *Org. Lett.* **2003**, *5*, 4721.
9. While not studied in detail, HOBt was not detected by ^{1}H NMR and LC–MS analyses.
10. Yield improvements from pulse microwave heating have been reported: (a) Arvela, R. K.; Leadbeater, N. E. *Org. Lett.* **2005**, *7*, 2101; (b) Mathew, F.; Jayaprakash, K. N.; Fraser-Reid, B.; Mathew, J.; Scicinski, J. *Tetrahedron Lett.* **2003**, *44*, 9051; (c) Chen, J. J.; Deshpande, S. V. *Tetrahedron Lett.* **2003**, *44*, 8873; (d) Strauss, C. R. *Angew. Chem., Int. Ed.* **2002**, *41*, 3589; (e) Kuhnert, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 1863.
11. (a) Clayton, J. P.; Luk, K.; Rogers, N. H. *J. Chem. Soc., Perkin Trans. 1* **1979**, 308; (b) Crimmin, M. J.; O'Hanlon, P. J.; Rogers, N. H.; Walker, G. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2047.