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Ugi Reactions with Ammonia Offer Rapid Access to a Wide Range of 5-Aminothiazole and Oxazole Derivatives

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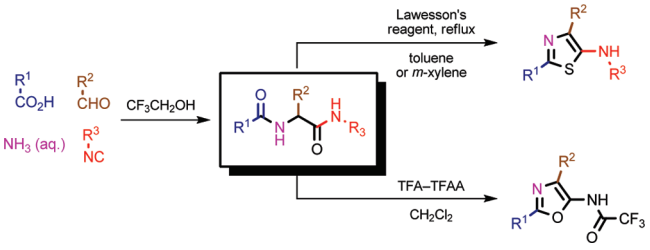

A series of Ugi reactions has been successfully performed using ammonia as the amine component, employing 2,2,2-trifluoroethanol as a non-nucleophilic solvent in order to suppress known side reactions. Utilizing concentrated aqueous ammonia as a convenient source, this approach offered a simple, one-step assembly of Ugi adducts suitable for elaboration into a variety of 5-aminoazole compounds through postcondensation modifications. Free or *N*-substituted 5-aminothiazoles and 5-(trifluoroacetamido)oxazoles were all prepared by this improved methodology. The scope of the synthetic route developed and application of the different products are discussed.

Introduction

The Ugi reaction, or Ugi four-component coupling (Ugi 4-CC),[1−3] is perhaps the best known example of the multicomponent reaction (MCR) and has been studied extensively since its discovery almost 50 years ago. The large range of structures accessible through this powerful reaction is continually expanding, through ongoing development of variations of the MCR, together with an increasing number of elaborate postcondensation modifications and cascade processes.[4−6] Despite such widespread application, use of ammonia as the amine component in the Ugi 4-CC has received comparatively little attention, with various reports commenting upon extensive byproduct formation[7−9] and one even suggesting it is inadequate for this purpose.[10] Low yields or complex product mixtures are often obtained where ammonia is employed, due to a number of possible side reactions which have been better characterized by more recent studies.[11,12]

In addition to the desired Ugi 4-CC product **1**, a related six-component coupling product (6-CC) **2** represents the most prevalent byproduct usually obtained during use of ammonia in the reaction (Scheme 1). Kazmaier deduced that since the 6-CC product is formed through participation of solvent, switching to the less nucleophilic 2,2,2-trifluoroethanol would suppress this pathway and improve the yield of the desired products **1**.[11,12] Synthesis of several Ugi 4-CC products derived from ammonia was subsequently achieved via this modified protocol, although meaningful yields were only obtained with the use of less reactive, sterically hindered aldehydes; similar observations were noted by Floyd et al. during preparation of a series of matrix metalloproteinase inhibitors via an MCR approach.[13] Similarly, using other

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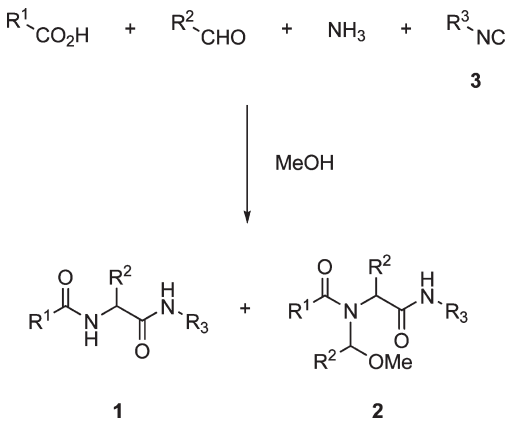
SCHEME 1. Major Products Obtained in Ugi Reactions Involving Ammonia



carbonyl components of lower reactivity, Ganem reported synthesis of a range of substituted 2-oxazolines from various β-ketomesylates.[14] A one-pot cascade process encompassing Ugi 4-CC followed by intramolecular cyclization provided these heterocycles in yields typically in the range of 60%. Thus, work to date has established ammonia as a viable nitrogen source for the Ugi reaction, though synthetically useful results have been restricted to cases involving less reactive carbonyl components.

Our interest in Ugi reactions employing ammonia was stimulated by shortcomings in an earlier approach to 5-aminothiazoles that used 2,4-dimethoxybenzylamine as an ammonia equivalent, wherein desired diamides of type **1** were obtained through cleavage of the 2,4-dimethoxybenzyl (DMB) group from initial 4-CC products **4** under acidic conditions (Scheme 2).[15]

When 1,1,3,3-tetramethylbutyl isocyanide **3a** (Walborsky's reagent) was employed in the initial Ugi 4-CC, several compounds of type **1** were synthesized in a two-step, one-pot procedure. However, limitations were encountered in the scope of this earlier protocol. Use of nicotinic acid to introduce a 3-pyridyl group at the R^1 position gave only DMB-protected product **4** after exposure to TFA, since protonation of the more basic ring nitrogen prevented acidic deprotection to the required product **1**. A different protection strategy was thus required, necessitating an additional synthetic step. 4-Methoxybenzylamine was used as the amine component of the Ugi 4-CC, followed by cleavage of the PMB group from the resultant intermediate using CAN. Chromatographic purification at each stage of this process was unavoidable.

Furthermore, additional problems were encountered when trying to expand the scope of the previous approach. Use of aliphatic aldehydes in the one-pot procedure proved most inefficient, leading to low yields of products at best, which were difficult to purify from quite complex mixtures; a similar scenario was encountered with variation of R^3 via the isocyanide component. It was found that these problems could usually—but not always—be remedied by chromatographic purification of intermediate **4** prior to a separate deprotection step, but the requirement for additional steps and purification procedures is not ideal for application of the methodology in chemical library synthesis.

We supposed that all of the problems identified above could be better addressed by direct use of ammonia in the Ugi 4-CC, thus providing a single-step route to key intermediates **1**. Development of such a generalized protocol is attractive inasmuch as it constitutes an example of "protecting-group-free" synthesis.[16] This area of growing interest offers self-evident financial and environmental benefits through reducing use of protection/deprotection steps, and in terms of accelerating the synthetic process, is particularly advantageous when applied to methodologies for the generation of chemical libraries.

Results and Discussion

Initial studies retaining Walborsky's reagent as the isocyanide component in the reaction confirmed 2,2,2-trifluoroethanol as a superior solvent to methanol for the synthesis of 4-CC adducts **1a**–**c** (Table 1). The ammonia source was a calculated amount of a concentrated aqueous solution of known concentration determined by titration. Whereas reactions in methanol (method A) gave low yields and more often than not required chromatographic separation of the desired product, the equivalent procedures in 2,2,2-trifluoroethanol (method B) gave much cleaner reactions and improved yields. Since preformation of the imine is generally assumed to be advantageous in the Ugi reaction,[2] this approach was also examined for the current examples (method C), though results were inconclusive at this stage.

TABLE 1. Comparison of Ugi 4-CC Protocols Varying Solvent and Addition Order

1	R^1	R^2	Yield (A)[a]	Yield (B)[b]	Yield (C)[c]
a			36	50	30
b			26[d]	51	49
c			16[d,e]	48	59

[a]Method A: MeOH as solvent. [b]Method B: 2,2,2-trifluoroethanol as solvent. [c]Method C: as method B, except with preformation of imine for 30 min before addition of aldehyde and isocyanide. [d]Column chromatography required. [e]Passerini product (1-(3,4-dichlorophenyl)-2-oxo-2-(2,4,4-trimethylpentan-2-ylamino)ethyl 4-methoxybenzoate) also isolated in 19% yield, possibly as a consequence of consumption of ammonia in side reactions.

Further examples **1d**–**j** were then carried out to allow direct comparison between the present protocol and the earlier two-step route (Scheme 2), this time with variation of all three R groups (Table 2). Broadly speaking, it can be seen that the ammonia-based method gives at least as good yields as the previous approach and often performs better, thus constituting a more efficient as well as shortened route to structures of type **1**. It is also appreciably wider in scope; nitrogen-containing heterocycles could now readily be introduced at the R^1 position (**1e**,**f**), and variation of the isocyanide building block was well tolerated. In particular, it

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SCHEME 2. Earlier Route to 5-Aminothiazoles Utilizing 2,4-Dimethoxybenzylamine as an Ammonia Equivalent

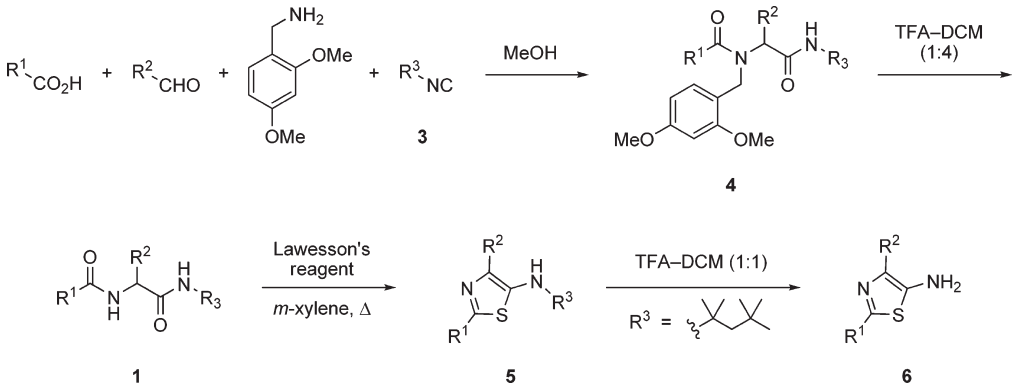
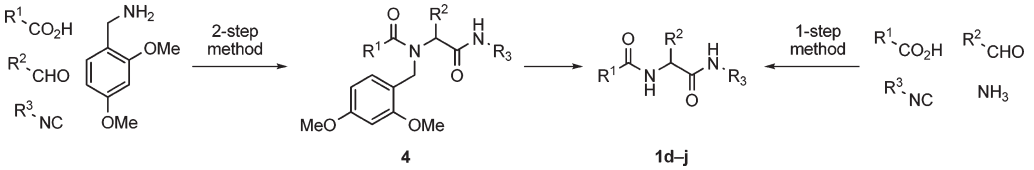
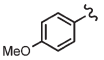
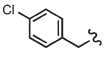
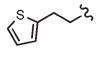


TABLE 2. Comparison of One-Step and Two-Step Procedures for Synthesis of Ugi 4-CC Adducts 1d−j



				2-step method			1-step method	
1	**R^1**	**R^2**	**R^3**	**Step 1 (4, %)**	**Step 2 (4→1, %)**	**Overall (1, %)**	**Method B (1, %)**	**Method C (1, %)**
d				18	57	10	31	23
e				64[a]	46[b]	29	–	28
f				–	–	–	51	49
g				40	69	28	–	21
h				40	69	28	28	15
i				43	54	23	–	18
j				43	66	28[c]	33	22

[a]Ugi 4-CC carried out using 4-methoxybenzylamine in place of 2,4-dimethoxybenzylamine. [b]Deprotection of 4-methoxybenzyl group carried out using CAN, MeOH−H_2O. [c]Product **1j** was only isolated in impure form via the two-step method.

was satisfying to isolate **1j** in good purity, as this had not been possible with the acidic deprotection conditions necessary in the older, two-step method. Significantly improved results were also obtained for **1d**, derived from an aliphatic aldehyde (3-phenylpropionaldehyde).

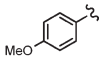
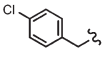
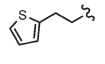
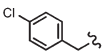
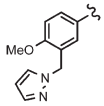
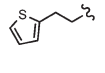
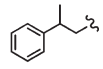
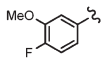
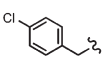
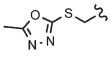
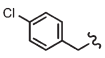
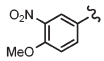
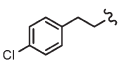
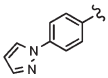
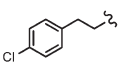
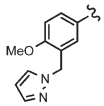
With respect to order of addition, preformation of the imine could now be seen as a slight disadvantage in the majority of cases and was therefore regarded as unnecessary within the present procedure. Only in one case did imine preformation lead to a higher yield (**1c**), in contrast to a number of reactions for which the yields were markedly lower (**1a**,**d**,**h**,**j**). This observation can putatively be explained in terms of the relatively high reactivity of ammonia, increasing the likelihood of side reactions during a separate imine formation step.

Thus, a straightforward mixing of all four starting materials in 2,2,2-trifluoroethanol at rt (method B) was established as the best procedure for synthesis of diamides **1**. Reactions were carried out for a minimum of 18 h, since following several of the examples by TLC indicated they proceeded rather slowly. Using this methodology, a further set of Ugi adducts **1k**−**t** (see Table 3) was prepared in yields ranging from 24−64%, with many above 40%, and most of the products isolated in good purity without the need for chromatography.

Elaboration of diamide intermediates **1f**−**t** to substituted 5-aminothiazoles **5** was then addressed (Table 3). To begin with, cyclizations were carried out at reflux in *m*-xylene in the presence of Lawesson's reagent as reported;[15] however,

TABLE 3. Cyclization of Ugi 4-CC Adducts to Substituted 5-Aminothiazoles[a]

1f–t 5a–o

1	R^1	R^2	R^3	5	Yield, %
f				a	39
g				b	45
h				c	41
i				d	53
j				e	44
k				f	43
l				g	45
m				h	23
n				i	–[b]
o				j	23
p				k	44
q				l	65
r				m	40
s				n	31
t				o	35

[a]Reactions performed on a 1 mmol scale in 20 mL of anhydrous solvent at reflux, in the presence of 1.2 equiv of Lawesson's reagent; **1f** in *m*-xylene for 3 h; **1g**–**j**, **1q**–**t** in *m*-xylene for 20 min; **1k**–**p** in toluene for 1 h. [b]Attempted synthesis of **5i** from **1n** failed apparently due to thermal instability, as under heating the reaction mixture rapidly darkened to a very deep brown color, and none of the desired product was isolated.

conversion was complete much more quickly than for the examples we have described previously. This observation is clearly attributable to lower steric demand of the substituents introduced at the R^3 position, relative to the 1,1,3,3-tetramethylbutyl group investigated in earlier work. Hence, for the present substrates **1g**–**j** bearing different R^3 groups, reactions to give **5b**–**e** were complete in 20 min, as opposed to 3 h for synthesis of **5a** from **1f**. Given the smoother cyclization observed in these new examples, synthesis of **5e** from **1j** was attempted at the lower reflux temperature of toluene and found to be complete in equivalent yield (43%) after 60 min. Cyclization of *N*-aryl derivative **1g** to **5b** was also successful in toluene, although a lower yield of 35% was obtained (compared to 45% in *m*-xylene). The preceding results were applied during preparation of the remainder of the library **5f**–**o**; most of the cyclizations were performed in toluene, whereas synthesis of the more hindered *N*-arylamines or *o*-substituted benzylamines (**5l**–**o**) was carried out in *m*-xylene.

Thus, a small library of 2,4,N^5-trisubstituted 5-aminothiazoles was successfully prepared to illustrate one relevant application of Ugi adducts **1**. These products **5a**–**j** were assembled in only two synthetic steps, yet contain three possible diversity points, all derived from widely variable building blocks. Performing the initial Ugi step with ammonia offered the advantage of permitting acid-sensitive components such as *N*-Boc-glycine to be incorporated (example **1k**), which would not have been compatible with the prior approach utilizing an acid-cleavable ammonia equivalent.

No examples are included containing an aliphatic substituent in the R^2 position, since as we have described previously, primary 5-aminothiazoles bearing an aliphatic group at C-4 are unstable.[15] We subsequently found that although they are relatively more stable, the secondary derivatives ($R^3 \neq H$) also decompose significantly over time, even upon cold storage. Clearly, such unstable compounds are not of interest as subjects for biological screening.

The direct synthesis of intermediates of type **1** also opened up the possibility of exploring alternatives to 1,1,3,3-tetramethylbutyl protection at the terminal amide position. Isocyanide **3b**[17,18] was used in place of Walborsky's reagent to introduce a 2,4-dimethoxybenzyl group at this site instead (Scheme 3), which we assumed would prove easier to remove. The resultant products **7a**–**d** could for the most part be successfully converted into 5-(trifluoroacetamido)oxazoles **8a**–**d** using a combined deprotection/cyclization procedure in one pot as illustrated, in the yields reported in Table 4. This approach mirrors a similar example reported recently by ourselves,[18] wherein a related, doubly DMB-protected diamide was converted into an oxazole derivative of type **8**. Unexpectedly though, attempted synthesis of **8c** failed, putatively due to preferential protonation of the pyrazole ring at C-2 preventing deprotection of the DMB group. About half of the starting material **7b** was recovered, suggesting a higher concentration of acid or longer reaction time would be required where a nitrogen-containing heterocycle is present.

Nonetheless, the majority of the 5-(trifluoroacetamido)-oxazoles were isolated in moderate to good yields. Utilizing a subsequent one-pot, acylation–deprotection procedure,

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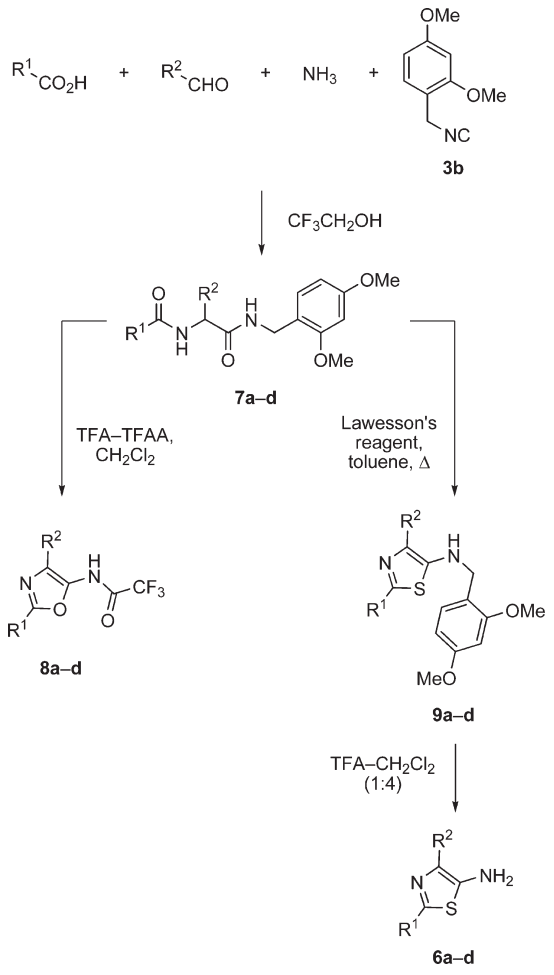
SCHEME 3. Alternative Protection Strategy Offering Access to a Wider Range of Post-Condensation Transformations



these intermediates represent valuable precursors to oxazole-5-amide libraries via methodology that we described recently.[18] The present examples confirm the general scope of such an approach, provided that removal of the DMB protecting group is not hindered by protonation of other basic groups within the molecule. Thus, rapid access to key intermediates for library synthesis (two diversity points and two synthetic steps) is again offered. Furthermore, in utilizing ammonia in the Ugi 4-CC step to reach the 5-(trifluoroacetamido)oxazoles **8**—instead of employing 2,4-dimethoxybenzylamine as an ammonia equivalent as in our earlier work—consumption of this relatively costly amine is reduced, compared to proceeding via the doubly DMB-protected intermediate, illustrating one advantage of the "protecting-group-free" approach to Ugi 4-CC adducts **1**.

In another application of DMB-protected compounds **7a**−**d**, they were cyclized to the corresponding *N*-(2,4-dimethoxybenzyl)-5-aminothiazoles **9a**−**d** in the presence of Lawesson's reagent (Scheme 3). Surprisingly, very low yields were obtained for these transformations at reflux in *m*-xylene (15% or lower), presumably due to thermal instability of the products at high temperature—though free 5-aminothiazoles were not isolated from the reaction mixtures, signifying other decomposition pathways than cleavage of the DMB group under heating. The lower reflux temperature of toluene gave better results, with longer reaction times required (60 min compared to 20 min), though yields of DMB-protected 5-aminothiazoles **9** were still relatively low (Table 4). In contrast, removal of the DMB group necessitated less strongly acidic conditions than those for cleavage of the 1,1,3,3-tetramethylbutyl group investigated previously, such that free 5-aminothiazoles **6a**−**d** were obtained in noticeably improved yields as compared to the earlier deprotection method.

TABLE 4. Percentage Yields of Synthetic Sequence Depicted in Scheme 3, with Differing Substituents at the Two Variable Positions

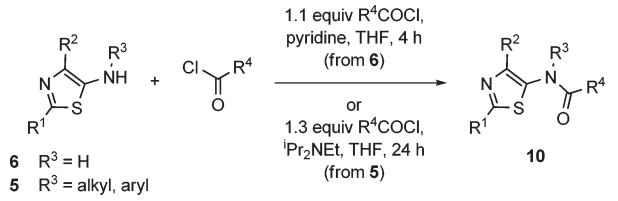
	R^1	R^2	7	8	9	6
a	Ph	S	28	50	25	67
b	Ph	MeO, MeO	42	79	13[a]	75[b]
c	N, N	F	33	0[c]	28	95
d	Me	MeO, F	44	50	23	57

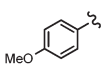
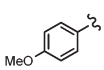
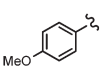
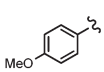
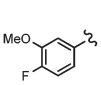
[a]Yield estimated by HPLC; **9b** was obtained as a mixture which was purified following deprotection. [b]HPLC yield: overall isolated yield of **6b** from **7b** was 7%. [c]No significant product formation (~50% of starting material recovered).

Although the route studied herein (Scheme 3) does present an interesting alternative approach to free 5-aminothiazoles **6**, given the unexpectedly low cyclization yields obtained, it appears that use of the 1,1,3,3-tetramethylbutyl group derived from Walborsky's reagent **3a** should usually be the first choice for accessing these intermediates. By way of example, deprotection of **5a** (1:1 TFA−CH_2Cl_2, 20 min) proceeded in 63% yield, resulting in an overall yield of 7.6% for the three-step synthesis of **6c** (Ugi 4-CC, cyclization and deprotection to the free amine). In comparison, the route to this same product outlined above (Scheme 3) offered a barely improved overall yield of 8.8%. Relatedly, **6d** was prepared in 10.6% overall yield beginning from **3a**, in contrast to a 5.8% overall yield for the route depicted in Scheme 3. Thus, 1,1,3,3-tetramethylbutyl protection for the amino group is preferred, though use of the DMB protection strategy presented above does offer another option employing milder reaction conditions, should such recourse be necessary.

The primary and secondary 5-aminothiazoles **5** and **6** synthesized as above were then utilized in further library synthesis via additional acylation reactions (Table 5). The primary 5-aminothiazoles **6** were previously acylated using pyridine as solvent;[19] an improved procedure was developed using only a small amount of pyridine (2.5 equiv) in alternative solvents. THF gave the best results, though CH_2Cl_2 also resulted in acceptable (albeit lower) yields. Secondary amines **5** required longer reaction times together with a larger excess of acylating agent, and Hünig's base was employed in these reactions in place of pyridine. Derivatization of the secondary amines with acyl chlorides proved to be the method of choice, since attempted amide formation from carboxylic acids mediated by benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate

TABLE 5. Thiazole-5-amides Prepared by Parallel Synthesis



R^1	R^2	R^3	R^4	10	%[a]
				**a**	32
				**b**	44
				**c**	46
				**d**	32
				**e**	47
				**f**	53
				**g**	40
				**h**	31
				**i**	52
				**j**	62
				k	61
				l	66
				m	44
				n	35
				o	59
				p	58

[a]Isolated yields.

was much slower, only resulting in a poor extent of conversion to the desired products **10**. This approach has already been ruled out for primary 5-aminothiazoles **6** as it was found to result in double acylation at N-5, presumably due to deprotonation of the initial amide product under the basic reaction conditions.[19]

Using the methods described, a representative library of amide products was prepared (Table 5), concluding the synthesis of final compounds containing up to four variable diversity points.

Conclusions

Using concentrated aqueous ammonia as a convenient source, a wide range of Ugi reactions employing ammonia as the amine component was carried out successfully in 2,2,2-trifluoroethanol. This synthetically useful protocol was shown to be wide in scope and provided quick access to diamide products **1** in yields at least as good, and often better, when compared to an alternative two-step procedure utilizing 2,4-dimethoxybenzylamine as an ammonia equivalent.

Through a series of postcondensation modifications, Ugi adducts **1** were transformed into useful synthetic intermediates including 5-(trifluoroacetamide)oxazoles **8**—valuable precursors to oxazole-5-amide libraries—and either primary or secondary 5-aminothiazoles. These aminothiazoles readily underwent *N*-acylation, giving compounds containing up to four diversity points in just three straightforward synthetic steps.

Experimental Section

Isocyanides. Walborsky's reagent **3a** and 4-methoxyphenyl isocyanide **3c** were sourced commercially; 2,4-dimethoxybenzyl isocyanide **3b**[18] and 4-chlorobenzyl isocyanide **3d**[20] were synthesized as reported. The other isocyanides **3e**−**h** were prepared as detailed below.

Preparation of Isocyanides 3e−g from Aliphatic Amines. General Procedure. The appropriate primary amine was stirred for 24 h with ethyl formate (1.2 equiv), at rt (**3e**, **3g**) or 50 °C (**3f**). Where the formamide intermediate was a liquid (**3f**, **3g**), the reaction mixture was simply dried under high vacuum for several hours before proceeding. Where the formamide was a solid (**3e**), it was collected by filtration, washed several times with hexane, then dried thoroughly. Either way, the formamide intermediate was then dissolved in anhydrous CH_2Cl_2 (2.5 mL $mmol^{-1}$) under N_2 and triethylamine (3.0 equiv) added. The solution was cooled to 0 °C and then phosphorus oxychloride (1.0 equiv) added portionwise over 10 min. After 1 h, 1.1 M aq Na_2CO_3 (1.0 equiv) was added and reaction continued for a further 1 h, ensuring efficient stirring of the thickening reaction mixture. The mixture was diluted with additional CH_2Cl_2 and water, the organic layer separated, and the aqueous layer extracted with a second portion of CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and evaporated to provide the crude product, which was purified by flash column chromatography on silica, as detailed for each individual example.

2-(2-Thienyl)ethyl Isocyanide (3e).[21] Prepared from 2-(2-thienyl)ethylamine (3.82 g, 30 mmol). Column eluent 5−10% EtOAc−hexane. Title compound obtained as a highly pungent, pale yellow oil (2.93 g, 71%): δ_H (400 MHz, $CDCl_3$) 7.24 (dd, 1H, J = 1.0, 5.0), 7.02−6.99 (m, 1H), 6.98−6.95 (m, 1H), 3.66

(19) Heal, W.; Thompson, M. J.; Mutter, R.; Cope, H.; Louth, J. C.; Chen, B. *J. Med. Chem.* **2007**, *50*, 1347–1353.
(20) Jacobsen, E. J.; Stelzer, L. S.; Belonga, K. L.; Carter, D. B.; Im, W. B.; Sethy, V. H.; Tang, A. H.; von Voigtlander, P. F.; Petke, J. D. *J. Med. Chem.* **1996**, *39*, 3820–3836.
(21) Thompson, M. J.; Hurst, J. M.; Chen, B. *Synlett* **2008**, 3183–3187.

(dt, 2H, J = 1.5, 7.0), 3.23 (t, 2H, J = 7.0); δ_C (100 MHz, $CDCl_3$) 157.2, 138.5, 127.2, 126.2, 124.7, 43.2, 30.0; m/z (EI), 137 (M^+); HRMS found 137.0297 (C_7H_7NS, M^+, requires 137.0299).

2-(Trifluoromethyl)benzyl Isocyanide (3f).[21] Prepared from 2-(trifluoromethyl)benzylamine (7.01 mL, 8.76 g, 50 mmol). Column eluent 2.5→5→10% ethyl acetate−hexane. Title compound obtained as a malodorous, pale yellow oil (3.78 g, 41%): δ_H (250 MHz, $CDCl_3$) 7.81−7.63 (m, 3H), 7.56−7.46 (m, 1H), 4.89 (s, 2H); δ_C (100 MHz, $CDCl_3$) 159.5, 132.7, 130.3, 128.6, 128.5, 127.3 (q, J = 30.5), 126.3, 124.0 (q, J = 273), 42.7; m/z (FAB), 185 (M^+); HRMS found 185.0455 ($C_9H_6F_3N$, M^+, requires 185.0452).

1-Chloro-4-(2-isocyanoethyl)benzene (3g). Prepared from 2-(4-chlorophenyl)ethylamine (4.67 g, 30 mmol). Column eluent 2.5→5→10→15% EtOAc−isohexane. Title compound obtained as a yellow oil (4.03 g, 83%): δ_H (400 MHz, $CDCl_3$) 7.34 (dd, 2H, J = 2.0, 9.0), 7.21−7.17 (m, 2H), 3.62 (tt, 2H, J = 1.5, 7.0), 3.00−2.94 (m, 2H); δ_C (100 MHz, $CDCl_3$) 157.0 (t, J = 5.5), 135.1, 133.2, 130.0, 129.0, 42.8 (t, J = 6.5), 34.9; m/z (EI), 165 ($[M]^+$); HRMS found 165.0353 (C_9H_8ClN requires 165.0345).

2-Fluoro-4-isocyano-1-methylbenzene (3h). The formamide derivative of this less reactive arylamine was prepared from 3-fluoro-4-methylaniline (5.00 g, 40 mmol) according to the method of Janza and Studer[22] and obtained as a greasy, yellow solid (3.34 g, 55%). This intermediate (3.06 g, 20 mmol) was then dissolved in anhydrous CH_2Cl_2 (130 mL) under N_2 and triethylamine (8.36 mL, 6.07 g, 60 mmol) added. The solution was cooled to 0 °C and then phosphorus oxychloride (1.86 mL, 3.07 g, 20 mmol) added portionwise over 10 min. After the mixture was stirred at 0 °C to rt over 3 h, 1.1 M aq Na_2CO_3 (1.0 equiv) was added and the reaction continued for a further 90 min, ensuring efficient stirring of the thickening reaction mixture. The mixture was diluted with additional CH_2Cl_2 and water, the organic layer separated, and the aqueous layer extracted with a second portion of CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and evaporated to provide the crude product, which was purified by flash column chromatography on silica, eluted with 2.5→5→10% EtOAc−isohexane. The title compound was obtained as a strong smelling, blue oil (2.18 g, 81%) which was stored at −20 °C: δ_H (400 MHz, $CDCl_3$) 7.22 (t, 1H, J = 8.0), 7.13−7.04 (m, 2H), 2.32 (d, 3H, J = 2.0); δ_C (100 MHz, $CDCl_3$) 164.5, 160.6 (d, J = 247), 132.1 (d, J = 5.5), 127.3 (d, J = 17.5), 125.3−124.8 (m), 122.1 (d, J = 3.5), 113.5 (d, J = 26.5), 14.5 (d, J = 3.0); m/z (EI), 135 ($[M]^+$); HRMS found 135.0489 (C_8H_6FN requires 135.0484).

Ugi Reactions with Ammonia. General Procedure. Prior to carrying out the reactions, the exact concentration of a 30% aqueous ammonia solution was determined by titration against a standard 2.00 M solution of hydrochloric acid. Values were typically in the range of 15 ± 0.5 M; thus, for example, the calculated amount of ammonia solution required for a 5 mmol scale reaction would be 330 μL of an ammonia solution determined as 15.2 M.

Method A. Methanol as Solvent. A calculated volume of ammonia solution of known concentration (5 mmol) was added to a stirred solution or suspension of the carboxylic acid (5 mmol) in methanol (5 mL). The aldehyde (5 mmol) and isocyanide (5 mmol) were then introduced, and stirring was continued at rt overnight (18−24 h). Solvent was removed by rotary evaporation and the crude product purified as detailed in the Supporting Information for each individual case.

Method B. 2,2,2-Trifluoroethanol as Solvent. The procedure was carried out exactly as above for method A, except that 2,2,2-trifluoroethanol (5 mL) was used in place of methanol.

(22) Janza, B.; Studer, A. *Org. Lett.* **2006**, *8*, 1875–1878.

Method C. With Preformation of the Imine Intermediate. The calculated volume of ammonia solution of known concentration (5 mmol) was added to a solution of the aldehyde (5 mmol) in 2,2,2-trifluoroethanol (2.5 mL). After 30 min, further 2,2,2-trifluoroethanol (2.5 mL) was added followed by the carboxylic acid (5 mmol) and isocyanide (5 mmol) and then stirring continued at rt overnight (18−24 h). Solvent was removed by rotary evaporation and the product purified as indicated (see the Supporting Information).

Two-Step Synthesis of Diamides 1d,g−j (Table 2). Step 1: Synthesis of 4d,g−j by Ugi 4-CC. 2,4-Dimethoxybenzylamine (751 μL, 836 mg, 5 mmol) was added to a solution of thiophene-2-carboxaldehyde (467 μL, 561 mg, 5 mmol) in methanol (2 mL). After the solution was stirred for 30 min, additional methanol (2 mL) was added followed by benzoic acid (611 mg, 5 mmol) and the relevant isocyanide (5 mmol). The reaction mixture was allowed to stir at room temperature overnight and then evaporated under vacuum. Purification of the DMB-protected adducts **4** was carried out by column chromatography as detailed below.

***N*-(2,4-Dimethoxybenzyl)-4-fluoro-*N*-(1-oxo-4-phenyl-1-(2,4,4-trimethylpentan-2-ylamino)butan-2-yl)benzamide (4d).** Basic alumina column, eluted with 0→1→2% MeOH−CH_2Cl_2. Glassy, yellow solid (514 mg, 18%): δ_H (400 MHz, $CDCl_3$) 7.52−7.41 (m, 2H), 7.35−7.15 (m, 5H), 7.14−6.82 (m, 4H), 6.46−6.29 (m, 2H), 4.61−4.33 (m, 2H), 4.24 (t, 1H, J = 7.0), 3.86−3.75 (m, 3H), 3.67 (br s, 2H), 2.70 (br s, 2H), 2.52 (br s, 1H), 2.26 (br s, 1H), 1.83−1.66 (m, 2H), 1.60−1.51 (m, 1H), 1.29 (s, 3H), 1.25 (s, 3H), 0.98 (s, 9H); δ_C (62.8 MHz, $CDCl_3$) 172.5, 169.3, 163.3 (d, J = 251), 160.8, 158.2, 141.2, 130.3, 129.4, 129.2, 128.5, 126.1, 115.4 (d, J = 21.5), 104.2, 98.7, 62.3, 55.4, 55.0, 54.8, 33.0, 31.54, 31.45, 30.4, 28.9; m/z (ESI) 563 ($[M + H]^+$); HRMS, found 563.3281 ($C_{34}H_{44}FN_2O_4$ requires 563.3285).

***N*-(2,4-Dimethoxybenzyl)-*N*-(2-(4-methoxyphenylamino)-2-oxo-1-(thiophene-2-yl)ethyl)benzamide (4g).** Silica column, eluted with 0→1→2→4% MeOH−CH_2Cl_2. Brown-colored foam (1.04 g, 40%): δ_H (400 MHz, $CDCl_3$) 8.44 (s, 1H), 7.62 (d, 2H, J = 6.5), 7.52−7.37 (m, 4H), 7.34−7.25 (m, 3H), 7.18 (d, 1H, J = 3.0), 7.03 (t, 1H, J = 4.5), 6.82 (d, 2H, J = 9.0), 6.46 (dd, 1H, J = 2.0, 8.5), 6.21 (d, 1H, J = 2.0), 5.71 (s, 1H), 4.57 (AB system, 2H, J = 15.5), 3.79 (s, 3H), 3.78 (s, 3H), 3.57 (s, 3H); δ_C (100 MHz, $CDCl_3$) 173.5, 166.6, 160.9, 158.5, 156.3, 137.0, 135.5, 133.4, 130.9, 130.6, 130.4, 130.1, 129.2, 127.6, 127.5, 126.3, 121.9, 113.9, 104.1, 98.4, 55.5, 55.4, 55.0; m/z (ESI) 517 ($[M + H]^+$); HRMS, found 517.1810 ($C_{29}H_{29}N_2O_5S$ requires 517.1797).

***N*-(2-(4-Chlorobenzylamino)-2-oxo-1-(thiophene-2-yl)ethyl)-*N*-(2,4-dimethoxybenzyl)benzamide (4h).** Silica column, eluted with 0→1→2% MeOH−CH_2Cl_2. Pale yellow, crystalline solid (1.08 g, 40%): δ_H (400 MHz, $CDCl_3$) 7.59−7.54 (m, 2H), 7.46−7.36 (m, 4H), 7.35−7.22 (m, 5H), 6.97 (d, 1H, J = 1.5), 6.93 (dd, 1H, J = 3.5, 5.0), 6.52−6.42 (m, 2H), 6.29 (d, 1H, J = 2.5), 5.31 (s, 1H), 4.59−4.50 (m, 3H), 4.33−4.25 (m, 1H), 3.81 (s, 3H), 3.57 (s, 3H); δ_C (100 MHz, $CDCl_3$) 172.5, 168.7, 160.8, 158.4, 137.4, 136.7, 135.6, 133.3, 133.0, 130.09, 130.05, 129.6, 128.9, 128.7, 128.4, 128.3, 127.9, 127.2, 126.2, 116.6, 104.0, 98.5, 61.1, 55.4, 54.9, 43.1, 26.9; m/z (ESI) 557 ($[M + Na]^+$); HRMS found 557.1291 ($C_{29}H_{27}ClN_2O_4SNa$ requires 557.1278).

***N*-(2,4-Dimethoxybenzyl)-*N*-(2-oxo-1-(thiophene-2-yl)-2-(2-(trifluoromethyl)benzylamino)ethyl)benzamide (4i).** Basic alumina column, eluted with 50→75→100% CH_2Cl_2−hexane then 1→2% MeOH−CH_2Cl_2. Off-white solid (1.22 g, 43%): δ_H (400 MHz, $CDCl_3$) 7.71 (d, 1H, J = 8.0), 7.61 (d, 1H, J = 8.0), 7.59−7.53 (m, 3H), 7.46−7.32 (m, 6H), 7.01−6.98 (m, 1H), 6.95 (dd, 1H, J = 3.5, 5.0), 6.52−6.45 (m, 2H), 6.30 (d, 1H, J = 2.0), 4.79−4.69 (m, 1H), 4.62−4.47 (m, 3H), 3.81 (s, 3H), 3.60 (s, 3H); δ_C (100 MHz, $CDCl_3$) 172.5, 168.7, 160.8, 158.4, 137.3, 136.6,

135.7, 132.5, 130.1, 129.8, 129.6, 128.3, 127.9, 127.2, 126.1, 125.7 (q, J = 5.5), 116.6, 104.0, 98.4, 61.0, 55.4, 54.9, 53.4, 40.2, 26.9; m/z (ESI) 569 ([M + H]$^+$); HRMS found 569.1704 ($C_{30}H_{28}F_3N_2O_4S$ requires 569.1722).

***N*-(2,4-Dimethoxybenzyl)-*N*-(2-oxo-1-(thiophene-2-yl)-2-(2-(thiophene-2-yl)ethylamino)ethyl)benzamide (4j).** Basic alumina column, eluted with 60→80→100% CH_2Cl_2−hexane then 1% MeOH−CH_2Cl_2. Bright yellow foam (1.18 g, 43%): δ_H (400 MHz, $CDCl_3$) 7.56 (d, 2H, J = 6.5), 7.49 (d, 1H, J = 8.5), 7.43−7.35 (m, 3H), 7.32 (dd, 1H, J = 1.5, 5.0), 7.28 (s, 1H), 7.13 (dd, 1H, J = 1.0, 5.0), 6.95−6.89 (m, 3H), 6.83−6.81 (m, 1H), 6.51 (dd, 1H, J = 2.0, 8.0), 6.33 (d, 1H, J = 2.5), 6.24 (t, 1H, J = 5.5), 5.23 (s, 1H), 4.59−4.47 (m, 2H), 3.82 (s, 3H), 3.65−3.53 (m, 4H), 3.46−3.35 (m, 1H), 3.02 (t, 2H, J = 6.5); δ_C (100 MHz, $CDCl_3$) 172.6, 168.6, 160.6, 158.3, 141.3, 137.5, 135.7, 130.1, 129.8, 129.5, 128.3, 127.7, 127.2, 127.0, 126.1, 125.6, 123.7, 116.8, 103.9, 98.4, 61.2, 55.4, 55.0, 41.3, 29.7; ν_{max} (solid)/cm^{-1} 1676, 1613, 1506, 1206, 1032, 696; m/z (ESI) 521 ([M + H]$^+$); HRMS found 521.1547 ($C_{28}H_{29}N_2O_4S_2$ requires 521.1569).

Two-Step Synthesis of Diamides 1d,g−j (Table 2). Step 2: Deprotection of 4d,g−j. The DMB-protected intermediate **4** was dissolved in TFA−DCM (1:4, 10 mL) and the mixture stirred at room temperature for 1 h and then evaporated to dryness. The diamide product **1** was purified as described below and isolated in the yields reported in Table 2; spectroscopic data were in agreement with those listed above for the samples prepared directly by the Ugi-4CC with ammonia.

1g−i. The crude product was triturated with satd aq $NaHCO_3$, and then ether (approximately 5 mL) was added to the mixture and trituration continued until the initially sticky gum had precipitated as a solid. The crude product was collected by filtration using a sintered funnel and washed successively with satd aq $NaHCO_3$ (×3), water (×2), and then ether (2 × 10 mL). Purified product was isolated by washing through the sinter slowly with chloroform (4 × 30 mL), in each case leaving behind a small amount of insoluble, pink residue. The chloroform solution was dried over $MgSO_4$, filtered, and then evaporated giving the diamide product.

1d,j. These compounds were more organically soluble and were thus extracted into ether (×2) and washed with satd $NaHCO_3$, and the organic layer was dried over $MgSO_4$ and then evaporated. Column chromatography on silica (**1j**) or basic alumina (**1d**), eluted with 0−1−2−4% MeOH−CH_2Cl_2, provided the title compounds.

Cyclization of Diamides to *N*-Substituted 5-Aminothiazoles 5a−k. The diamide **1** (1 mmol) was suspended in anhydrous *m*-xylene (**1f−j,q−t**) or toluene (**1k−p**, 20 mL), together with Lawesson's reagent (485 mg, 1.2 mmol) under N_2. The mixture was heated at reflux for either 20 min (**1g−j,q−t**), 1 h (**1k−p**), or 3 h (**1f**). Following evaporation of the solvent, the thiazole product **5a−o** was isolated by column chromatography as described for each individual example (see the Supporting Information for details).

DMB-Protected Ugi Adducts (7a−d). General Procedure. A calculated volume of ammonia solution of known concentration (10 mmol) was added to a stirred solution or suspension of the carboxylic acid (10 mmol) in 2,2,2-trifluoroethanol (10 mL). The aldehyde (10 mmol) and 2,4-dimethoxybenzyl isocyanide (1.77 g, 10 mmol) were then introduced, and stirring continued at rt overnight (18−24 h). Solvent was removed by rotary evaporation and the crude product purified by column chromatography on basic alumina, eluted with 0→1→2% MeOH−CH_2Cl_2, followed by further crystallization as indicated.

***N*-(2-(2,4-Dimethoxybenzylamino)-2-oxo-1-(thiophene-2-yl)ethyl)-benzamide (7a).** Crystallized from ether/hexane. Pale brown solid (1.16 g, 28%): mp 160−163 °C dec; δ_H (400 MHz, DMSO-d_6) 8.98 (d, 1H, J = 8.0), 8.56 (t, 1H, J = 5.5), 7.96−7.91 (m, 2H), 7.58−7.53 (m, 1H), 7.51−7.45 (m, 2H), 7.14−7.12 (m, 2H), 7.08 (d, 1H, J = 8.5), 7.01 (dd, 1H, J = 3.z, 5.0), 6.54 (d, 1H, J = 2.5), 6.44 (dd, 1H, J = 2.5, 8.5), 6.00 (d, 1H, J = 8.0), 4.29−4.17 (m, 2H), 3.76 (s, 3H), 3.74 (s, 3H); δ_C (100 MHz, DMSO-d_6) 168.8, 166.0, 159.8, 157.7, 141.1, 133.7, 131.5, 128.9, 128.2, 127.7, 126.6, 125.9, 125.6, 118.4, 104.2, 98.2, 55.3, 55.2, 52.7, 37.3; ν_{max} (solid)/cm^{-1} 3278, 1627, 1509, 1296, 1206, 1031, 823, 695; m/z (ESI) 411 ([M + H]$^+$); HRMS, found 411.1370 ($C_{22}H_{23}N_2O_4S$ requires 411.1379).

***N*-(2-(2,4-Dimethoxybenzylamino)-1-(4-methoxy-3-(methoxymethyl)phenyl)-2-oxoethyl)-3-phenylbutanamide (7b).** The initial reddish gum was triturated thoroughly with ether; addition of a small amount of CH_2Cl_2 with continued trituration induced crystallization. The product was obtained as a mixture of diastereoisomers, as indicated by the presence of two sets of peaks in the NMR spectra. Off-white solid (2.17 g, 42%): mp 149−152 °C; δ_H (400 MHz, $CDCl_3$) 7.31−7.13 (m, 6.5H), 7.09−7.00 (m, 1.5H), 6.83−6.77 (m, 1H), [6.88 (d, 0.3H, J = 7.0) and 6.73 (d, 0.7H, J = 8.5)], 6.41−6.36 (m, 2H), [6.22 (t, 0.65H, J = 6.0) and 6.16 (t, 0.35H, J = 6.0)], 5.33 (t, 1H, J = 6.5), 4.49−4.24 (m, 4H), 3.83 (s, 3H), 3.80−3.78 (m, 3H), 3.71−3.69 (m, 3H), [3.39 (s, 1H) and 3.38 (s, 2H)], 3.29−3.19 (m, 1H), 2.56−2.37 (m, 2H), [1.27 (d, 2H, J = 7.0) and 1.22 (d, 1H, J = 7.0)]; δ_C (100 MHz, $CDCl_3$) 170.9, [169.69 and 169.62], 160.6, 158.4, [156.97 and 156.94], [145.97 and 145.85], 130.4, [130.18 and 130.13], [128.54 and 128.49], [128.06 and 128.01], [127.81 and 127.71], [127.08 and 126.96], [126.75 and 126.73], [126.31 and 126.24], 118.2, 110.5, 103.8, 98.5, [69.46 and 69.44], 58.4, [56.63 and 56.53], 55.5, 55.4, 55.2, [45.40 and 45.13], [39.46 and 39.41], [36.87 and 37.77], [21.66 and 21.57]; ν_{max} (solid)/cm^{-1} 3294, 2934, 1623, 1540, 1508, 1294, 1250, 1207, 1099, 1034, 704; m/z (ESI) 521 ([M + H]$^+$); HRMS, found 521.2643 ($C_{30}H_{37}N_2O_6$ requires 521.2652).

***N*-(2-(2,4-Dimethoxybenzylamino)-1-(4-fluorophenyl)-2-oxoethyl)-1,3-dimethyl-1*H*-pyrazole-5-carboxamide (7c).** Crystallized from ether/hexane. Pale brown solid (1.45 g, 33%): mp 172−173 °C; δ_H (400 MHz, DMSO-d_6) 8.75 (d, 1H, J = 8.0), 8.50 (t, 1H, J = 5.5), 7.58−7.46 (dd, 2H, J = 5.5, 8.5), 7.20 (t, 2H, J = 8.5), 6.98 (d, 1H, J = 8.5), 6.85 (s, 1H), 6.52 (d, 1H, J = 1.5), 6.41 (dd, 1H, J = 2.0, 8.0), 5.68 (d, 1H, J = 8.0), 4.27−4.08 (m, 2H), 3.94 (s, 3H), 3.72 (s, 6H), 2.15 (s, 3H); δ_C (100 MHz, DMSO-d_6) 170.1, 162.5 (d, J = 244), 160.7, 159.9, 158.6, 146.1, 136.0, 135.4, 130.5 (d, J = 8.0), 129.7, 119.2, 115.9 (d, J = 21.5), 108.2, 105.0, 99.1, 56.5, 56.2, 56.0, 39.3, 38.2, 13.9; ν_{max} (solid)/cm^{-1} 3297, 1634, 1508, 1210, 1158, 1132, 1039, 833, 790; m/z (ESI) 441 ([M + H]$^+$); HRMS, found 441.1920 ($C_{23}H_{26}FN_4O_4$ requires 441.1938).

2-Acetamido-*N*-(2,4-dimethoxybenzyl)-2-(4-fluoro-3-methoxyphenyl)acetamide (7d). No column chromatography necessary; recrystallized directly from EtOAc. White powder (1.72 g, 44%): mp 200 °C; δ_H (400 MHz, DMSO-d_6) 8.58 (d, 1H, J = 8.0), 8.51 (t, 1H, J = 5.5), 7.24 (dd, 1H, J = 2.0, 8.0), 7.21−7.15 (m, 1H), 7.02−6.93 (m, 2H), 6.53 (d, 1H, J = 2.5), 6.40 (dd, 1H, J = 2.5, 8.5), 5.51 (d, 1H, J = 8.0), 4.14 (ddd, 2H, J = 6.0, 9.0, 15.0), 3.80 (s, 3H), 3.73 (s, 6H), 1.91 (s, 3H); δ_C (100 MHz, DMSO-d_6) 170.5, 169.7, 160.6, 158.5, 151.7 (d, J = 242), 147.6 (d, J = 11.0), 136.8 (d, J = 3.0), 129.5, 120.3 (d, J = 7.0), 119.4, 116.3 (d, J = 18.0), 113.6, 105.0, 99.1, 56.7, 56.5, 56.2, 56.0, 37.9, 23.3; ν_{max} (solid)/cm^{-1} 3306, 1631, 1614, 1509, 1288, 1261, 1207, 1156, 1132, 1031; m/z (ESI) 391 ([M + H]$^+$); HRMS, found 391.1672 ($C_{20}H_{24}FN_2O_5$ requires 391.1669).

Cyclization of 7a−d to DMB-Protected 5-Aminothiazoles 9a−d. The DMB-protected diamide **7** (1 mmol) was suspended in anhydrous toluene (20 mL) under N_2, together with Lawesson's reagent (485 mg, 1.2 mmol). The mixture was refluxed for 1 h, the solvent evaporated, and the residue purified by column chromatography on basic alumina, as indicated for each case.

***N*-(2,4-Dimethoxybenzyl)-2-phenyl-4-(thiophene-2-yl)thiazol-5-amine (9a).** Column eluent 2→8→15→20% EtOAc−hexane.

Thick, yellow gum (102 mg, 25%): δ_H (400 MHz, $CDCl_3$) 7.90−7.84 (m, 2H), 7.40 (t, 2H, J = 7.5), 7.37−7.31 (m, 2H), 7.30−7.23 (m, 2H), 7.11 (dd, 1H, J = 3.5, 5.0), 6.50 (d, 1H, J = 2.0), 6.49−6.45 (m, 1H), 4.86 (br s, 1H), 4.36 (s, 2H), 3.85 (s, 3H), 3.83 (s, 3H); δ_C (100 MHz, $CDCl_3$) 160.8, 158.6, 152.4, 145.7, 138.5, 134.1, 130.4, 129.9, 128.7, 127.3, 125.5, 123.2, 122.2, 118.3, 103.9, 98.8, 55.4, 55.3, 50.1; ν_{max} (neat)/cm^{-1} 2932, 1613, 1588, 1540, 1498, 1449, 1287, 1206, 1155, 1131, 1031, 824, 758, 687; m/z (ESI) 391 ([M + H]$^+$); HRMS, found 391.1672 ($C_{20}H_{24}FN_2O_5$ requires 391.1669).

***N*-(2,4-Dimethoxybenzyl)-4-(4-methoxy-3-(methoxymethyl)-phenyl)-2-(2-phenylpropyl)thiazol-5-amine (9b).** Column eluent 5→10→15→20→25% EtOAc−hexane. Thick, yellow oil seen to be a mixture by NMR and HPLC analysis (213 mg): δ_H (400 MHz, $CDCl_3$) 7.63 (d, 1H, J = 2.5), 7.55 (dd, 1H, J = 2.5, 8.5), 7.36−7.30 (m, 2H), 7.29−7.21 (m, 3H), 7.11 (d, 1H, J = 8.0), 6.91 (d, 1H, J = 9.0), 6.46−6.41 (m, 2H), 4.53 (s, 2H), 4.48 (br s, 1H), 4.18−4.12 (m, 2H), 3.88 (s, 3H), 3.82 (s, 3H), 3.75 (s, 3H), 3.42 (s, 3H), 3.27−3.06 (m, 3H), 1.35 (d, 3H, J = 6.5); δ_C (100 MHz, $CDCl_3$) 160.6, 158.5, 156.1, 154.8, 146.2, 144.2, 134.0, 130.3, 128.8, 128.4, 127.9, 127.8, 127.1, 126.5, 126.3, 119.1, 110.5, 103.7, 98.6, 69.7, 58.2, 55.6, 55.4, 55.2, 50.3, 42.1, 40.7, 21.6; ν_{max} (neat)/cm^{-1} 2927, 1612, 1589, 1501, 1250, 1207, 1027, 700; m/z (ESI) 519 ([M + H]$^+$); HRMS, found 519.2336 ($C_{30}H_{35}N_2O_4S$ requires 519.2318).

***N*-(2,4-Dimethoxybenzyl)-2-(1,3-dimethyl-1*H*-pyrazol-5-yl)-4-(4-fluorophenyl)thiazol-5-amine (9c).** Column eluent 10→15→20→25→30% EtOAc−isohexane. Thick, bright yellow gum (122 mg, 28%), which gradually solidified on standing: δ_H (400 MHz, $CDCl_3$) 7.71 (dd, 2H, J = 5.5, 9.0), 7.20 (d, 1H, J = 8.0), 7.13 (t, 2H, J = 9.0), 6.50−6.44 (m, 2H), 6.28 (s, 1H), 4.84 (t, 1H, J = 6.0), 4.27 (d, 2H, J = 6.0), 4.19 (s, 3H), 3.82 (s, 3H), 3.80 (s, 3H), 2.29 (s, 3H); δ_C (100 MHz, $CDCl_3$) 162.7, 159.7 (d, J = 233), 147.3, 146.7, 142.3, 136.5, 133.3, 131.2, 130.5, 128.7 (d, J = 8.0), 118.1, 115.6 (d, J = 21.5), 105.3, 103.9, 98.8, 55.4, 55.3, 50.3, 38.8, 13.4; ν_{max} (solid)/cm^{-1} 1616, 1504, 1206, 1159, 1030, 832, 762, 566; m/z (ESI) 439 ([M + H]$^+$); HRMS, found 439.1599 ($C_{23}H_{24}FN_4O_2S$ requires 439.1604).

***N*-(2,4-Dimethoxybenzyl)-4-(4-fluoro-3-methoxyphenyl)-2-methylthiazol-5-amine (9d).** Column eluent 5→10→15→20→25% EtOAc−isohexane. Thick, yellow gum (89 mg, 23%): δ_H (400 MHz, $CDCl_3$) 7.36 (dd, 1H, J = 2.0, 8.5), 7.18−7.13 (m, 2H), 7.09 (dd, 1H, J = 8.5, 11.0), 6.47−6.44 (m, 1H), 6.43 (d, 1H, J = 2.5), 4.55 (t, 1H, J = 6.5), 4.19 (d, 2H, J = 6.5), 3.92 (s, 3H), 3.82 (s, 3H), 3.77 (s, 3H), 2.60 (s, 3H); δ_C (100 MHz, $CDCl_3$) 160.7, 158.6, 151.8, 145.1, 130.4, 119.1, 118.8, 115.9 (d, J = 18.5 Hz), 113.0, 103.8, 98.6, 56.2, 55.4, 55.2, 50.4, 19.3; ν_{max} (neat)/cm^{-1} 2940, 1606, 1588, 1507, 1456, 1288, 1262, 1206, 1156, 1117, 1031, 823, 772, 735; m/z (ESI) 389 ([M + H]$^+$); HRMS, found 389.1338 ($C_{20}H_{22}FN_2O_3S$ requires 389.1335).

Deprotection to 5-Aminothiazoles 6a−d. General Procedure. The DMB-protected derivative **9** was dissolved in TFA−CH_2Cl_2 (1:4, 10 mL $mmol^{-1}$) and the solution stirred at rt for 20 min and then carefully partitioned between satd $NaHCO_3$ and CH_2Cl_2. The organic layer was separated, dried over $MgSO_4$, and evaporated, followed by purification of the crude material by basic alumina (**9b**, **9c**) or neutral alumina (**9a**, **9d**) column chromatography using the eluent specified.

2-Phenyl-4-(thiophene-2-yl)thiazol-5-amine (6a). Prepared from **9a** (141 mg, 0.35 mmol). Column eluent 10→20→30% EtOAc−hexane, then neat CH_2Cl_2: pale green powder (60 mg, 87%); mp 143−145 °C; δ_H (400 MHz, $CDCl_3$) 7.90−7.85 (m, 2H), 7.46−7.35 (m, 4H), 7.32 (dd, 1H, J = 1.0, 5.0), 7.15 (dd, 1H, J = 3.5, 5.0), 4.12 (br s, 2H); δ_C (100 MHz, $CDCl_3$) 153.7, 140.3, 137.8, 133.8, 132.4, 129.2, 128.8, 127.5, 125.8, 124.0, 123.2; ν_{max} (solid)/cm^{-1} 3259, 3141, 1606, 1536, 1493, 1469, 1432, 1188, 967, 760, 686; m/z (ESI) 259 ([M + H]$^+$); HRMS, found 259.0367 ($C_{13}H_{11}N_2S_2$ requires 259.0364).

4-(4-Methoxy-3-(methoxymethyl)phenyl)-2-(2-phenylpropyl)-thiazol-5-amine (6b). Prepared from **9b** (210 mg, 0.40 mmol). Column eluent 0→1→2% MeOH−CH_2Cl_2. This gave mixed material as a thick, orange gum (112 mg). Further purification by preparative HPLC (Alltech Alltima HP C18 HL 5 μm column, 22 × 150 mm, eluted with 80:20 MeOH−H_2O at 20 mL min^{-1}; UV detection at 254 nm) provided the title compound as an amorphous, pale orange gum (25 mg, 7% overall from **7b**): δ_H 7.68 (d, 1H, J = 2.0), 7.65−7.61 (dd, 1H, J = 1.5, 8.5), 7.37−7.21 (m, 4H), 6.96 (d, 1H, J = 8.5), 4.55 (s, 2H), 3.89 (s, 3H), 3.45 (s, 3H), 3.29−3.13 (br m, 3H), 1.37 (d, 3H, J = 6.5); δ_C (100 MHz, $CDCl_3$) 156.2, 155.3, 145.8, 139.0, 128.5, 128.3, 128.0, 127.2, 126.7, 126.4, 110.7, 69.6, 58.4, 55.6, 41.8, 40.7, 21.8; ν_{max} (solid)/cm^{-1} 2926, 1595, 1498, 1453, 1252, 908, 729, 700; m/z (ESI) 369 ([M + H]$^+$); HRMS, found 369.1649 ($C_{21}H_{25}N_2O_2S$ requires 369.1637).

2-(1,3-Dimethyl-1*H*-pyrazol-5-yl)-4-(4-fluorophenyl)thiazol-5-amine (6c). Prepared from **9c** (119 mg, 0.27 mmol). Column eluent 0→1→2% MeOH−CH_2Cl_2. Yellowish to orange solid (74 mg, 95%): mp 205−207 °C. δ_H (400 MHz, DMSO-d_6) 7.84 (dd, 2H, J = 5.5, 9.0), 7.25 (t, 2H, J = 9.0), 6.34 (s, 1H), 6.17 (s, 2H), 4.08 (s, 3H), 2.16 (s, 3H); δ_C (100 MHz, DMSO-d_6) 161.2 (d, J = 243), 147.1, 146.3, 140.2, 136.5, 132.4 (d, J = 3.0), 131.6, 129.0 (d, J = 8.0), 116.1 (d, J = 21.0), 105.9, 39.4, 13.9; ν_{max} (solid)/cm^{-1} 3293, 3152, 1630, 1498, 1211, 955, 847, 774, 667, 652, 560; m/z (ESI) 289 ([M + H]$^+$); HRMS, found 289.0917 ($C_{14}H_{14}FN_4S$ requires 289.0923).

4-(4-Fluoro-3-methoxyphenyl)-2-methylthiazol-5-amine (6d). Prepared from **9d** (209 mg, 0.54 mmol). Column eluent 10→20→30→40→50→100% EtOAc−isohexane. Thick yellow oil (74 mg, 57%), which crystallized on standing to give a pale yellow solid: mp 116 °C. δ_H (400 MHz, $CDCl_3$) 7.39 (d, 1H, J = 8.0), 7.24−7.17 (m, 1H), 7.11 (t, 1H, J = 10.0), 3.94 (s, 3H), 3.84 (br s, 2H), 2.59 (s, 3H); δ_C (100 MHz, $CDCl_3$) 152.0, 151.3 (d, J = 247), 147.8 (d, J = 10.0), 140.0, 134.4, 131.3 (d, J = 3.5), 119.3 (d, J = 6.5), 116.0 (d, J = 18.5), 112.8, 56.3, 19.2; ν_{max} (solid)/cm^{-1} 3407, 3260, 3152, 1604, 1513, 1266, 1203, 1166, 1118, 1031, 862, 832, 772; m/z (ESI) 239 ([M + H]$^+$); HRMS, found 239.0656 ($C_{11}H_{12}FN_2OS$ requires 239.0654).

Synthesis of Oxazoles 8a−d from Amides 7a−d. General Procedure. Diamide **7** (1 mmol) was dissolved in CH_2Cl_2 (4 mL), and then TFA (2 mL) was added. After 20 min, TFAA (2 mL) was also added and stirring continued for 40 min more. The mixture was evaporated and the residue redissolved in CH_2Cl_2 and then washed with satd $NaHCO_3$. The organic layer was evaporated and the crude material recrystallized from $CHCl_3$−hexane to afford the oxazole-5-trifluoroacetamide **8**.

2,2,2-Trifluoro-*N*-(2-phenyl-4-(thiophene-2-yl)oxazol-5-yl)-acetamide (8a). Pale brown powder (168 mg, 50%): mp 178−180 °C dec; δ_H (400 MHz, DMSO-d_6) 12.35 (br s, 1H), 8.06−8.00 (m, 2H), 7.70 (dd, 1H, J = 1.0, 5.0), 7.62−7.56 (m, 3H), 7.40 (dd, 1H, J = 1.0, 3.5), 7.21 (dd, 1H, J = 3.5, 5.0); δ_C (100 MHz, DMSO-d_6) 158.3, 156.5 (q, J = 38.0), 133.7, 131.5, 131.4, 129.3, 128.9, 128.1, 127.2, 126.1, 125.8, 125.5, 115.4 (q, J = 288); ν_{max} (solid)/cm^{-1} 3238, 1717, 1636, 1537, 1508, 1156, 1028, 713, 684; m/z (ESI) 339 ([M + H]$^+$); HRMS, found 339.0419 ($C_{15}H_{10}F_3N_2O_2S$ requires 339.0415).

2,2,2-Trifluoro-*N*-(4-(4-methoxy-3-(methoxymethyl)phenyl)-2-(2-phenylpropyl)oxazol-5-yl)acetamide (8b). Viscous, pale yellow oil (356 mg, 79%): δ_H (400 MHz, $CDCl_3$) 8.61 (s, 1H), 7.54 (d, 1H, J = 2.5), 7.50 (dd, 1H, J = 2.5, 8.5), 7.33 (t, 2H, J = 7.5), 7.28−7.20 (m, 3H), 6.86 (d, 1H, J = 8.5), 4.49 (s, 2H), 3.85 (s, 3H), 3.45 (s, 3H), 3.40−3.30 (m, 1H), 3.06−2.91 (m, 2H), 1.35 (d, 3H, J = 7.0); δ_C (100 MHz, $CDCl_3$) 161.4, 157.2, 156.3 (q, J = 39.5), 145.3, 132.4, 131.7, 128.6, 126.9, 126.8, 126.7, 126.6, 122.0, 115.5 (q, J = 288), 110.4, 69.3, 58.5, 55.5, 38.2, 37.0, 21.3; ν_{max} (neat)/cm^{-1} 2965, 1750, 1500, 1149, 1024,

699; m/z (ESI) 449 ([M + H]$^+$); HRMS, found 449.1698 ($C_{23}H_{24}F_3N_2O_4$ requires 449.1688).

2,2,2-Trifluoro-*N*-(4-(4-fluoro-3-methoxyphenyl)-2-methyloxazol-5-yl)acetamide (8d). Off-white, microcrystalline solid (158 mg, 50%): mp 140−141 °C; δ_H (400 MHz, $CDCl_3$) 8.19 (s, 1H), 7.29−7.24 (m, 1H), 7.13−7.06 (m, 2H), 3.91 (s, 3H), 2.50 (s, 3H); δ_C (100 MHz, $CDCl_3$) 159.8, 156.4 (q, J = 38.5), 152.4 (d, J = 248), 147.9 (d, J = 10.0), 132.7, 132.2, 126.1 (d, J = 3.5), 118.7 (d, J = 7.0), 116.4 (d, J = 18.0), 115.4 (q, J = 288), 111.6, 56.1, 14.2; ν_{max} (solid)/cm^{-1} 3230, 1722, 1541, 1518, 1279, 1206, 1175, 872, 780, 737, 668; m/z (ESI) 319 ([M + H]$^+$); HRMS, found 319.0702 ($C_{13}H_{11}F_4N_2O_3$ requires 319.0706).

Thiazole-5-amides 10. Method A, from Primary 5-Aminothiazoles 6. Pyridine (2.5 equiv) was added to a solution or suspension of the primary 5-aminothiazole **6** (between 0.25−0.5 mmol) in dry THF (10 mL mmol^{-1}) under N_2. The relevant acyl chloride (1.1 equiv) was introduced to the reaction mixture, which was then stirred at rt for 4 h, after which time the solvent was evaporated. The remaining material was stirred rapidly with ethyl acetate (20 mL) and 1 M HCl (10 mL) for 10−15 min, and then the organic layer was separated by passing through a liquid−liquid extraction column. After evaporation of the organic extract, the amide product was further purified as indicated for each example (see the Supporting Information); typically, a single recrystallization from EtOAc−hexane gave a sample of good purity.

Method B, from Secondary 5-Aminothiazoles 5. *N*,*N*-Diisopropylethylamine (1.5 equiv) was added to a 0.1 M solution of the secondary 5-aminothiazole **5** (between 0.30−0.75 mmol) in dry THF, under N_2. The relevant acyl chloride (1.3 equiv) was introduced, followed by DMAP (catalytic amount), and the mixture stirred at rt for 24 h. Workup and purification were carried out as detailed for method A.

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Supporting Information Available: Characterization data for libraries **1**, **5**, and **10**; copies of ^{1}H and ^{13}C NMR spectra for all compounds; analysis of compound purity by HPLC. This material is available free of charge via the Internet at http://pubs.acs.org.