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Development of a Diversity-Oriented Approach to Oxazole-5-amide Libraries

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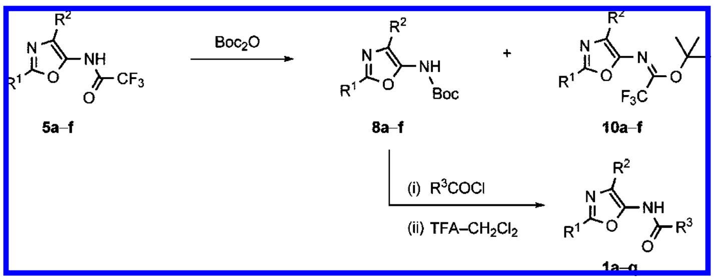

A highly versatile route to oxazole-5-amides is presented. Conversion of readily accessible oxazole-5-trifluoroacetamides into their Boc-protected 5-aminooxazole derivatives provides intermediates amenable to parallel amide synthesis utilizing a reliable, one-pot, acylation−deprotection procedure. During preparation of the *N*-Boc compounds from trifluoroacetamides, a competing intramolecular rearrangement giving rise to novel *N*-(oxazol-5-yl)-2,2,2-trifluoroacetimidates was identified, the extent of which is primarily determined by the choice of reaction conditions.

Introduction

The oxazole ring occurs in a multitude of natural products[1] and has been widely employed as a component of biologically active compounds in medicinal chemistry. For example, oxazoles are present in the anti-inflammatory drug oxaprozin[2] and also aleglitazar, a compound under evaluation for treatment of type II diabetes.[3] As part of an ongoing screening program, we required a flexible route to oxazole-5-amides **1** (Figure 1) suitable for parallel synthesis of chemical libraries, and as such, the widest possible scope for variation at each diversity point (R^1, R^2, and R^3) was sought.

Particular difficulty in accessing target compounds **1**is presented by the general instability of free 5-aminooxazoles, which are prone to ring-opening in solution;[4] thus, formation of the amide linkage through derivatization of such intermediates is precluded. Examples of stable 5-aminooxazoles are essentially limited to those bearing an electron-withdrawing functionality at the 4-position, typically a cyano group,[5−9] an amide,[10,11] or an additional heterocycle.[12−14] In order to resolve this difficulty, we recently reported[15] a preparation of *N*-Boc compound **2a** via phosgene-mediated cyclization of α-acylaminonitrile **3a**, followed by trapping with *tert*-butyl alcohol (Scheme 1). This

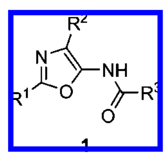

FIGURE 1. Generic structure of oxazole-5-amide library compounds.

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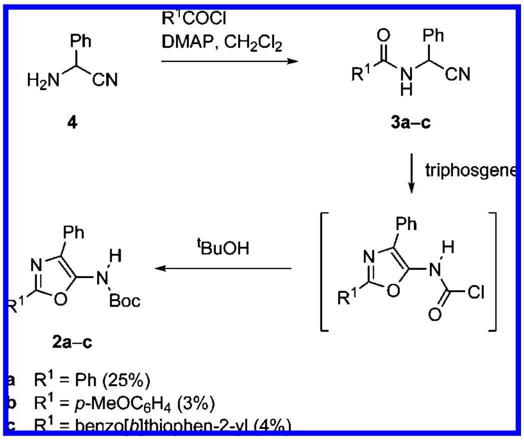
SCHEME 1. Route to *N*-Boc-5-aminooxazoles Employing a Phosgene-Mediated Cyclization Step



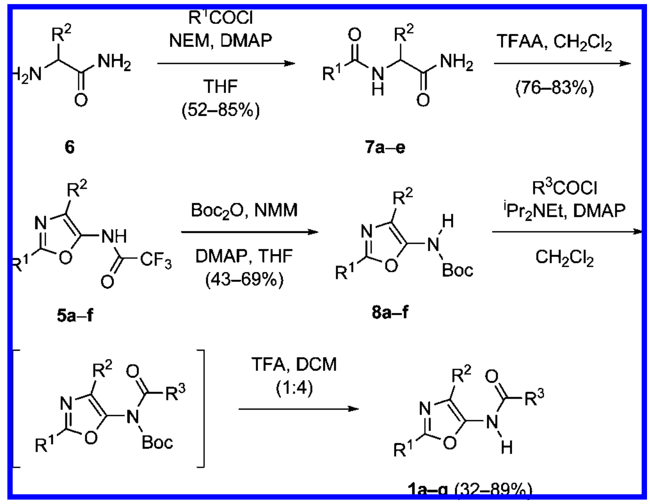
Boc-protected intermediate served as a suitable precursor to a library of 2,4-diphenyloxazole-5-amides that were evaluated for their antiprion activity. Since **2a** was applied successfully in amide library synthesis, we wished to explore the scope and generality of this promising protocol more fully; that is, with variation of substitution at the 2- and 4-positions of the oxazole ring (R^1 and R^2), leading to a wider diversity of products.

A one-pot adaption of the previous synthesis was subsequently developed, permitting more expeditious synthesis of **2a** from aminonitrile **4**, though it was also established that this phosgene-mediated approach was not generally applicable. If the acid chloride component was varied as in the case of **2b**,**c**, yields of the Boc-protected 5-aminooxazoles dropped sharply to impractical levels, and the uncyclized α-acylaminonitriles **3b**,**c** became by far the major product of these reactions. The low yields obtained by the above route could conceivably be due to generation of acid-sensitive compounds **2** under acidic conditions, although in an attempt to address this, it was found that use of an amine base during the reaction sequence did not improve the outcome.

An alternative route to compounds of the type **2a**−**c** was thus necessary and was inspired by the work of Lipshutz et al., who reported conditions for the transformation of an oxazole-5-trifluoroacetamide into its *N*-Boc-5-aminooxazole derivative.[16] Based upon this precedent, a series of oxazole-5-trifluoroacetamides **5a**−**e** were prepared as substrates in order to develop generalized conditions for the conversion (Scheme 2). Oxazoles **5a**−**e** were synthesized by acylation of substituted glycinamides **6**, followed by TFAA-mediated cyclization[17,18] of the intermediate diamides **7a**−**e**.

We first sought to optimize conversion of trifluoroacetamides **5a**−**f** into their *N*-Boc derivatives **8a**−**f** in order to facilitate

SCHEME 2. Modified Approach to *N*-Boc-5-aminooxazoles[a,b]



[a] Compound **5f** was not accessible by the route depicted here, since the appropriate derivative of **6** (R^2 = thiophene-2-yl) is not available. Instead, **5f** was prepared by alternative methods, as discussed later (see Scheme 5). [b] Abbreviations: *N*-methylmorpholine (NMM); *N*-ethylmorpholine (NEM).

diversity oriented library synthesis using these intermediates. They were then to be investigated as a starting point for an amide library **1a**−**q** via acylation and Boc deprotection in one pot (Scheme 2).

Results and Discussion

In order to evaluate and improve the conditions reported by Lipshutz and co-workers in their published example, compound **5a** was selected as starting material for a series of model reactions (Scheme 3), since *N*-Boc product **8a** had already been synthesized by other means. The transformation is assumed to proceed via *N*-acylation in the presence of excess Boc_2O, giving *N*,*N*-disubstituted intermediate **9**, whose trifluoroacetyl group is then cleaved under the basic reaction conditions to afford desired product **8a**.

Optimization with respect to solvent, temperature, and reaction time quickly established some key findings (Table 1). THF or 1,4-dioxane as solvent gave the best yields, and heating above room temperature was disfavored. In contrast to the reported reaction time of 20 min,[16] we found the process to be significantly slower, taking 24 h to reach completion by TLC.

Notably, a second product was isolated in every case and was actually the major product under some of the conditions studied. The compound was crystallized and identified as *N*-(oxazol-5-yl)-2,2,2-trifluoroacetimidate **10a** (Scheme 3).[19] This species presumably arises via migration of the *tert*-butyl group from the carbamate to the acyl oxygen atom of **9**, with concomitant loss of CO_2. Participation of a trifluoroacetyl oxygen atom as a nucleophile in intramolecular reactions is quite well precedented,[20−23] usually where a suitable leaving group is present within the molecule, though to the best of our

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(19) CCDC-720689 (**1k**), CCDC-720690 (**8a**), CCDC-720691 (**10a**), and CCDC-720692 (**11**) contain the crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request_cif.

(20) Gómez-Sánchez, E.; Soriano, E.; Marco-Contelles, J. *J. Org. Chem.* **2007**, *72*, 8656–8670.
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(22) Jin, C.; Burgess, J. P.; Kepler, J. A.; Cook, C. E. *Org. Lett.* **2007**, *9*, 1887–1890.

SCHEME 3. Transformation of Oxazole-5-trifluoroacetamides into the Corresponding *N*-Boc Derivatives Proceeds in Competition with Observed Side Reactions

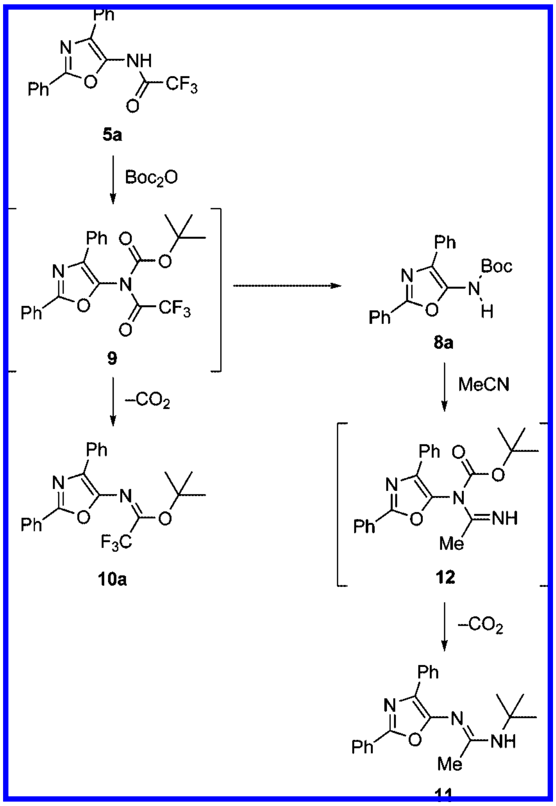


TABLE 1. Investigation of Varying Reaction Conditions for the Preparation of 8a from 5a[a]

solvent	*T*, °C	time, h	**8a**, %	**10a**, %
CH_2Cl_2	rt	24	25	22
CH_2Cl_2	rt	72	23	17
CH_2Cl_2[b]	rt	24	19	31
CH_2Cl_2	40	24	21	29
THF	rt	24	50	11
THF	40	24	41	15
dioxane	rt	24	48	11
MeCN	rt	24	48[c]	3

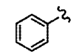
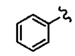
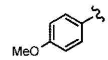
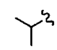
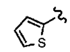
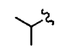
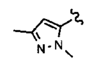
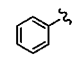
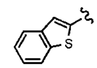
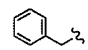
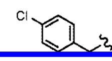
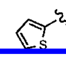
[a] Reactions carried out on a 1 mmol scale using 1.5 equiv of NMM, 3 equiv of Boc_2O, and 0.2 equiv of DMAP in 7 mL of the specified solvent. [b] 2.5 equiv of NMM used. [c] Isolated product is **11**, not **8a**.

knowledge, the present case represents the first example of intramolecular capture of a *tert*-butyl group by this moiety.

Furthermore, when acetonitrile was used as solvent (final entry, Table 1), the expected product **8a** was not obtained at all. Further reaction of the product with the solvent itself was implicated, since the isolated product **11** must be formed through rearrangement of addition product **12** by a mechanism analogous to that noted above—migration of the *tert*-butyl group of the carbamate and loss of CO_2. X-ray crystallography also confirmed the structure of **11** (Scheme 3).

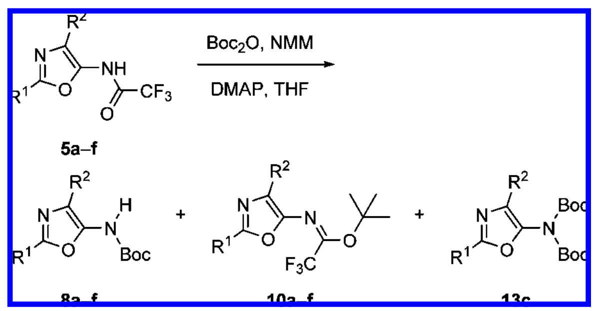
Having ascertained optimal conditions for the conversion of **5a** to **8a** (1.5 equiv of NMM, 3.0 equiv of Boc_2O, THF, rt, 24 h), the scope of the reaction was explored using other oxazole-5-trifluoroacetamides **5b−f** (Table 2). The yield and

TABLE 2. Conversion of Differently Substituted Oxazole-5-trifluoroacetamides 5a−f into the *N*-Boc-Protected Derivatives 8a−f

	R[1]	R[2]	*t*, h	**8**[a]	**10**[b]	**13**[c]
a			24	50	11	–
b			24	69	3	–
c			24 6	68 67	2 <1[d]	6 3
d			24	42	15	–
e			24 6	57 32	4 <1[d]	– –
f			24 6	38 43	8 3	–

[a] Boc-protected product yield (%). [b] Trifluoroacetimidate product yield (%). [c] Bis-Boc-protected product yield (%). [d] Small amount detected by TLC analysis, but not isolated.

SCHEME 4. Product Distribution Observed during *N*-Boc-5-aminooxazole Synthesis

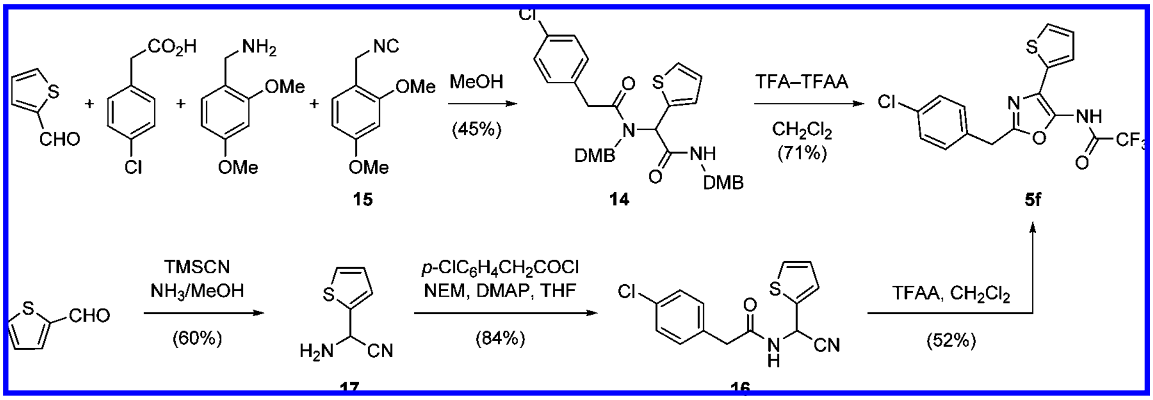


product distribution were found to be quite sensitive to the exact nature of the 2- and 4-substituents (Scheme 4), although desired compounds **8b−f** were always isolated as the major product. Small quantities (up to 15% yield) of the corresponding *N*-(oxazol-5-yl)-2,2,2-trifluoroacetimidate byproducts **10b−f** were formed in each case, and with **5c** as substrate, a small amount of the bis-Boc-protected derivative **13c** (R^1 = thiophene-2-yl, R^2 = ^{i}Pr) was also produced. Cutting the reaction time from 24 to 6 h reduced the amount of this doubly protected byproduct but did not affect the overall yield of the reaction. Comparison of the reaction time in two other examples (**5e**,**f**) revealed that the longer 24 h duration is usually preferable.

With the above general route to *N*-Boc-5-aminooxazoles firmly established, an obvious shortcoming of the approach was considered. Only a limited number of substituted glycinamides **6** (Scheme 2) are available from commercial sources, restricting the choice of R^2. To enrich the diversity of libraries which may be generated by the present methodology, two variations were explored, both of which derive the 4-substituent of the final oxazoles from a readily available aldehyde building block (Scheme 5). 2-Thiophenecarboxaldehyde was chosen as starting material, since we wished to introduce a thiophene-2-yl group at the 4-position of the oxazoles, but 2-(thiophene-2-yl)glyci-

(23) Feng, Z.; Mohapatra, S.; Klimko, P. G.; Hellberg, M. R.; May, J. A.; Kelly, C.; Williams, G.; McLaughlin, M. A.; Sharif, N. A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2998–3002.

SCHEME 5. Alternative Approaches to Oxazole-5-trifluoroacetamide Intermediates[a]



[a] DMB = 2,4-dimethoxybenzyl group.

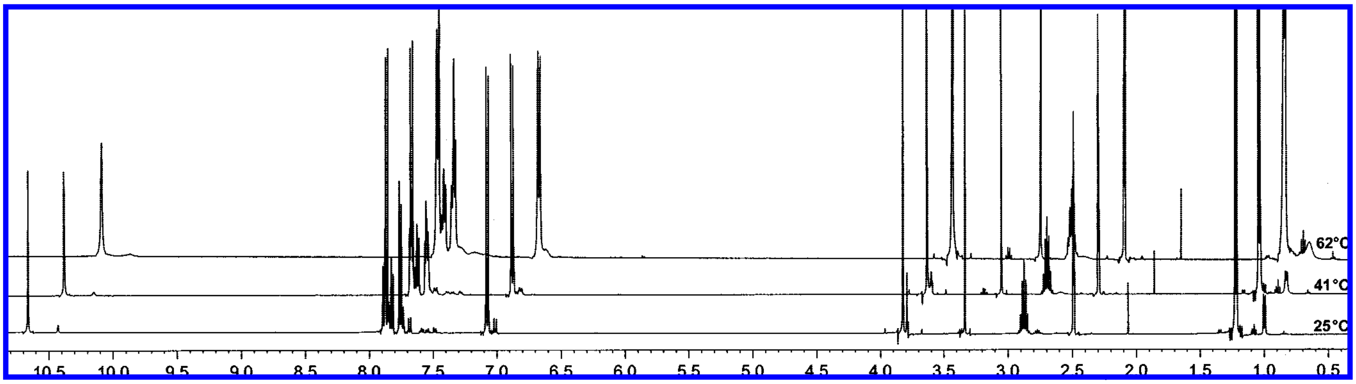


FIGURE 2. Variable-temperature ^{1}H NMR of compound **1b** shows simplification of the spectrum as the temperature is raised.

namide is not commercially available; thus, **5f** could not be prepared by the method outlined previously (Scheme 2).

Compound **14**, a diamide analogous to **7** but employing double 2,4-dimethoxybenzyl (DMB) protection, was prepared via an Ugi four-component coupling as shown, using isocyanide **15**[24] to introduce the terminal DMB protecting group. When this intermediate was treated with a TFA/TFAA mixture, deprotection and cyclization occurred in one pot, concluding a useful and flexible two-step synthesis of **5f**. Alternatively, this product was prepared by TFAA-mediated cyclization of α-acylaminonitrile **16**, in turn derived from the same starting aldehyde by way of aminonitrile **17**. Both alternative routes offer access to oxazole-5-trifluoroacetamides with increased diversity at the 4-position, though the former avoids the use of hazardous cyanide compounds necessary for the preparation of α-aminonitriles.

A small number of amide derivatives were then made from each of the new *N*-Boc-protected precursors **5b**−**f** (Table 3). Pleasingly, the acylation−deprotection sequence reported previously,[6] and introduced above in Scheme 2, did prove applicable to all substrates employed, leading to good yields of the final amide products **1a**−**q**. Chromatography on a short column of neutral alumina was sufficient for the isolation of pure compounds in the large majority of cases.

A handful of library members (**1b**, **1e**, **1j**) displayed interesting NMR properties, showing evidence of more than one solution conformer in $CDCl_3$. The effect was much less pronounced in DMSO-d_6 than $CDCl_3$ with the exception of **1b**, for which variable-temperature ^{1}H NMR spectra were recorded (Figure 2). Two sets of peaks can clearly be seen at room temperature, which collapse and/or broaden as the temperature is raised. Thus, this compound in particular displays evidence of restricted rotation, or other conformational restriction, on the NMR time scale when in solution.

Conclusions

A flexible strategy for the synthesis of varied oxazole-5-amides of general structure **1** (Figure 1) has been realized and is applicable to the preparation of small to moderate-sized libraries. Complementary routes to the key trifluoroacetamides **5** are also presented, enhancing the diversity of the final compounds which may be synthesized.

Conversion of the intermediate oxazole-5-trifluoroacetamides into their corresponding *N*-Boc-amino derivatives **8** seems wide in scope, but occurs in competition with an intramolecular rearrangement which afforded novel *N*-(oxazol-5-yl)-2,2,2-trifluoroacetimidates **10**. Heating or less polar solvents were found to drive the reaction toward the latter products, should these be required.

Experimental Section

4-Phenyl-5-*N*-Boc-aminooxazoles (2a−c). General Procedure. 2-Phenylglycinonitrile hydrochloride **4** was suspended in anhydrous CH_2Cl_2 (10 mL mmol^{-1}) under N_2. The acid chloride (1.0 equiv), $^iPr_2NEt$ (2.0 equiv), and DMAP (0.1 equiv) were added in quick succession, and then the mixture was stirred at rt for 1 h, after which time a homogeneous solution resulted. Triphosgene (1.0 equiv) was added directly, followed 15 min later by *tert*-butyl

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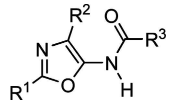
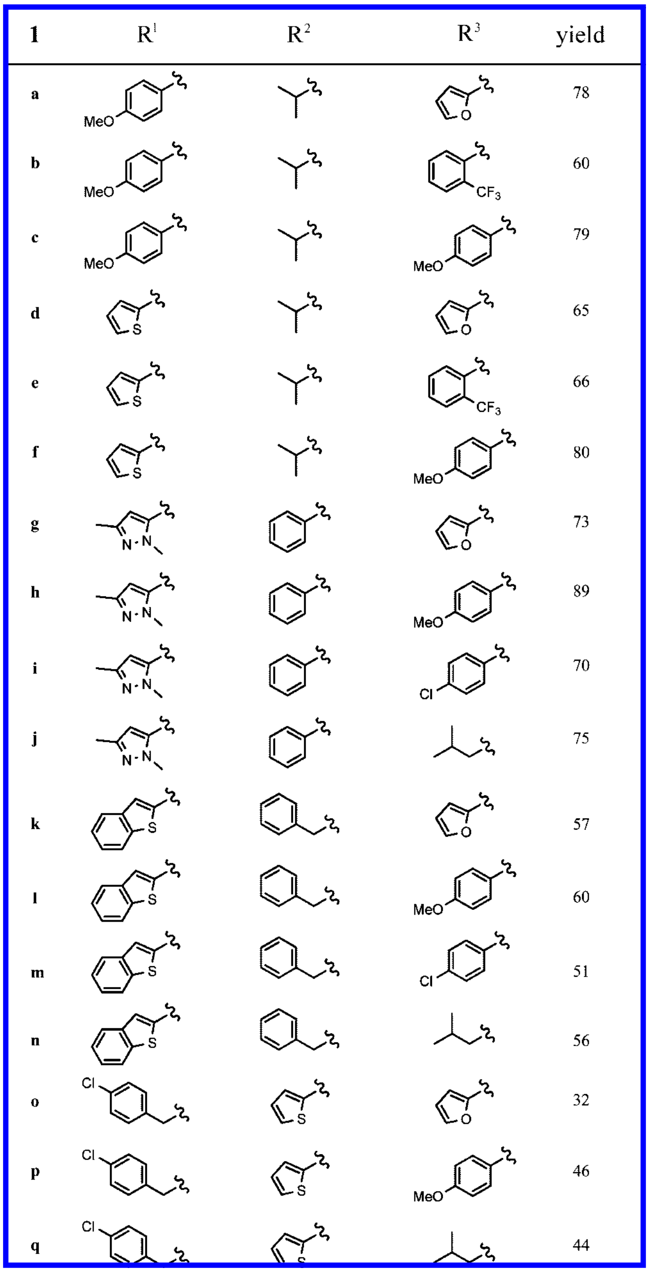
TABLE 3. Illustrative Oxazole-5-amide Library Prepared by Parallel Synthesis





1	yield
a	78
b	60
c	79
d	65
e	66
f	80
g	73
h	89
i	70
j	75
k	57
l	60
m	51
n	56
o	32
p	46
q	44

alcohol (2 mL mmol^{-1}). After a further 10 min, the reaction was quenched by careful addition of 0.2 M K_2CO_3 and then extracted into CH_2Cl_2. The organic layer was washed twice more with 0.2 M K_2CO_3 and then separated, dried over $MgSO_4$, and evaporated to dryness. Purification was carried out by flash column chromatography on silica gel using the eluent specified.

***tert*-Butyl 2,4-Diphenyloxazol-5-ylcarbamate (2a).** Prepared as above using **4** (844 mg, 5.0 mmol), benzoyl chloride (0.58 mL, 0.70 g, 5.0 mmol), ^{i}Pr$_2$NEt (1.74 mL, 1.29 g, 10.0 mmol), DMAP (61 mg, 0.5 mmol), and triphosgene (1.49 g, 5.0 mmol). Column eluent 75−100% CH_2Cl_2−hexane. Isolated as an amorphous, bright yellow solid (417 mg, 25%): δ_H (400 MHz, $CDCl_3$) 8.12−8.07 (m, 2H), 7.91−7.87 (m, 2H), 7.51−7.42 (m, 5H), 7.35 (tt, 1H, J = 1.0, 6.5), 6.45 (s, 1H), 1.48 (br s, 9H); δ_C (100 MHz, $CDCl_3$) 158.0, 153.2, 137.2, 130.9, 130.4, 128.7, 128.5, 127.9, 127.4, 126.40, 126.36, 82.1, 28.1; ν_{max} (solid)/cm^{-1} 3259, 2977, 1708, 1245, 1152, 777, 716, 689; m/z (ESI) 337 ([M + H]$^+$); HRMS found 337.1563 ($C_{20}H_{21}N_2O_3$ requires 337.1552).

***N*-(Cyanophenylmethyl)benzamide (3a).** Obtained during synthesis of **2a**, as a beige powder (134 mg, 11%): δ_H (250 MHz, DMSO-d_6) 9.79 (dd, 1H, J = 8.0), 7.96−7.89 (m, 2H), 7.64−7.36 (m, 8H), 6.44 (d, 1H, J = 8.0); δ_C (62.8 MHz, DMSO-d_6) 166.5, 135.0, 133.2, 132.6, 129.4, 129.0, 128.1, 127.5, 119.0, 44.4; ν_{max} (solid)/cm^{-1} 3248, 1643, 1524, 1493, 1327, 875, 730, 693, 666, 618; m/z (ES) 237 ([M + H]$^+$); HRMS, found 237.1021 ($C_{15}H_{13}N_2O$ requires 237.1028).

***tert*-Butyl 2-(4-Methoxyphenyl)-4-phenyloxazol-5-ylcarbamate (2b).** Prepared as above using **4** (2.95 g, 17.5 mmol), 4-methoxybenzoyl chloride (2.37 mL, 2.99 g, 17.5 mmol), ^{i}Pr$_2$NEt (6.27 mL, 4.25 g, 36.0 mmol), DMAP (214 mg, 1.75 mmol), and triphosgene (5.2 g, 17.5 mmol). Column eluent 1−5−10% EtOAc−toluene. Isolated as a bright orange solid (210 mg, 3%): δ_H (250 MHz, $CDCl_3$) 8.04−7.97 (m, 2H), 7.88−7.81 (m, 2H), 7.45−7.37 (m, 2H), 7.35−7.27 (m, 1H), 7.00−6.92 (m, 2H), 6.32 (s, 1H), 3.86 (s, 3H), 1.45 (s, 9H); δ_C (62.8 MHz, $CDCl_3$) 161.5, 153.2, 136.6, 136.2, 131.0, 129.1, 128.5, 128.2, 126.4, 120.2, 114.1, 82.1, 55.4, 28.1; ν_{max} (solid)/cm^{-1} 3158, 2964, 1730, 1613, 1495, 1243, 1151, 1081, 1024, 835, 746, 692; m/z (ESI) 367 ([M + H]$^+$); HRMS found 367.1664 ($C_{21}H_{23}N_2O_4$ requires 367.1658).

***N*-(Cyanophenylmethyl)-4-methoxybenzamide (3b).** Obtained during synthesis of **2b** as a cream-colored powder (3.46 g, 74%): δ_H (250 MHz, DMSO-d_6) 9.66 (d, 1H, J = 7.5), 7.93 (d, 2H, J = 8.5), 7.65−7.30 (m, 5H), 7.03 (d, 2H, J = 8.5), 6.42 (d, 1H, J = 8.0), 3.82 (s, 3H); δ_C (62.8 MHz, DMSO-d_6) 165.4, 162.2, 134.7, 129.6, 128.9, 128.7, 127.0, 124.8, 118.6, 113.7, 55.4, 43.8; ν_{max} (solid)/cm^{-1} 3245, 1631, 1607, 1495, 1256, 842, 748, 693, 681; m/z (ESI) 267 ([M + H]$^+$); HRMS, found 267.1123 ($C_{16}H_{15}N_2O_2$ requires 267.1134).

***tert*-Butyl 2-(Benzo[*b*]thiophene-2-yl)-4-phenyloxazol-5-ylcarbamate (2c).** Prepared as above using **4** (844 mg, 5.0 mmol), benzo[*b*]thiophene-2-carbonyl chloride (983 mg, 5.0 mmol), ^{i}Pr$_2$NEt (1.74 mL, 1.29 g, 10.0 mmol), DMAP (61 mg, 0.5 mmol), and triphosgene (1.49 g, 5 mmol). Column eluent 5−10−20% EtOAc−hexane. Isolated as a yellow, amorphous solid (80 mg, 4%): δ_H (250 MHz, $CDCl_3$) 7.91−7.78 (m, 5H), 7.48−7.28 (m, 5H), 6.57 (s, 1H), 1.45 (s, 9H); δ_C (62.8 MHz, $CDCl_3$) 154.2, 153.0, 140.5, 139.5, 137.3, 130.5, 129.5, 128.6, 128.1, 126.5, 125.9, 124.9, 124.60, 124.55, 122.5, 82.3, 28.1; ν_{max} (solid)/cm^{-1} 3268, 2973, 1734, 1634, 1476, 1456, 1370, 1245, 1144, 1052, 1039, 832, 754, 717, 690, 679; m/z (ESI) 393 ([M + H]$^+$); HRMS found 393.1282 ($C_{22}H_{21}N_2O_3S$ requires 393.1273).

***N*-(Cyanophenylmethyl)benzo[*b*]thiophene-2-carboxamide (3c).** Obtained during synthesis of **2c** as a brownish solid (0.69 g, 47%): δ_H (250 MHz, $CDCl_3$) 7.86−7.77 (m, 3H), 7.58−7.50 (m, 2H), 7.48−7.34 (m, 5H), 7.07 (d, 1H, J = 8.0), 6.31 (d, 1H, J = 8.5); δ_C (62.8 MHz, $CDCl_3$) 161.6, 141.3, 138.8, 136.1, 132.9, 129.7, 129.5, 127.2, 127.0, 126.8, 125.4, 125.2, 122.7, 117.3, 44.6; ν_{max} (solid)/cm^{-1} 3268, 1625, 1530, 1289, 1205, 866, 757, 735, 718, 694; m/z (ESI) 315 ([M + Na]$^+$); HRMS found 315.0572 ($C_{17}H_{12}N_2OSNa$ requires 315.0568).

α-Acylaminoglycinamides (7a−e). General Procedure. The substituted glycinamide (or its hydrochloride salt) was suspended in anhydrous THF (7.5 mL mmol^{-1}) under N_2. *N*-Ethylmorpholine (NEM; 1.2 equiv), an acid chloride (1.1 equiv), and DMAP (0.1 equiv) were added, and the mixture was maintained at rt for 2 h with vigorous stirring. The solvent was evaporated and the residue triturated thoroughly with water, collected by filtration, washed with water (×2), 1 M HCl (×), water, satd $NaHCO_3$ (×2), water, and ether (×2), and finally dried under vacuum.

***N*-(2-Amino-2-oxo-1-phenylethyl)benzamide (7a).** Prepared using D-phenylglycinamide (5.0 g, 33.3 mmol), NEM (4.88 mL, 4.41 g, 38.3 mmol), benzoyl chloride (4.26 mL, 5.15 g, 36.7 mmol), and DMAP (0.40 g, 3.3 mmol): white powder (6.18 g, 73%); δ_H

(400 MHz, DMSO-d_6) 8.76 (d, 1H, J = 8.0), 7.95−7.91 (m, 2H), 7.75 (s, 1H), 7.57−7.52 (m, 3H), 7.47 (t, 2H, J = 7.5), 7.37 (t, 2H, J = 7.0), 7.33−7.26 (m, 2H), 5.65 (d, 1H, J = 8.0); δ_C (100 MHz, DMSO-d_6) 171.7, 165.9, 138.8, 133.9, 131.4, 128.21, 128.18, 127.6, 127.5, 56.8; ν_{max} (solid)/cm^{-1} 3368, 3317, 3174, 1697, 1632, 1523, 689, 660, 640; m/z (ESI) 277 ([M + Na]$^+$); HRMS found 277.0939 ($C_{15}H_{14}N_2O_2Na$ requires 277.0953).

***N*-(1-Amino-3-methyl-1-oxobutan-2-yl)-4-methoxybenzamide (7b).** Prepared using D-valine amide hydrochloride (1.53 g, 10.0 mmol), NEM (2.80 mL, 2.53 g, 22.0 mmol), 4-methoxybenzoyl chloride (1.49 mL, 1.88 g, 11.0 mmol), and DMAP (122 mg, 1.0 mmol): off-white powder (1.31 g, 52%); δ_H (400 MHz, DMSO-d_6) 8.04 (d, 1H, J = 8.5), 7.89 (d, 2H, J = 8.5), 7.50 (s, 1H), 7.09 (s, 1H), 7.00 (d, 2H, J = 8.5), 4.25 (t, 1H, J = 8.0), 3.81 (s, 3H), 2.17−2.05 (m, 1H), 0.96−0.88 (m, 6H); δ_C (100 MHz, DMSO-d_6) 173.8, 166.3, 162.0, 129.8, 127.0, 113.8, 59.2, 55.8, 30.5, 19.9, 19.2; ν_{max} (solid)/cm^{-1} 3385, 3302, 3194, 2960, 1662, 1626, 1528, 1505, 1331, 1255, 1177, 1028, 845, 770, 670, 628; m/z (ESI) 251 ([M + H]$^+$); HRMS found 251.1391 ($C_{13}H_{19}N_2O_3$ requires 251.1396).

***N*-(1-Amino-3-methyl-1-oxobutan-2-yl)thiophene-2-carboxamide (7c).** Prepared using D-valine amide hydrochloride (1.53 g, 10.0 mmol), NEM (2.80 mL, 2.53 g, 22.0 mmol), thiophene-2-carbonyl chloride (1.17 mL, 1.61 g, 11.0 mmol), and DMAP (122 mg, 1.0 mmol): microcrystalline white solid (1.65 g, 73%); δ_H (400 MHz, DMSO-d_6) 8.27 (d, 1H, J = 9.0), 7.98 (d, 1H, J = 3.0), 7.76 (d, 1H, J = 5.0), 7.54 (s, 1H), 7.17−7.09 (m, 2H), 4.23 (t, 1H, J = 8.5), 2.14−2.03 (m, 1H), 0.92 (dd, 6H, J = 4.5, 6.5); δ_C (100 MHz, DMSO-d_6) 172.9, 161.0, 139.6, 130.9, 128.6, 127.8, 58.5, 30.0, 19.4, 18.6; ν_{max} (solid)/cm^{-1} 3390, 3299, 3198, 2964, 1622, 1527, 1506, 1420, 1273, 718, 650; m/z (ESI) 249 ([M + Na]$^+$); HRMS found 249.0668 ($C_{10}H_{14}N_2O_2SNa$ requires 249.0674).

***N*-(2-Amino-2-oxo-1-phenylethyl)-1,3-dimethyl-1*H*-pyrazole-5-carboxamide (7d).** Prepared using D-phenylglycinamide (1.80 g, 12.0 mmol), NEM (1.83 mL, 1.66 g, 14.4 mmol), 1,3-dimethyl-1*H*-pyrazole-5-carbonyl chloride (2.09 g, 13.2 mmol), and DMAP (145 mg, 1.2 mmol): white powder (2.54 g, 78%); δ_H (400 MHz, DMSO-d_6) 8.65 (d, 1H, J = 8.0), 7.73 (s, 1H), 7.50 (d, 2H, J = 7.0), 7.40−7.27 (m, 4H), 6.87 (s, 1H), 5.58 (d, 1H, J = 7.5), 3.95 (s, 3H), 2.16 (s, 3H); δ_C (100 MHz, DMSO-d_6) 171.8, 159.4, 145.8, 138.9, 135.7, 128.7, 128.07, 127.98, 107.7, 56.7, 38.9, 13.5; ν_{max} (solid)/cm^{-1} 3338, 3153, 1680, 1644, 1545, 1518, 1407, 699, 647; m/z (ESI) 273 ([M + H]$^+$); HRMS found 273.1348 ($C_{14}H_{17}N_4O_2$ requires 273.1352).

***N*-(1-Amino-1-oxo-3-phenylpropan-2-yl)benzo[*b*]thiophene-2-carboxamide (7e).** Prepared using L-phenylalanine amide hydrochloride (2.81 g, 14.0 mmol), NEM (3.92 mL, 3.55 g, 30.8 mmol), benzo[*b*]thiophene-2-carbonyl chloride (3.03 g, 15.4 mmol), and DMAP (169 mg, 1.4 mmol): white solid (3.84 g, 85%); δ_H (400 MHz, DMSO-d_6) 8.93 (d, 1H, J = 8.5), 8.22 (s, 1H), 8.02−7.94 (m, 2H), 7.70 (s, 1H), 7.48−7.41 (m, 2H), 7.38 (d, 2H, J = 7.0), 7.29−7.20 (m, 3H), 7.16 (t, 1H, J = 7.5), 4.66 (ddd, 1H, J = 2.0, 4.0, 10.5), 3.16 (dd, 1H, J = 4.0, 13.5), 3.02 (dd, 1H, J = 10.5, 13.5); δ_C (100 MHz, DMSO-d_6) 173.6, 161.9, 140.6, 140.1, 139.6, 138.9, 129.6, 128.6, 126.72, 126.67, 125.7, 125.6, 125.4, 123.2, 55.3, 37.8; ν_{max} (solid)/cm^{-1} 3394, 3306, 3182, 1664, 1629, 1530, 1506, 1298, 742, 617; m/z (ESI) 325 ([M + H]$^+$); HRMS found 325.1022 ($C_{18}H_{17}N_2O_2S$ requires 325.1011).

Oxazole-5-trifluoroacetamides (5a−e). General Procedure. Trifluoroacetic anhydride (2.5 mL mmol^{-1}) was added to an α-acylaminoglycinamide **7a−e** with stirring. The same volume of CH_2Cl_2 was then added and stirring continued at rt for 45 min. After this time, the mixture was evaporated, the residue taken up in CH_2Cl_2 and washed carefully with satd $NaHCO_3$, and then the organic layer dried over $MgSO_4$ and evaporated. Recrystallization from $CHCl_3$−hexane provided the pure trifluoroacetamide.

***N*-(2,4-Diphenyloxazol-5-yl)-2,2,2-trifluoroacetamide (5a).** Prepared from **7a** (6.11 g, 24.0 mmol): white solid (6.61 g, 83%); δ_H (400 MHz, DMSO-d_6) 8.16 (s, 1H), 8.06 (dd, 2H, J = 1.5, 7.5), 7.73−7.69 (m, 2H), 7.53−7.37 (m, 6H); δ_C (100 MHz, DMSO-d_6) 158.2, 156.7 (q, J = 38.0), 135.0, 132.4, 131.3, 129.6, 129.3, 128.9, 128.6, 126.10, 126.06, 125.9, 115.5 (q, J = 288); ν_{max} (solid)/cm^{-1} 2973, 1745, 1657, 1148, 686; m/z (ESI) 325 ([M + H]$^+$); HRMS, 333 ([M + H]$^+$); HRMS found 333.0857 ($C_{17}H_{12}F_3N_2O_2$ requires 333.0851).

2,2,2-Trifluoro-*N*-(4-isopropyl-2-(4-methoxyphenyl)oxazol-5-yl)acetamide (5b). Prepared from **7b** (1.21 g, 4.83 mmol): cream-colored needles (1.23 g, 78%); δ_H (400 MHz, DMSO-d_6) 8.01 (s, 1H), 7.91 (d, 2H, J = 9.0), 6.96 (d, 2H, J = 9.0), 3.87 (s, 3H), 2.85 (septet, 1H, J = 7.0), 1.28 (d, 6H, J = 7.0); δ_C (100 MHz, DMSO-d_6) 161.6, 159.3, 156.4 (q, J = 38.0), 140.9, 131.1, 128.1, 119.8, 115.4 (q, J = 286), 114.2, 55.4, 25.8, 21.1; ν_{max} (solid)/cm^{-1} 3136, 2985, 2841, 1754, 1657, 1610, 1495, 1260, 1233, 1209, 1150, 1135, 1103, 1066, 1030, 832, 750, 731, 715, 690, 652; m/z (ESI) 329 ([M + H]$^+$); HRMS found 329.1124 ($C_{15}H_{16}F_3N_2O_3$ requires 329.1113).

2,2,2-Trifluoro-*N*-(4-isopropyl-2-(thiophene-2-yl)oxazol-5-yl)acetamide (5c). Prepared from **7c** (1.37 g, 6.05 mmol): large, off-white needles (1.43 g, 77%); δ_H (400 MHz, DMSO-d_6) 11.82 (s, 1H), 7.81 (dd, 1H, J = 1.0, 5.0), 7.69 (dd, 1H, J = 1.0, 3.5), 7.22 (dd, 1H, J = 3.5, 5.0), 2.81 (septet, 1H, J = 7.0), 1.19 (d, 6H, J = 7.0); δ_C (100 MHz, DMSO-d_6) 156.5 (q, J = 40.0), 154.1, 138.9, 133.3, 129.8, 128.7, 128.5, 128.1, 115.4 (q, J = 287), 24.9, 20.9; ν_{max} (solid)/cm^{-1} 3346, 3153, 2973, 1750, 1646, 1584, 1520, 1196, 1145, 1063, 714, 664; m/z (ESI) 305 ([M + H]$^+$); HRMS found 305.0558 ($C_{12}H_{12}N_2O_2F_3S$ requires 305.0572).

***N*-(2-(1,3-Dimethyl-1*H*-pyrazol-5-yl)-4-phenyloxazol-5-yl)-2,2,2-trifluoroacetamide (5d).** Prepared from **7d** (2.50 g, 9.19 mmol): white solid (2.45 g, 76%); δ_H (400 MHz, DMSO-d_6) 12.39 (s, 1H), 7.80−7.76 (m, 2H), 7.53 (t, 2H, J = 7.5), 7.43 (tt, 1H, J = 2.0, 7.5), 6.73 (s, 1H), 4.20 (s, 3H), 2.22 (s, 3H); δ_C (100 MHz, DMSO-d_6) 157.1 (q, J = 39.0), 151.6, 147.3, 135.1, 132.3, 129.9, 129.7, 129.4, 129.2, 126.4, 115.9 (q, J = 287), 107.5, 39.2, 13.4; ν_{max} (solid)/cm^{-1} 2940, 2810, 1746, 1638, 1625, 1510, 1223, 1191, 1144, 1078, 776, 730, 714, 693, 676; m/z (ESI) 351 ([M + H]$^+$); HRMS found 351.1055 ($C_{16}H_{14}F_3N_4O_2$ requires 351.1069).

***N*-(2-(Benzo[*b*]thiophene-2-yl)-4-benzyloxazol-5-yl)-2,2,2-trifluoroacetamide (5e).** Prepared from **7e** (3.79 g, 11.7 mmol): white solid (3.80 g, 81%); δ_H (400 MHz, DMSO-d_6) 12.04 (s, 1H), 8.08−7.94 (m, 3H), 7.50−7.43 (m, 2H), 7.35−7.27 (m, 4H), 7.26−7.21 (m, 1H), 3.87 (s, 2H); δ_C (100 MHz, DMSO-d_6) 156.2 (q, J = 38.0), 154.0, 139.6, 139.2, 137.7, 136.5, 133.1, 128.7, 128.3, 128.1, 126.4, 125.3, 125.03, 124.99, 122.8, 115.3 (q, J = 289), 31.0; ν_{max} (solid)/cm^{-1} 3167, 3007, 2856, 1746, 1644, 1549, 1205, 1147, 756, 707, 693; m/z (ESI) 403 ([M + H]$^+$); HRMS found 403.0747 ($C_{20}H_{14}F_3N_2O_2S$ requires 403.0728).

***N*-Boc-5-aminooxazoles (8a−f). General Procedure.** Trifluoroacetamide **5a−f** was dissolved in dry THF (7 mL mmol^{-1}) under N_2. *N*-Methylmorpholine (NMM; 1.5 equiv), di-*tert*-butyl dicarbonate (Boc_2O; 3.0 equiv), and DMAP (0.2 equiv) were then added and the mixture stirred at rt for either 6 or 24 h, as indicated in Table 2. At this point, the solution was concentrated under vacuum, and the resultant oily residue was redissolved in CH_2Cl_2 and then stirred rapidly with satd NH_4Cl for 10 min. The organic layer was separated, dried over $MgSO_4$, and evaporated to give a thick, yellow or orange oil. Column chromatography on neutral alumina, eluted with 5−10−15−25−35% EtOAc−hexane, afforded the *N*-Boc compound and, in addition, the higher running trifluoroacetimidate product **10a−f**.

***tert*-Butyl 2,4-Diphenyloxazol-5-ylcarbamate (8a).** Prepared from **5a** (332 mg, 1.0 mmol), NMM (165 μL, 149 mg, 1.5 mmol), Boc_2O (0.69 mL, 0.65 g, 3.0 mmol), and DMAP (24 mg, 0.20 mmol). Glassy, amorphous, colorless solid (168 mg, 50%). Spectroscopic data agreed with that for **2a**, prepared via the earlier protocol. Furthermore, the identity of **8a** was confirmed by X-ray crystallography after crystallization from hexane.

***tert*-Butyl 4-Isopropyl-2-(4-methoxyphenyl)oxazol-5-ylcarbamate (8b).** Prepared from **5b** (1.16 g, 3.54 mmol), NMM (583

μL, 536 mg, 5.30 mmol), Boc_2O (2.44 mL, 2.32 g, 10.6 mmol), and DMAP (86 mg, 0.71 mmol): glassy, amorphous, colorless solid (0.81 g, 69%); δ_H (400 MHz, $CDCl_3$) 7.93 (dt, 2H, J = 2.5, 9.0), 6.94 (d, 2H, J = 9.0), 6.16 (s, 1H), 3.86 (s, 3H), 2.91 (septet, 1H, J = 7.0), 1.51 (br s, 9H), 1.29 (d, 6H, J = 7.0); δ_C (100 MHz, $CDCl_3$) 161.1, 158.1, 153.6, 139.8, 135.5, 127.9, 120.7, 114.0, 81.5, 55.3, 28.2, 25.8, 21.3; ν_{max} (solid)/cm^{-1} 3134, 2969, 1728, 1497, 1249, 1159, 1057, 1025, 910, 840, 750; m/z (ESI) 333 ([M + H]$^+$); HRMS found 333.1805 ($C_{18}H_{25}N_2O_4$ requires 333.1814).

***tert*-Butyl 4-Isopropyl-2-(thiophene-2-yl)oxazol-5-ylcarbamate (8c).** Prepared from **5c** (1.17 g, 3.85 mmol), NMM (645 μL, 584 mg, 5.78 mmol), Boc_2O (2.65 mL, 2.52 g, 11.6 mmol), and DMAP (93 mg, 0.77 mmol): thick, amorphous gum (0.80 g, 68%); δ_H (400 MHz, $CDCl_3$) 7.62 (dd, 1H, J = 1.0, 3.5), 7.40 (dd, 1H, J = 1.0, 5.0), 7.09 (dd, 1H, J = 4.0, 5.0), 6.14 (s, 1H), 2.91 (septet, 1H, J = 7.0), 1.51 (br s, 9H), 1.29 (d, 6H, J = 7.0); δ_C (100 MHz, $CDCl_3$) 154.3, 153.4, 140.0, 135.5, 130.5, 127.8, 127.7, 127.4, 81.7, 28.1, 25.8, 21.2; ν_{max} (solid)/cm^{-1} 3268, 2971, 1703, 1655, 1497, 1366, 1273, 1253, 1155, 1064, 1047, 1025, 729; m/z (ESI) 309 ([M + H]$^+$); HRMS, found 309.1277 ($C_{15}H_{21}N_2O_3S$ requires 309.1273).

***tert*-Butyl 2-(1,3-Dimethyl-1*H*-pyrazol-5-yl)-4-phenyloxazol-5-ylcarbamate (8d).** Prepared from **5d** (0.82 g, 2.34 mmol), NMM (392 μL, 355 mg, 3.51 mmol), Boc_2O (1.61 mL, 1.53 g, 7.02 mmol), and DMAP (57 mg, 0.47 mmol): greasy, off-white solid (345 mg, 42%); δ_H (400 MHz, $CDCl_3$) 7.85 (d, 2H, J = 7.5), 7.44 (t, 2H, J = 7.5), 7.36 (t, 1H, J = 7.5), 6.62−6.58 (m, 2H), 4.27 (s, 3H), 2.31 (s, 3H), 1.48 (br s, 9H); δ_C (100 MHz, $CDCl_3$) 152.9, 150.8, 147.6, 136.8, 130.9, 130.5, 128.6, 128.2, 126.3, 106.9, 82.4, 39.0, 28.1, 13.3; ν_{max} (solid)/cm^{-1} 3136, 2972, 2938, 1734, 1508, 1366, 1250, 1154, 730, 691; m/z (ESI) 355 ([M + H]$^+$); HRMS found 355.1786 ($C_{19}H_{23}N_4O_3$ requires 355.1770).

***tert*-Butyl 2-(Benzo[*b*]thiophene-2-yl)-4-benzyloxazol-5-ylcarbamate (8e).** Prepared from **5e** (1.13 g, 2.81 mmol), NMM (471 μL, 426 mg, 4.22 mmol), Boc_2O (1.94 mL, 1.84 g, 8.43 mmol), and DMAP (68 mg, 0.56 mmol): cream-colored powder (655 mg, 57%); δ_H (400 MHz, DMSO-d_6) 9.55 (s, 1H), 8.06−7.99 (m, 2H), 7.97−7.92 (m, 1H), 7.48−7.41 (m, 2H), 7.34−7.28 (m, 4H), 7.26−7.19 (m, 1H), 3.79 (s, 2H), 1.46 (br s, 9H); δ_C (100 MHz, DMSO-d_6) 153.4, 140.7, 139.82, 139.76, 138.9, 129.3, 129.2, 128.8, 126.7, 126.6, 125.7, 125.3, 124.7, 123.2, 80.9, 31.4, 28.3; ν_{max} (solid)/cm^{-1} 3238, 3172, 2936, 1720, 1655, 1331, 1247, 1154, 1036, 1008, 770, 744, 704, 693; m/z (ESI) 407 ([M + H]$^+$); HRMS found 407.1429 ($C_{23}H_{23}N_2O_3S$ requires 407.1429).

***tert*-Butyl 2-(4-Chlorobenzyl)-4-(thiophene-2-yl)oxazol-5-ylcarbamate (8f).** Prepared from **5f** (0.88 g, 2.28 mmol), NMM (376 μL, 346 mg, 3.42 mmol), Boc_2O (1.57 mL, 1.49 g, 6.84 mmol), and DMAP (55 mg, 0.46 mmol): bright yellow, glassy, amorphous solid (382 mg, 43%); δ_H (400 MHz, $CDCl_3$) 7.40−7.37 (m, 1H), 7.34−7.25 (m, 5H), 7.08 (dd, 1H, J = 3.5, 5.0), 6.25 (s, 1H), 4.08 (s, 2H), 1.59−1.37 (br s, 9H); δ_C (100 MHz, $CDCl_3$) 159.5, 152.8, 136.1, 133.5, 133.1, 132.8, 130.2, 128.9, 127.6, 125.5, 124.9, 82.3, 34.3, 28.1; ν_{max} (solid)/cm^{-1} 3233, 2978, 1711, 1492, 1368, 1245, 1154, 1016, 699; m/z (ESI) 391 ([M + H]$^+$); HRMS found 391.0897 ($C_{19}H_{20}ClN_2O_3S$ requires 391.0883).

***tert*-Butyl *N*-2,4-Diphenyloxazol-5-yl-2,2,2-trifluoroacetimidate (10a).** Isolated during preparation of **8a**: bright yellow oil, which crystallized to give a pale yellow solid on standing (42 mg, 11%): δ_H (400 MHz, $CDCl_3$) 8.13−8.08 (m, 2H), 8.03 (d, 2H, J = 7.5), 7.54−7.43 (m, 5H), 7.35 (t, 1H, J = 7.5), 1.71 (s, 9H); δ_C (100 MHz, $CDCl_3$) 156.6, 140.8, 131.6, 130.3, 128.8, 128.4, 127.6, 127.3, 126.9, 126.2, 116.3 (q, J = 286 Hz), 86.3, 28.0; ν_{max} (solid)/cm^{-1} 2978, 1658, 1326, 1193, 1152, 1134, 881, 779, 711, 692; m/z (ESI) 389 ([M + H]$^+$); HRMS found 389.1490 ($C_{21}H_{20}F_3N_2O_2$ requires 389.1477).

***tert*-Butyl 2,2,2-Trifluoro-*N*-(4-isopropyl-2-(4-methoxyphenyl)oxazol-5-yl)acetimidate (10b).** Isolated during preparation of **8b**: bright yellow oil (35 mg, 3%); NMR showed a mixture of one major and one minor component, possibly (*E*)- and (*Z*)-isomers; δ_H (400 MHz, $CDCl_3$) 7.95 (d, 2H, J = 9.0), 6.96 (d, 2H, J = 9.0), [3.88 (s, 0.5H) and 3.87 (s, 2.5H)], [3.09 (septet, 0.85H, J = 7.0 and 2.86 (septet, 0.15H, J = 7.0)], [1.63 (s, 6.5H) and 1.47 (s, 2.5H)], [1.32 (d, 5.2H, J = 7.0) and 1.28 (d, 0.8H, J = 7.0)]; δ_C (100 MHz, $CDCl_3$) 161.2, 157.2, 141.1 (q, J = 40.0), 150.0, 138.9, 127.7, 120.6, 116.6 (q, J = 283), 114.1, [84.8 and 83.7], 55.3, [27.9 and 27.8], 25.8, [21.9 and 20.8]; m/z (ESI) 385 ([M + H]$^+$); HRMS found 385.1725 ($C_{19}H_{24}F_3N_2O_3$ requires 385.1739).

***tert*-Butyl 2,2,2-Trifluoro-*N*-(4-isopropyl-2-(thiophene-2-yl)oxazol-5-yl)acetimidate (10c).** Isolated during preparation of **8c**: bright yellow oil (26 mg, 2%); δ_H (400 MHz, $CDCl_3$) 7.62 (dd, 1H, J = 1.5, 3.5), 7.40 (dd, 1H, J = 1.0, 5.0), 7.10 (dd, 1H, J = 3.5, 5.0), 3.08 (septet, 1H, J = 7.0), 1.63 (s, 9H), 1.32 (d, 6H, J = 7.0); δ_C (100 MHz, $CDCl_3$) 153.3, 141.8 (q, J = 38.0), 139.7, 138.9, 130.4, 127.9, 127.3, 116.5 (q, J = 284), 85.2, 27.9, 25.8, 21.8; m/z (ESI) 383 ([M + Na]$^+$); HRMS found 383.1024 ($C_{16}H_{19}F_3N_2NaO_2S$ requires 383.1017).

***tert*-Butyl *N*-2-(1,3-Dimethyl-1*H*-pyrazol-5-yl)-4-phenyloxazol-5-yl-2,2,2-trifluoroacetimidate (10d).** Isolated during preparation of **8d**: pale yellow powder (138 mg, 15%); δ_H (400 MHz, $CDCl_3$) 8.01−7.94 (m, 2H), 7.49−7.40 (m, 2H), 7.34 (tt, 1H, J = 2.5, 7.0), 6.59 (s, 1H), 4.29 (s, 3H), 2.33 (s, 3H), 1.70 (s, 9H); δ_C (100 MHz, $CDCl_3$) 149.3, 147.7, 140.4, 131.3, 130.8, 128.4, 127.7, 126.7, 116.2 (q, J = 286), 106.8, 86.8, 38.9, 28.0, 13.3; ν_{max} (solid)/cm^{-1} 2993, 1653, 1508, 1335, 1193, 1164, 1131, 1074, 1008, 883, 773, 724, 691; m/z (ESI) 407 ([M + H]$^+$); HRMS, found 407.1679 ($C_{20}H_{22}F_3N_4O_2$ requires 407.1695).

***tert*-Butyl *N*-2-(Benzo[*b*]thiophene-2-yl)-4-benzyloxazol-5-yl-2,2,2-trifluoroacetimidate (10e).** Isolated during preparation of **8e**: greasy, pale yellow solid (51 mg, 4%); δ_H (400 MHz, $CDCl_3$) 7.89−7.81 (m, 3H), 7.44−7.38 (m, 2H), 7.37−7.30 (m, 4H), 7.24 (dt, 1H, J = 2.0, 7.0), 4.01 (s, 2H), 1.63 (s, 9H); δ_C (100 MHz, $CDCl_3$) 153.5, 143.2 (q, J = 40.0), 141.6, 140.5, 139.6, 138.8, 133.2, 129.7, 128.6, 128.5, 126.4, 125.8, 124.9, 124.5, 124.0, 122.5, 116.3 (q, J = 283), 85.8, 32.0, 27.9; ν_{max} (solid)/cm^{-1} 2980, 1677, 1584, 1330, 1125, 888, 836, 751, 708; m/z (ESI) 459 ([M + H]$^+$); HRMS found 459.1368 ($C_{24}H_{22}F_3N_2O_2S$ requires 459.1354).

***tert*-Butyl *N*-2-(4-Chlorobenzyl)-4-(thiophene-2-yl)oxazol-5-yl-2,2,2-trifluoroacetimidate (10f).** Isolated during preparation of **8f**: bright yellow oil (26 mg, 3%); δ_H (400 MHz, $CDCl_3$) 7.49 (s, 1H), 7.35−7.27 (m, 5H), 7.10 (dd, 1H, J = 4.0 Hz, 5.0 Hz), 4.08 (s, 2H), 1.67 (s, 9H); δ_C (100 MHz, $CDCl_3$) 158.0, 133.7, 133.5, 133.1, 130.2, 128.8, 127.5, 125.5, 124.9, 116.3 (q, J = 281), 86.6, 34.3, 27.9; ν_{max} (solid)/cm^{-1} 2982, 1652, 1492, 1326, 1154, 1129, 875, 836, 766, 689; m/z (ESI) 443 ([M + H]$^+$); HRMS found 443.0798 ($C_{20}H_{19}ClF_3N_2O_2S$ requires 443.0808).

5-(Bis(*tert*-butyloxycarbonyl)amino)-4-isopropyl-2-(thiophene-2-yl)oxazole (13c). This product was also isolated during preparation of **8c**: sweet-smelling, pale yellow oil (101 mg, 6%); δ_H (400 MHz, $CDCl_3$) 7.64 (dd, 1H, J = 1.0, 3.5), 7.43 (dd, 1H, J = 1.0, 5.0), 7.12 (dd, 1H, J = 3.5, 5.0), 2.85 (septet, 1H, J = 7.0), 1.47 (s, 18H), 1.26 (d, 6H, J = 7.0); δ_C (100 MHz, $CDCl_3$) 154.6, 149.9, 139.8, 136.4, 130.3, 128.0, 127.8, 127.5, 83.9, 27.8, 25.8, 20.8; ν_{max} (solid)/cm^{-1} 2976, 1755, 1369, 1250, 1142, 1117, 1027, 866, 846, 777, 725; m/z (ESI) 409 ([M + H]$^+$); HRMS found 409.1809 ($C_{20}H_{29}N_2O_5S$ requires 409.1797).

***N-tert*-Butyl-*N*′-(2,4-diphenyloxazol-5-yl)acetimidamide (11).** Trifluoroacetamide **5a** (332 mg, 1 mmol) was dissolved in dry acetonitrile (7 mL) under N_2, and then NMM (165 μL, 149 mg, 1.5 mmol), Boc_2O (0.69 mL, 0.65 g, 3.0 mmol), and DMAP (24 mg, 0.20 mmol) were added. The reaction mixture was stirred at rt for 24 h and then evaporated, and the residue was redissolved in CH_2Cl_2. This solution was stirred vigorously with satd NH_4Cl (15 mL) for 10 min, and then the organic layer separated using a liquid−liquid extraction column (20 mL loading capacity) and evaporated. The crude material was purified by column on neutral alumina, eluted with 2.5−5−10−15−25−35% EtOAc−hexane, affording **11** as a thick yellow gum, which was crystallized from CH_2Cl_2_-hexane (160 mg, 48%): δ_H (400 MHz, $CDCl_3$) 8.09−8.04 (m, 4H), 7.49−7.37 (m, 5H), 7.25−7.19 (m, 1H), 4.78 (s, 1H), 2.12 (s, 3H), 1.57 (s, 9H); δ_C (100 MHz, $CDCl_3$) 158.0, 154.0, 150.0, 133.6, 129.0, 128.6, 128.3, 128.2, 125.6, 125.5, 123.0, 52.4, 28.9, 21.9; ν_{max} (solid)/cm^{-1} 3422, 2967, 1702, 1666, 1596, 1581, 1517, 1488, 1464, 1447, 1394, 1288, 1212, 1196, 770, 702, 692, 669; *m/z* (ESI) 334 ([M + H]$^+$); HRMS found 334.1910 ($C_{21}H_{24}N_3O$ requires 334.1919).

1-(Isocyanomethyl)-2,4-dimethoxybenzene (15). A mixture of ethyl formate (5.31 mL, 4.89 g, 66 mmol) and 2,4-dimethoxybenzylamine (8.26 mL, 9.20 g, 55 mmol) was stirred at 40 °C overnight. The precipitate was collected by filtration, washed several times with hexane, and then dried to give crude *N*-(2,4-dimethoxybenzyl)formamide (10.14 g, 95%) which was used in the next step without further purification. The formamide (10.12 g, 51.9 mmol) was dissolved in dry CH_2Cl_2 (120 mL) under N_2, triethylamine (21.7 mL, 15.8 g, 156 mmol) was added, and the solution was cooled to 0 °C. Phosphorus oxychloride (4.84 mL, 7.96 g, 52 mmol) was introduced to the reaction mixture dropwise over 10 min, and then stirring was continued for 1 h, at which point 1.1 M Na_2CO_3 (47 mL) was added. The mixture was stirred vigorously for an additional 1 h and then transferred to a separating funnel. The organic layer was separated and the aqueous phase extracted with additional CH_2Cl_2 (100 mL). The combined extracts were dried over $MgSO_4$ and evaporated, and the residue was purified by flash column chromatography on silica, eluted with 5−10−20% EtOAc−hexane, yielding **15** as a white solid (5.70 g, 62%): δ_H (400 MHz, $CDCl_3$) 7.30 (d, 1H, *J* = 8.5), 6.53 (dd, 1H, *J* = 2.5, 8.5), 6.48 (d, 1H, *J* = 2.5), 4.57 (s, 2H), 3.85 (s, 3H), 3.84 (s, 3H); δ_C (100 MHz, $CDCl_3$) 161.2, 157.5, 156.3 (t, *J* = 5.5), 128.8, 113.5, 104.2, 98.5, 55.47, 55.45, 40.7 (t, *J* = 7.0); ν_{max} (solid)/cm^{-1} 2948, 2835, 2156, 1619, 1592, 1506, 1265, 1214, 1158, 1117, 1045, 1029, 954, 917, 834, 779; *m/z* (EI) 177 ([M]$^+$); HRMS found 177.0790 ($C_{10}H_{11}NO_2$ requires 177.0790).

2-(4-Chlorophenyl)-*N*-(2,4-dimethoxybenzyl)-*N*-(2-(2,4-dimethoxybenzylamino)-2-oxo-1-(thiophene-2-yl)ethyl)acetamide (14). 2,4-Dimethoxybenzylamine (2.25 mL, 2.51 g, 15 mmol) was added to a solution of thiophene-2-carboxaldehyde (1.40 mL, 1.68 g, 15 mmol) in methanol (6 mL) with stirring. After 30 min, additional methanol (6 mL) was added, together with 4-chlorophenylacetic acid (2.56 g, 15 mmol) and isocyanide **15** (2.66 g, 15 mmol). After the mixture was stirred for a further 18 h, solvent was evaporated and the residue chromatographed on silica gel, eluting with 0−1−2% MeOH−CH_2Cl_2, to provide **14** as a pale yellow foam (4.13 g, 45%): δ_H (400 MHz, $CDCl_3$) 7.28−7.23 (m, 3H), 7.18−7.12 (m, 3H), 7.03 (d, 1H, *J* = 9.0), 6.95−6.91 (m, 1H), 6.87 (dd, 1H, *J* = 3.5, 5.0), 6.47 (t, 1H, *J* = 6.0), 6.44−6.39 (m, 2H), 6.37−6.32 (m, 2H), 5.68 (s, 1H), 4.55 (s, 2H), 4.36 (t, 2H, *J* = 5.5), 3.81 (s, 3H), 3.79 (s, 3H), 3.71 (s, 2H), 3.69 (s, 3H), 3.67 (s, 3H); δ_C (100 MHz, $CDCl_3$) 171.7, 168.0, 160.4, 158.5, 157.8, 137.1, 133.5, 132.5, 130.5, 130.2, 129.2, 128.8, 128.6, 127.4, 126.1, 118.5, 116.9, 103.8, 98.5, 98.4, 59.4, 55.39, 55.37, 55.1, 53.5, 46.8, 40.0, 39.4; ν_{max} (solid)/cm^{-1} 3322, 2937, 2834, 1613, 1588, 1506, 1206, 1155, 1118, 1032, 828, 799, 706; *m/z* (ESI) 631 ([M + Na]$^+$); HRMS found 631.1629 ($C_{32}H_{33}ClN_2O_6SNa$ requires 631.1646).

2-Amino-2-(thiophene-2-yl)acetonitrile (17). Thiophene-2-carboxaldehyde (3.14 mL, 3.77 g, 33.6 mmol) was dissolved in 7 N NH_3−MeOH (160 mL) and the solution cooled to 0 °C. Trimethylsilyl cyanide (5.0 g, 50.4 mmol) was added dropwise over 5 min, and then after an extra 15 min, cooling was removed and the reaction mixture heated at 45 °C for 5 h. The solution was evaporated to dryness and then flash column chromatographed on silica gel, eluting with 0−2−5% MeOH−CH_2Cl_2, to give **17** as a brownish oil (2.81 g, 60%): δ_H (400 MHz, $CDCl_3$) 7.37 (dd, 1H, *J* = 1.0, 5.0), 7.27−7.24 (m, 1H), 7.03 (dd, 1H, *J* = 3.5, 5.0), 5.14 (s, 1H), 2.15 (s, 2H); δ_C (100 MHz, $CDCl_3$) 139.7, 127.0, 126.7, 126.0, 120.1, 43.4; *m/z* (EI) 138 ([M]$^+$); HRMS found 138.0249 ($C_6H_6N_2S$ requires 138.0252).

2-(4-Chlorophenyl)-*N*-(cyano(thiophene-2-yl)methyl)acetamide (16). NEM (1.48 mL, 1.34 g, 11.7 mmol), 4-chlorophenylacetyl chloride (1.56 mL, 2.02 g, 10.7 mmol), and DMAP (117 mg, 0.97 mmol) were added to a solution of α-aminonitrile **17** (1.34 g, 9.71 mmol) in anhydrous THF (55 mL). After 90 min, the solvent was evaporated and the residue triturated thoroughly with water, collected by filtration, washed with water (×2), 1 M HCl (×2), water, satd $NaHCO_3$ (×2), water, and ether (×2), and dried. Compound **16** was obtained as a yellowish-brown solid (2.36 g, 84%): δ_H (400 MHz, DMSO-d_6) 9.58 (d, 1H, *J* = 7.5), 7.65−7.60 (m, 1H), 7.39 (d, 2H, *J* = 8.5), 7.29 (d, 2H, *J* = 8.5), 7.24 (d, 1H, *J* = 3.5), 7.06 (dd, 1H, *J* = 3.5, 5.0), 6.41 (d, 1H, *J* = 7.0), 3.55 (s, 2H); δ_C (100 MHz, DMSO-d_6) 169.6, 136.6, 134.3, 131.4, 130.9, 128.2, 127.6, 127.3, 127.0, 117.9, 40.7, 39.4; ν_{max} (solid)/cm^{-1} 3265, 1651, 1518, 1492, 1229, 792, 701, 681; *m/z* (ESI) 313 ([M + Na]$^+$); HRMS found 313.0174 ($C_{14}H_{11}ClN_2NaOS$ requires 313.0178).

***N*-(2-(4-Chlorobenzyl)-4-(thiophene-2-yl)oxazol-5-yl)-2,2,2-trifluoroacetamide (5f). Method A, from 14.** Compound **14** (2.63 g, 4.33 mmol) was dissolved in CH_2Cl_2 (12 mL), and then TFA (12 mL) was added, followed 20 min later by addition of TFAA (18 mL). After an additional 45 min, the mixture was evaporated and the residue taken up in CH_2Cl_2. The solution was washed with satd $NaHCO_3$, dried over $MgSO_4$, and evaporated. The crude material was recrystallized from $CHCl_3$−hexane to give **5f** as a pale brown powder (1.18 g, 71%): δ_H (400 MHz, DMSO-d_6) 12.11 (s, 1H), 7.64 (d, 1H, *J* = 5.0), 7.45 (d, 2H, *J* = 8.5), 7.38 (d, 2H, *J* = 8.5), 7.26 (d, 1H, *J* = 3.5), 7.18−7.13 (m, 1H), 4.23 (s, 2H); δ_C (100 MHz, DMSO-d_6) 160.5, 156.3 (q, *J* = 38.0), 134.1, 133.5, 131.8, 131.6, 130.7, 128.7, 128.0, 127.6, 126.8, 125.1, 115.4 (q, *J* = 287), 32.9; ν_{max} (solid)/cm^{-1} 3224, 3074, 1722, 1584, 1556, 1490, 1210, 1151, 910, 706, 685; *m/z* (ESI) 387 ([M + H]$^+$); HRMS,found 387.0184 ($C_{16}H_{11}ClF_3N_2O_2S$ requires 387.0182).

Method B, from 16. α-Acylaminonitrile **16** (2.24 g, 7.72 mmol) was stirred in TFAA (20 mL) and DCM (20 mL) for 45 min and then evaporated. Workup and recrystallization as above afforded **5f** as fine, pale brown needles (1.55 g, 52%). Spectroscopic data were in agreement with those for the sample synthesized from **14**.

Oxazole-5-amides (1a−q). General Procedure. The appropriate *N*-Boc compound **8a−f** was dissolved in dry CH_2Cl_2 (7.5 mL mmol^{-1}) under N_2, and then $^iPr_2NEt$ (1.15 equiv), an acid chloride (1.1 equiv), and DMAP (catalytic amount) were added in sequence. After 3 h, TFA was added up to a final concentration of 20% TFA−CH_2Cl_2, and then stirring was continued at rt for another 4 h. The reaction mixture was then evaporated, redissolved in CH_2Cl_2 (15 mL), and stirred vigorously with satd $NaHCO_3$ (15 mL) for 10 min. The organic layer was collected by passing through a liquid−liquid extraction column (20 mL loading capacity), evaporated, and the residue purified by column chromatography on neutral alumina, eluted with 0−1−2% MeOH−DCM, providing the pure amide derivative. Yields were as recorded in Table 3.

***N*-(4-Isopropyl-2-(4-methoxyphenyl)oxazol-5-yl)furan-2-carboxamide (1a):** δ_H (400 MHz, $CDCl_3$) 8.06 (s, 1H), 7.91 (d, 2H, *J* = 9.0), 7.54 (s, 1H), 7.31−7.25 (m, 1H), 6.93 (d, 2H, *J* = 9.0), 6.56 (s, 1H), 3.84 (s, 3H), 2.92 (septet, 1H, *J* = 7.0, 1.29 (d, 6H, *J* = 7.0); δ_C (100 MHz, $CDCl_3$) 161.2, 158.6, 157.4, 146.8, 145.0, 140.1, 133.9, 127.9, 120.5, 116.5, 114.0, 112.6, 55.3, 25.8, 21.3; ν_{max} (solid)/cm^{-1} 2964, 1676, 1649, 1613, 1585, 1494, 1485, 1287, 1251, 1172, 1025, 836, 748; *m/z* (ESI) 327 ([M + H]$^+$); HRMS found 327.1333 ($C_{18}H_{19}N_2O_4$ requires 327.1345).

***N*-(4-Isopropyl-2-(4-methoxyphenyl)oxazol-5-yl)-2-(trifluoromethyl)benzamide (1b).** Further purification by preparative HPLC was required (Alltima HP C18 HL 5 μm column, 22 × 150 mm; isocratic conditions, 60:40 MeCN−H_2O; flow rate 20 mL min^{-1}; UV detection @ 254 nm): δ_H (400 MHz, DMSO-d_6) 10.69 (s, 1H), 7.93−7.81 (m, 4H), 7.77 (d, 2H, *J* = 7.5), 7.09 (d, 2H, *J* = 9.0), 3.84 (s, 3H), 2.89 (septet, 1H, *J* = 7.0), 1.24 (d, 6H, *J* = 7.0); δ_C (125 MHz, DMSO-d_6) 167.3, 160.9, 157.1, 138.1, 135.5, 134.7, 132.7, 130.6, 128.5, 127.3, 126.5 (q, *J* = 4.0), 126.1 (q, *J* = 31.5), 123.7 (q, *J* = 273), 119.6, 114.5, 55.3, 24.8, 21.3; ν_{max}

(solid)/cm^{-1} 3131, 2969, 1706, 1495, 1311, 1254, 1172, 1140, 1031, 843, 767; *m/z* (ESI) 405 ([M + H]$^+$); HRMS found 405.1435 ($C_{21}H_{20}F_3N_2O_3$ requires 405.1426).

***N*-(4-Isopropyl-2-(4-methoxyphenyl)oxazol-5-yl)-4-methoxybenzamide (1c):** δ_H (400 MHz, $CDCl_3$) 8.29 (br s, 1H), 7.90−7.81 (m, 4H), 6.90 (d, 2H, J = 8.5), 6.84 (d, 2H, J = 8.5), 3.83 (s, 3H), 3.77 (s, 3H), 2.87 (septet, 1H, J = 7.0), 1.25 (d, 6H, J = 7.0); δ_C (100 MHz, $CDCl_3$) 162.9, 161.1, 158.4, 139.8, 135.4, 129.6, 127.8, 124.9, 120.5, 114.0, 113.9, 55.37, 55.35, 25.8, 21.3; ν_{max} (solid)/cm^{-1} 3258, 2968, 1666, 1650, 1605, 1500, 1283, 1253, 1180, 1024, 848, 836, 766, 746; *m/z* (ESI) 367 ([M + H]$^+$); HRMS found 367.1657 ($C_{21}H_{23}N_2O_4$ requires 367.1658).

***N*-(4-Isopropyl-2-(thiophene-2-yl)oxazol-5-yl)furan-2-carboxamide (1d):** δ_H (400 MHz, $CDCl_3$) 7.86 (s, 1H), 7.65−7.62 (m, 1H), 7.58−7.56 (m, 1H), 7.43−7.40 (m, 1H), 7.31 (br s, 1H), 7.12−7.08 (m, 1H), 6.62−6.59 (m, 1H), 2.93 (septet, 1H, J = 7.0), 1.31 (d, 6H, J = 7.0); δ_C (100 MHz, $CDCl_3$) 157.1, 154.8, 146.7, 145.0, 140.5, 133.8, 130.3, 128.0, 127.8, 127.6, 116.8, 112.8, 25.8, 21.2; ν_{max} (solid)/cm^{-1} 3219, 2971, 1673, 1645, 1585, 1507, 1290, 1055, 1016, 760, 737, 726; *m/z* (ESI) 303 ([M + H]$^+$); HRMS found 303.0798 ($C_{15}H_{15}N_2O_3S$ requires 303.0803).

***N*-(4-Isopropyl-2-(thiophene-2-yl)oxazol-5-yl)-2-(trifluoromethyl)benzamide (1e):** δ_H (400 MHz, DMSO-d_6, 50 °C) 10.59 (s, 1H), 7.86 (d, 1H, J = 8.0), 7.82 (t, 1H, J = 7.5), 7.77−7.71 (m, 3H), 7.63 (d, 1H, J = 3.5), 7.19 (t, 1H, J = 4.5), 2.89 (septet, 1H, J = 7.0), 1.22 (d, 6H, J = 7.0); δ_C (125 MHz, DMSO-d_6, 50 °C) 167.0, 153.2, 138.2, 135.5, 134.5, 132.4, 130.4, 129.2, 129.0, 128.3, 128.1, 127.3, 126.33−126.24 (m), 126.0 (q, J = 31.5), 123.4 (q, J = 272), 24.6, 20.9; ν_{max} (solid)/cm^{-1} 3148, 2966, 1708, 1652, 1515, 1488, 1313, 1267, 1166, 1125, 1106, 1052, 1034, 765, 717; *m/z* (ESI) 381 ([M + H]$^+$); HRMS found 381.0902 ($C_{18}H_{16}F_3N_2O_2S$ requires 381.0885).

***N*-(4-Isopropyl-2-(thiophene-2-yl)oxazol-5-yl)-4-methoxybenzamide (1f):** δ_H (400 MHz, $CDCl_3$) 8.17 (s, 1H), 7.85 (d, 2H, J = 8.0), 7.56 (d, 1H, J = 3.0), 7.39−7.36 (m, 1H), 7.06 (dd, 1H, J = 4.0, 5.0), 6.88 (d, 2H, J = 9.0), 3.81 (s, 3H), 2.89 (septet, 1H, J = 7.0), 1.25 (d, 6H, J = 7.0); δ_C (100 MHz, $CDCl_3$) 166.7, 163.0, 154.6, 140.1, 135.4, 130.3, 129.7, 127.9, 127.8, 127.5, 124.8, 113.9, 55.4, 25.8, 21.3; ν_{max} (solid)/cm^{-1} 3232, 2966, 1667, 1641, 1604, 1579, 1485, 1253, 1175, 1022, 843, 765, 704; *m/z* (ESI) 343 ([M + H]$^+$); HRMS, found 343.1118 ($C_{18}H_{19}N_2O_3S$ requires 343.1116).

***N*-(2-(1,3-Dimethyl-1*H*-pyrazol-5-yl)-4-phenyloxazol-5-yl)furan-2-carboxamide (1g):** δ_H (400 MHz, $CDCl_3$) 7.84−7.79 (m, 2H), 7.57 (br s, 1H), 7.40 (t, 2H, J = 7.5), 7.33 (t, 2H, J = 7.5), 6.60 (dd, 1H, J = 1.5, 3.5), 6.56 (s, 1H), 4.25 (s, 3H), 2.29 (s, 3H); δ_C (100 MHz, $CDCl_3$) 157.2, 151.3, 147.6, 146.5, 145.4, 135.3, 133.1, 130.7, 130.2, 128.7, 128.3, 126.4, 117.1, 112.8, 107.0, 39.0, 13.3; ν_{max} (solid)/cm^{-1} 3123, 2946, 1674, 1585, 1506, 1448, 1279, 1075, 1007, 759, 730, 693, 679; *m/z* (ESI) 349 ([M + H]$^+$); HRMS found 349.1302 ($C_{19}H_{17}N_4O_3$ requires 349.1301).

***N*-(2-(1,3-Dimethyl-1*H*-pyrazol-5-yl)-4-phenyloxazol-5-yl)-4-methoxybenzamide (1h):** δ_H (400 MHz, $CDCl_3$) 8.28 (s, 1H), 7.89 (d, 2H, J = 8.5), 7.82−7.77 (m, 2H), 7.37 (t, 2H, J = 8.0), 7.30 (tt, J = 2.0, 7.5), 6.93 (d, 2H, J = 8.5), 6.51 (s, 1H), 4.23 (s, 3H), 3.87 (s, 3H), 2.27 (s, 3H); δ_C (100 MHz, $CDCl_3$) 166.4, 163.3, 151.2, 147.6, 136.6, 132.8, 130.8, 130.4, 129.8, 128.7, 128.2, 126.3, 124.5, 114.1, 107.0, 55.5, 39.0, 13.3; ν_{max} (solid)/cm^{-1} 3276, 1661, 1636, 1602, 1454, 1439, 1255, 1200, 1175, 1025, 1005, 994, 846, 765, 730, 694; *m/z* (ESI) 389 ([M + H]$^+$); HRMS found 389.1627 ($C_{22}H_{21}N_4O_3$ requires 389.1614).

4-Chloro-*N*-(2-(1,3-dimethyl-1*H*-pyrazol-5-yl)-4-phenyloxazol-5-yl)benzamide (1i): δ_H (400 MHz, DMSO-d_6) 11.14 (s, 1H), 8.09 (d, 2H, J = 8.0), 7.87−7.81 (m, 2H), 7.69 (d, 2H, J = 7.5), 7.47 (t, 2H, J = 7.0), 7.37 (t, 1H, J = 7.5), 6.71 (s, 1H), 4.22 (s, 3H), 2.22 (s, 3H); δ_C (100 MHz, DMSO-d_6) 165.8, 150.6, 146.8, 137.9, 137.7, 131.5, 131.0, 130.0, 129.9, 129.8, 128.9, 128.8, 128.2, 125.8, 106.7, 38.7, 13.0; ν_{max} (solid)/cm^{-1} 3226, 1663, 1623, 1592, 1508, 1486, 1280, 1092, 1079, 1012, 849, 754, 724, 689, 673; *m/z* (ESI) 391 ([M + H]$^+$); HRMS found 391.0977 ($C_{21}H_{16}ClN_4O_2$ requires 391.0962).

***N*-(2-(1,3-Dimethyl-1*H*-pyrazol-5-yl)-4-phenyloxazol-5-yl)-3-methylbutanamide (1j):** δ_H (400 MHz, DMSO-d_6) 10.41 (s, 1H), 7.79 (d, 2H, J = 7.0), 7.45 (t, 2H, J = 7.5), 7.36 (t, 1H, J = 7.5), 6.64 (s, 1H), 4.17 (s, 3H), 2.30 (d, 2H, J = 7.0), 2.20 (s, 3H), 2.09 (septet, 1H, J = 7.0), 0.96 (d, 6H, J = 7.0); δ_C (100 MHz, DMSO-d_6) 172.6, 150.2, 146.7, 138.1, 130.8, 130.1, 129.9, 128.6, 128.1, 125.8, 106.6, 44.3, 25.4, 22.2, 12.9; ν_{max} (solid)/cm^{-1} 3238, 2954, 1670, 1635, 1508, 1480, 1370, 1279, 1216, 1076, 1010, 766, 725, 687; *m/z* (ESI) 339 ([M + H]$^+$); HRMS found 339.1833 ($C_{19}H_{23}N_4O_2$ requires 339.1821).

***N*-(2-(Benzo[*b*]thiophene-2-yl)-4-benzyloxazol-5-yl)furan-2-carboxamide (1k):** δ_H (400 MHz, $CDCl_3$) 7.89−7.80 (m, 3H), 7.70 (br s, 1H), 7.53−7.49 (m, 1H), 7.44−7.37 (m, 2H), 7.34 (d, 2H, J = 7.5), 7.31−7.24 (m, 3H), 7.19 (t, 1H, J = 7.5), 6.58 (dd, 1H, J = 1.5, 3.5), 4.00 (s, 2H); δ_C (100 MHz, $CDCl_3$) 156.5, 154.7, 146.5, 145.0, 140.4, 139.5, 137.7, 137.2, 133.6, 129.5, 128.9, 128.5, 126.5, 125.9, 124.9, 124.6, 124.4, 122.5, 116.7, 112.7, 32.4; ν_{max} (solid)/cm^{-1} 3360, 1697, 1656, 1583, 1488, 1454, 1272, 1163, 1014, 746, 706, 695; *m/z* (ESI) 401 ([M + H]$^+$); HRMS found 401.0953 ($C_{23}H_{17}N_2O_3S$ requires 401.0960). The identity of **1k** was also confirmed by X-ray crystallography, following crystallization from CH_2Cl_2−hexane.

***N*-(2-(Benzo[*b*]thiophene-2-yl)-4-benzyloxazol-5-yl)-4-methoxybenzamide (1l).** δ_H (400 MHz, DMSO-d_6) 10.58 (s, 1H), 8.09−7.93 (m, 5H), 7.50−7.42 (m, 2H), 7.37−7.26 (m, 4H), 7.24−7.17 (m, 1H), 7.14−7.08 (m, 2H), 3.91−3.81 (m, 5H); δ_C (100 MHz, DMSO-d_6) 166.0, 162.6, 153.3, 140.1, 139.4, 139.3, 138.4, 132.6, 130.0, 128.8, 128.3, 126.2, 125.2, 124.8, 124.6, 124.3, 122.7, 113.9, 55.5, 31.1; ν_{max} (solid)/cm^{-1} 3214, 1660, 1638, 1604, 1477, 1254, 1172, 1022, 840, 745, 699; *m/z* (ESI) 441 ([M + H]$^+$); HRMS found 441.1276 ($C_{26}H_{21}N_2O_3S$ requires 441.1273).

***N*-(2-(Benzo[*b*]thiophene-2-yl)-4-benzyloxazol-5-yl)-4-chlorobenzamide (1m):** δ_H (400 MHz, DMSO-d_6) 10.83 (s, 1H), 8.07−7.93 (m, 5H), 7.66 (d, 2H, J = 8.5), 7.49−7.42 (m, 2H), 7.34−7.26 (m, 4H), 7.23−7.17 (m, 1H), 3.87 (s, 2H); δ_C (100 MHz, DMSO-d_6) 165.7, 153.4, 139.6, 139.4, 139.3, 138.2, 137.4, 132.6, 131.3, 129.9, 128.76, 128.72, 128.3, 126.2, 125.2, 124.9, 124.4, 122.7, 31.1; ν_{max} (solid)/cm^{-1} 3221, 1664, 1641, 1477, 1296, 1277, 1258, 1093, 1015, 841, 746, 705, 695, 680, 649; *m/z* (ESI) 445 ([M + H]$^+$); HRMS found 445.0791 ($C_{25}H_{18}ClN_2O_2S$ requires 445.0778).

***N*-(2-(Benzo[*b*]thiophene-2-yl)-4-benzyloxazol-5-yl)-3-methylbutanamide (1n):** δ_H (400 MHz, DMSO-d_6) 10.24 (s, 1H), 8.07−7.92 (m, 3H), 7.50−7.41 (m, 2H), 7.35−7.26 (m, 4H), 7.25−7.18 (m, 1H), 3.78 (s, 2H), 2.25 (d, 2H, J = 7.0), 2.15−2.04 (m, 1H), 0.97 (d, 6H, J = 6.5); δ_C (100 MHz, DMSO-d_6) 172.8, 153.5, 140.3, 139.8, 139.7, 138.9, 132.2, 129.3, 129.2, 128.8, 126.7, 126.6, 125.7, 125.3, 124.6, 123.2, 44.7, 31.5, 25.9, 22.7; ν_{max} (solid)/cm^{-1} 3231, 2960, 1668, 1646, 1511, 1261, 838, 746, 692, 649, 600; *m/z* (ESI) 391 ([M + H]$^+$); HRMS found 391.1484 ($C_{23}H_{23}N_2O_2S$ requires 391.1480).

***N*-(2-(4-Chlorobenzyl)-4-(thiophene-2-yl)oxazol-5-yl)furan-2-carboxamide (1o):** δ_H (400 MHz, $CDCl_3$) 7.91 (s, 1H), 7.57 (s, 1H), 7.38−7.27 (m, 7H), 7.06 (dd, 1H, J = 3.5, 5.0), 6.64−6.60 (m, 1H), 4.12 (s, 2H); δ_C (100 MHz, $CDCl_3$) 160.4, 157.5, 146.9, 145.7, 134.9, 133.8, 133.6, 132.9, 130.7, 129.3, 128.1, 126.1, 125.5, 117.5, 113.3, 34.8; ν_{max} (solid)/cm^{-1} 3244, 1665, 1509, 1491, 1464, 1298, 1185, 1022, 763, 704; *m/z* (ESI) 385 ([M + H]$^+$); HRMS found 385.0399 ($C_{19}H_{14}ClN_2O_3S$ requires 385.0414).

***N*-(2-(4-Chlorobenzyl)-4-(thiophene-2-yl)oxazol-5-yl)-4-methoxybenzamide (1p):** δ_H (400 MHz, DMSO-d_6) 10.56 (s, 1H), 8.00 (d, 2H, J = 8.5), 7.53 (d, 1H, J = 5.5), 7.44 (d, 2H, J = 8.5), 7.39 (d, 2H, J = 8.5), 7.28−7.25 (m, 1H), 7.13−7.07 (m, 3H), 4.21 (s, 2H), 3.86 (s, 3H); δ_C (100 MHz, DMSO-d_6) 166.8, 163.5, 160.6, 138.2, 135.3, 133.6, 132.6, 131.6, 130.8, 129.5, 128.6, 128.3, 126.9, 125.4, 125.2, 114.9, 56.4, 34.0; ν_{max} (solid)/cm^{-1} 3214, 1663, 1606, 1491, 1256, 1182, 1016, 836, 690, 605; *m*/*z* (ESI) 425 ([M + H]$^+$); HRMS found 425.0713 ($C_{22}H_{18}ClN_2O_3S$ requires 425.0727).

***N*-(2-(4-Chlorobenzyl)-4-(thiophene-2-yl)oxazol-5-yl)-3-methylbutanamide (1q):** δ_H (400 MHz, DMSO-d_6) 10.17 (s, 1H), 7.55 (dd, 1H, J = 1.0, 5.0), 7.45−7.41 (m, 2H), 7.36 (d, 2H, J = 8.5), 7.26 (dd, 1H, J = 1.0, 3.5), 7.11 (dd, 1H, J = 3.5, 5.0), 4.16 (s, 2H), 2.25 (d, 2H, J = 7.0), 2.09 (septet, J = 6.5), 0.95 (d, 6H, J = 7.0); δ_C (100 MHz, DMSO-d_6) 173.2, 160.2, 137.8, 135.3, 133.7, 132.6, 131.6, 129.5, 128.6, 127.6, 126.8, 125.2, 45.1, 33.9, 26.1, 23.2; ν_{max} (solid)/cm^{-1} 3240, 2962, 1670, 1643, 1533, 1491, 1205, 1093, 958, 698; *m*/*z* (ESI) 375 ([M + H]$^+$); HRMS found 375.0918 ($C_{19}H_{20}ClN_2O_2S$ requires 375.0934).

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra for all compounds, additional results and discussion, ORTEP plots of structures confirmed by X-ray crystallography, and analysis of compound purity by HPLC. This material is available free of charge via the Internet at http://pubs.acs.org.

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