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Solution versus Fluorous versus Solid-Phase Synthesis of 2,5-Disubstituted 1,3-Azoles. Preliminary Antibacterial Activity Studies

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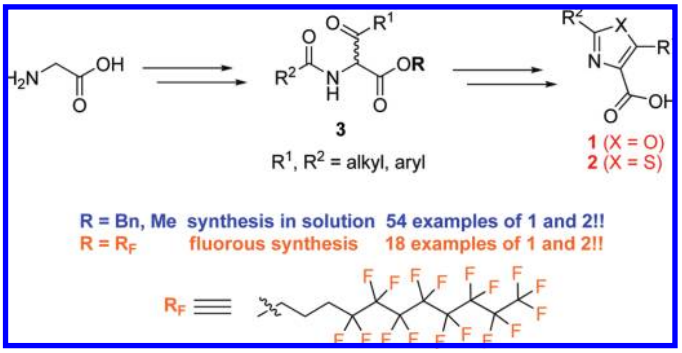

A small library of compounds with an oxa(thia)zole scaffold and structural diversity in both positions 2 and 5 has been synthesized. Double acylation of a protected glycine affords intermediate α-amido-β-ketoesters, which in turn can be dehydrated to afford 1,3-oxazoles or reacted with Lawesson's reagent to furnish 1,3-thiazoles. This procedure was designed with its adaptation to fluorous techniques in mind. Thus, when a protected glycine with a fluorous tag in the ester moiety is used as a starting material, the synthesis can be easily completed without column chromatography purification of intermediate compounds with good to excellent yields, thus affording a suitable entry to the preparation of small libraries of these bioactive compounds. The prepared oxa(thia)zoles were assayed for their antibacterial activity, and several of them were active against *Staphylococcus aureus*.

Introduction

The synthesis of 1,3-oxazoles and 1,3-thiazoles has attracted the attention of many chemists due to their presence in a large number of natural products, many of which have been isolated from marine organisms.[1] Most of these compounds display significant biological activities as cytotoxic, antifungal, antiviral, antibacterial, antileukemia agents, enzyme inhibitors, and peripheral analgesics.[2] The structural diversity of complex naturally occurring 1,3-azoles and the biological activity of synthetic analogues have ensured that new methods continue to be developed for their synthesis. In Nature, oxazoles are formed through enzyme-catalyzed cyclodehydration−oxidation of derivates of acylserine,[3] and most of the synthetic methods developed somehow mimic this scheme. Typical procedures for the preparation of oxazoles include cyclodehydration of α-acylamino-ketones, esters, or amides (known as the Robinson−Gabriel oxazole synthesis),[4] treatment of tosylmethyl isonitrile with

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aldehydes under basic catalysis,[5] reaction of α-metalated isonitriles with acid chlorides,[6] addition of α-diazocarbonyl compounds to nitriles, and decomposition in the presence of a Lewis acid or a transition metal catalyst and different copper-,[7] gold-,[8] ruthenium-,[9] and rhodium-catalyzed[10] reactions.

Similar methods employed for the synthesis of 1,3-oxazoles can be used for the preparation of 1,3-thiazoles. The most common method for the synthesis of the latter was developed by Hantzsch and entails the condensation of a suitably substituted α-haloketone with a thioamide.[11] Other methods include the reaction of α-aminonitriles with CS_2, COS, derivatives of dithiocarboxylic acids, and isothiocyanates,[12] as well as the reaction of α-acylaminoketones with phosphorus pentasulfide or the Lawesson's reagent, which affords 1,3-thiazoles.[13]

On the basis of the aforementioned biological activity of 1,3-oxa(thia)zoles, these compounds seem to be good candidates for the preparation of a library of potentially bioactive compounds. In this context, fluorous synthesis is now widely accepted as a key methodology for the preparation of large numbers of chemical libraries avoiding tedious and time-consuming purification steps.[14] Fluorous synthesis displays the advantages of both solid-phase and solution syntheses. Like in solid-phase techniques, the separation and purification of the compounds are fast and easy. However, instead of a solid support, a fluorous tag (perfluoroalkyl chain) is attached to our compound.[15] The presence of the fluorous tag facilitates the purification of the products through fluorous solid-phase extraction (F-SPE)[16] and at the same time makes it possible to follow the reactions by means of techniques such as TLC, GC, or NMR. Naturally, the perfluorinated chain must be compatible with the reaction conditions and easy to remove at the end of the synthetic strategy to furnish the desired product.[17]

Herein, we would like to report on a simple and efficient synthesis of a small library of 1,3-oxazoles **1** and 1,3-thiazoles **2** in solution starting from glycine, employing inexpensive and accessible compounds. The synthesis starts with a double C,N-acylation, which affords α-amido-β-ketoester intermediates **3**, which in turn will be finally transformed into the corresponding oxazoles **1** or thiazoles **2** with a variety of groups in positions 2 and 5. We will also describe the adaptation of the synthetic strategy to fluorous synthesis (Scheme 1). Finally, we will indicate the outcome of some preliminary studies of the antibacterial activity of the 1,3-oxazoles **1** and 1,3-thiazoles **2** synthesized.

SCHEME 1. Preparation of 1,3-Oxazoles 1 and 1,3-Thiazoles 2 by Means of Solution and Fluorous Syntheses

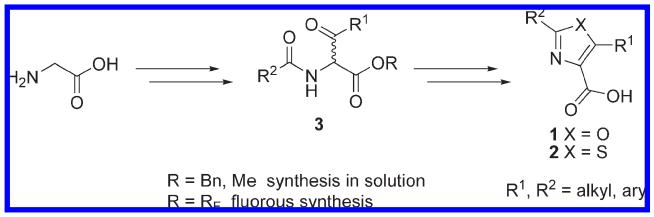
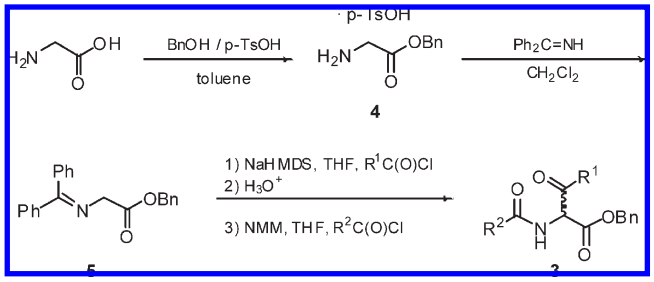


TABLE 1. Synthesis of Double α-Amido-β-Ketoesters 3 from Protected Glycine 5

entry	Product	R^1	R^2	yield (%)[a]
1	**3a**	C_6H_5	C_6H_5	55
2	**3b**	C_6H_5	*o*-FC_6H_4	57
3	**3c**	C_6H_5	*o*-$MeOC_6H_4$	87
4	**3d**	C_6H_5	*o*-$CF_3OC_6H_4$	87
5	**3e**	C_6H_5	*m*-$MeOC_6H_4$	74
6	**3f**	C_6H_5	*m*-$CF_3OC_6H_4$	78
7	**3g**	C_6H_5	*p*-$MeOC_6H_4$	61
8	**3h**	C_6H_5	*p*-$CF_3OC_6H_4$	62
9	**3i**	C_6H_5	3,4,5-$(OMe)_3C_6H_2$	79
10	**3j**	C_6H_5	Piperonyl	80
11	**3k**	C_6H_5	*p*-$NO_2C_6H_4$	62
12	**3l**	C_6H_5	*p*-$CF_3OC_6H_4$	68
13	**3m**	C_6H_5	Me	80
14	**3n**	C_6H_5	*t*-Bu	91
15	**3o**	*o*-$MeOC_6H_4$	C_6H_5	64
16	**3p**	*o*-$MeOC_6H_4$	*o*-$MeOC_6H_4$	62
17	**3q**	*p*-$MeOC_6H_4$	C_6H_5	52
18	**3r**	*p*-$MeOC_6H_4$	*o*-$MeOC_6H_4$	52
19	**3s**	*t*-Bu	C_6H_5	42
20	**3t**	*i*-Pr	C_6H_5	24
21	**3u**	Me	C_6H_5	
22	**3v**	*p*-MeC_6H_4	C_6H_5	65
23	**3w**	*p*-ClC_6H_4	*p*-ClC_6H_4	53
24	**3x**	*p*-$NO_2C_6H_4$	C_6H_5	54

[a]Reactions carried out on a 1 mmol scale. Overall yields of purified products after three steps (from compound **5**).

SCHEME 2. Double Acylation of Protected Glycine



Results and Discussion

Solution Synthesis of 1,3-Oxazoles 1 and 1,3-Thiazoles 2: The synthetic strategy starts with a double glycine protection. Thus, the first step consists of the double protection of the carboxylic moiety of glycine by means of treatment with benzyl alcohol in the presence of a catalytic amount of

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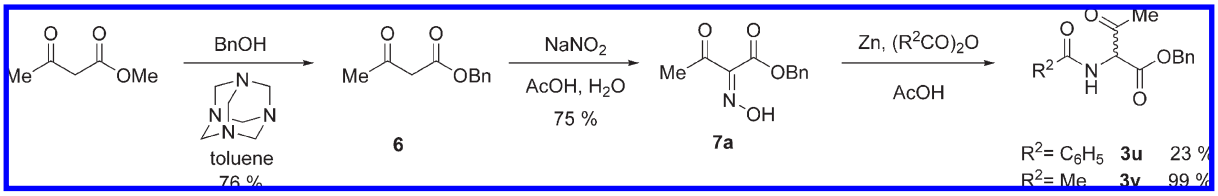
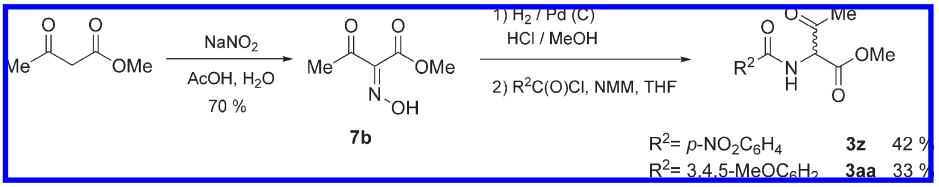
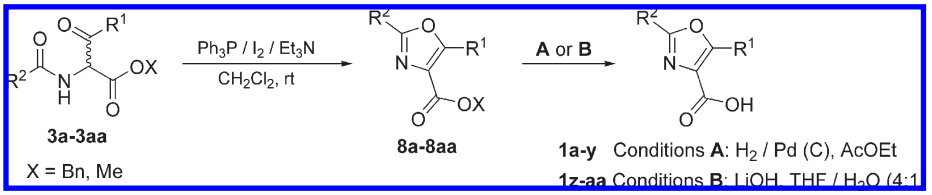
SCHEME 3. Alternative Synthesis of α-Amido-β-Ketoesters 3u and 3y



SCHEME 4. Synthesis of α-Amido-β-Ketoesters 3z and 3aa



SCHEME 5. Cyclization and Deprotection of α-Amido-β-Ketoesters 3



p-toluenesulfonic acid in toluene and, then, in the second step, benzophenone imine is added to a solution of the benzyl-protected glycine to furnish the double-protected glycine **5**.[18] Condensation of **5** with several different acyl chlorides in the presence of NaHMDS as a base, followed by imine hydrolysis and subsequent acylation of the free amino, gave α-amido-β-ketoester intermediates **3** in good to excellent yields for the three steps (52−91%) when R^1 is aromatic (Table 1, entries 1−18) and in low yield when R^1 is aliphatic (Table 1, entries 19 and 20) (Scheme 2).

It was not possible to obtain the desired product when R^1 = Me (Table 1, entry 21). This anomalous behavior might be understood assuming that acetyl chloride undergoes an elimination reaction in the basic reaction medium to afford ketene, which might escape the reaction medium.

The unsuccessful synthesis of the α-amido-β-ketoester **3u** prompted us to look for an alternative synthesis of 2-substituted 5-methyloxa(thia)zole-4-carboxylic acid derivatives, so we altered the initial steps of the proposed synthetic path shown in Scheme 2. Thus, commercially available methyl acetoacetate was transesterified and conveniently nitrosated to achieve oxime **7a** in good yields.[19] Reduction of oxime **7a** with Zn dust in glacial acetic acid and subsequent reaction with benzyl anhydride gave the desired α-amido-β-ketoester **3u** although in low yield (23%). However, in a different example in which acetic anhydride was employed as the acylating reagent, α-amido-β-ketoester **3y** was obtained in almost quantitative yield (Scheme 3).

In an attempt to improve the total yield of this alternative strategy, two later modifications were performed; first, and given that the last step of the strategy is the deprotection of the ester moiety in position 4 of the oxazole ring, the transesterification reaction was eliminated, and second, due to a smaller number of available commercial acid anhydrides in comparison with commercial acid chlorides, oxime **7b** (obtained directly from methyl acetoacetate through nitrosation) was catalytically reduced with hydrogen and reacted with two different acid chlorides (R^2 = *p*-$NO_2C_6H_4$, 3,4,5-$(MeO)_3C_6H_2$) to afford methyl α-amido-β-ketoesters **3z** and **3aa** in 42 and 33% yield, respectively (Scheme 4). In this way, we achieved higher yields than, for example, **3u** and skipped one synthetic step.

The next step for the synthesis of the oxazoles is the cyclization of compounds **3**. This reaction was performed by treating the α-amido-β-ketoesters **3** with triphenylphosphine in the presence of iodine and triethylamine in dichloromethane at room temperature to give 2,5-disubstituted oxazoles **8** in good to excellent yields (62−98%) (Scheme 5 and Table 2).[20] Finally, the deprotection of the ester in position 4 of the oxazole ring through palladium-catalyzed hydrogenation (benzyl ester in the case of **8a**−**8y**) or hydrolysis with LiOH in THF/H_2O (methyl ester in the case of **8z** and **8aa**) gave the final oxazole compounds **1** in excellent yields (96−99%) (Scheme 5 and Table 2).

Moreover, it is possible to obtain thiazoles from the same α-amido-β-ketoesters **3** by reaction of such intermediates with Lawesson's reagent. Thus, thiazoles **9** were obtained in high to excellent yields (60−97%) except in the case of **9d**, which was obtained in only 30% yield. This drop in yield might be caused by steric hindrance between Lawesson's phosphine and the trifluoromethyl group in the *ortho* position of the R^2 group. Finally, the ester deprotection was

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TABLE 2. Synthesis of 2,5-Disubstituted Oxazoles 8 and 1

entry	3	8[a]	yield (%)[b]	1	yield (%)[b]
1	**3a**	**8a**	73	**1a**[c]	99
2	**3b**	**8b**	83	**1b**[c]	99
3	**3c**	**8c**	96	**1c**[c]	97
4	**3d**	**8d**	85	**1d**[c]	99
5	**3e**	**8e**	91	**1e**[c]	99
6	**3f**	**8f**	92	**1f**[c]	99
7	**3g**	**8g**	91	**1g**[c]	97
8	**3h**	**8h**	89	**1h**[c]	99
9	**3i**	**8i**	91	**1i**[c]	98
10	**3j**	**8j**	97	**1j**[c]	96
11	**3k**	**8k**	98	**1k**[d]	99
12	**3l**	**8l**	96	**1l**[c]	98
13	**3m**	**8m**	81	**1m**[c]	99
14	**3n**	**8n**	83	**1n**[c]	99
15	**3o**	**8o**	86	**1o**[c]	99
16	**3p**	**8p**	91	**1p**[c]	98
17	**3q**	**8q**	94	**1q**[c]	98
18	**3r**	**8r**	74	**1r**[c]	99
19	**3s**	**8s**	91	**1s**[c]	99
20	**3t**	**8t**	93	**1t**[c]	99
21	**3u**	**8u**	75	**1u**[c]	99
22	**3v**	**8v**	70	**1v**[c]	99
23	**3w**	**8w**	99	**1w**[c]	98
24	**3x**	**8x**	62	**1x**[d]	98
25	**3y**	**8y**	82	**1y**[c]	99
26	**3z**	**8z**	80	**1z**[e]	99
27	**3aa**	**8aa**	80	**1aa**[e]	96

[a]Reactions carried out on a 0.2 mmol scale. A solution of α-amido-β-ketoesters **3** in CH_2Cl_2 (2 mL) is added to a solution of triphenylphosphine (2 equiv) and iodine (2 equiv) in CH_2Cl_2 (4 mL) and stirred at rt until the reaction is complete (TLC). [b]Yields of purified products. [c]Hydrogenolysis carried out through treatment of oxazole **8** with Pd(C) (10%) in AcOEt (5 mL) under 1 atm of H_2. [d]$Pd(OH)_2$ was used as catalyst to reduce the nitro group to amino simultaneously. [e]Hydrolysis performed by means of treatment of oxazole **8** with LiOH (3 equiv) in THF/H_2O (4:1) (5 mL).

achieved in the same way as for oxazoles **1**, which is palladium-catalyzed hydrogenolysis for **9a**−**y** and hydrolysis by LiOH in THF/H_2O in the case of **9z** and **9aa** (Scheme 6 and Table 3).

Fluorous Synthesis of 1,3-Oxazoles 1 and 1,3-Thiazoles 2: The synthetic strategy is analogous to that described previously for compounds **1** and **2**, although now it is necessary to attach a fluorous tag to a suitably protected glycine. Thus, in the first step, commercially available alcohol **10** is attached to *N*-Boc-protected glycine by means of esterification to give compound **11** with excellent yield (97%). The Boc protecting group was then replaced by phenonimine in good yield to give an intermediate **12** analogous to double-protected glycine **5**. In the same way as for the synthesis of α-amido-β-ketoesters **3**, substrate **12** was subjected to double C,N-acylation to afford fluorous α-amido-β-ketoesters **13** (Scheme 7). This reaction displayed good yields (49−60% for three steps) when R^1 is aromatic (Table 4, entries 1−5), although the yields are somewhat lower than in the corresponding solution synthesis (42−91%). When R^1 is aliphatic (Table 4, entries 6 and 7), the yields are moderate and in this case similar to those obtained in solution (53 and 22% vs 42 and 24%).

Once again, it was not possible to obtain the desired product **13h** when R^1 = Me (Table 4, entry 8) possibly because of ketene formation. Like in the corresponding solution synthesis, we made use of an alternative strategy. Thus, we started with a transesterification reaction to obtain fluorous ketoester **14**;[19] the reaction, however, was not complete, and some starting fluorous alcohol **10** remained in the reaction mixture. This fact meant that the mixture had to be purified by means of flash chromatography on silica gel, which allowed us to recover the fluorous alcohol. A nitrosation reaction on **14** gave oxime **15** in good yield. Catalytic reduction of **15** with hydrogen in the presence of Pd (C) followed by reaction with benzoyl chloride (procedure A, Scheme 8) gave a complex mixture of fluorous products, and thus intermediate **13h** had to be purified by flash chromatography with a yield of the purified compound of only 23%. In contrast, reduction of **14** with Zn dust in acetic medium and subsequent reaction with acetic anhydride (procedure B, Scheme 8) exclusively gave fluorous α-amido-β-ketoester **13i** in 84% yield.

The cyclization of fluorous α-amido-β-ketoesters **13** was achieved by means of treatment with triphenylphosphine in the presence of iodine and triethylamine in good to excellent yields (71−98%) except for compounds **13d** and **13e** (in these two compounds, R^2 = alkyl group), in which the reaction stopped with still a large amount of starting material unreacted (the reaction progress was followed by TLC in both cases). A temperature increase or a bigger excess of reagents did not improve the yield. Finally, we determined that when concentrated H_2SO_4 was used as a dehydrating agent to perform this reaction α-amido-β-ketoesters **13d** and **13e** were obtained in good yields (63 and 73%, respectively). The last step was, as in the synthesis in solution, the deprotection of the carboxylic moiety, which was achieved by means of basic hydrolysis with LiOH in THF/H_2O (4:1) to give 2,5-disubstituted 1,3-oxazoles in high yields (95−99%) (Scheme 9 and Table 5).

The cyclization of fluorous α-amido-β-ketoesters **13** with Lawesson's reagent gave fluorous 1,3-thiazoles **17** in high yields (54−82%), which are only slightly lower than those obtained for the analogous nonfluorous 1,3-thiazoles **9** (67−97%).[21] Again, the last step was the basic hydrolysis with LiOH in THF/H_2O (4:1) to deprotect the carboxylic moiety, which gave 2,5-disubstituted 1,3-thiazoles **2** in high yields (95−99%) (Scheme 10 and Table 6).

Although the yields are somewhat lower in the fluorous synthesis when compared to the solution synthesis, the former has several advantages, which are mostly related to the ease and speed of purification for the intermediate compounds. These processes are both faster and less expensive in the fluorous synthesis because the cartridges for the fluorous solid-phase extraction (F-SPE) can be recycled and reused many times.

We have previously described the synthesis of various fluorinated compounds in solid phase as, for example, fluorinated partially modified retropeptides,[22] fluorinated uracils and thiouracils,[23] and β,β-difluorinated cyclic quaternary α-amino acid derivatives.[24] We were also interested in the synthesis of the 2,5-disubstituted 1,3-oxazoles **1** and 2,5-disubstituted 1,3-thiazoles **2** in solid phase, and we

(21) Compare **3a** with **13a**, **3g** with **13b**, **3h** with **13c**, **3m** with **13d**, **3n** with **13e**, **3s** with **13f**, **3t** with **13g**, and **3u** with **13h**.

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SCHEME 6. Synthesis of Thiazoles 2 from α-Amido-β-Ketoesters 3

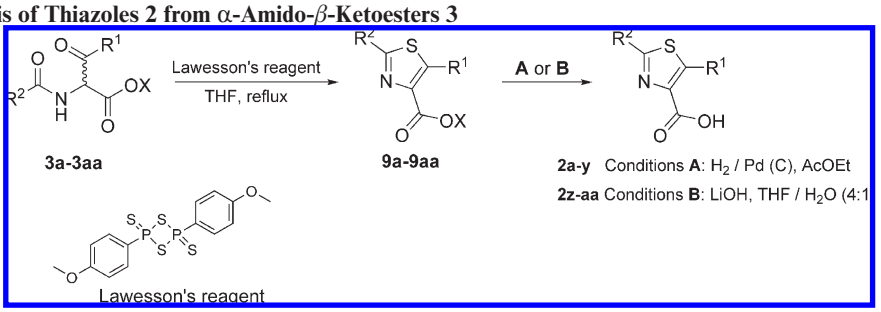


TABLE 3. Synthesis of 2,5-Disubstituted Thiazoles 9 and 2

entry	3	9[a]	yield (%)[b]	2	yield (%)[b]
1	**3a**	**9a**	97	**2a**[c]	99
2	**3b**	**9b**	95	**2b**[c]	99
3	**3c**	**9c**	68	**2c**[c]	96
4	**3d**	**9d**	30	**2d**[c]	97
5	**3e**	**9e**	98	**2e**[c]	97
6	**3f**	**9f**	95	**2f**[c]	96
7	**3g**	**9g**	67	**2g**[c]	99
8	**3h**	**9h**	92	**2h**[c]	99
9	**3i**	**9i**	83	**2i**[c]	96
10	**3j**	**9j**	60	**2j**[c]	96
11	**3k**	**9k**	89	**2k**[d]	97
12	**3l**	**9l**	61	**2l**[c]	97
13	**3m**	**9m**	81	**2m**[c]	99
14	**3n**	**9n**	89	**2n**[c]	97
15	**3o**	**9o**	80	**2o**[c]	99
16	**3p**	**9p**	68	**2p**[c]	99
17	**3q**	**9q**	73	**2q**[c]	97
18	**3r**	**9r**	84	**2r**[c]	96
19	**3s**	**9s**	67	**2s**[c]	97
20	**3t**	**9t**	70	**2t**[c]	97
21	**3u**	**9u**	87	**2u**[c]	98
22	**3v**	**9v**	90	**2v**[c]	98
23	**3w**	**9w**	67	**2w**[c]	99
24	**3x**	**9x**	60	**2x**[d]	97
25	**3y**	**9y**	86	**2y**[c]	99
26	**3z**	**9z**	86	**2z**[e]	99
27	**3aa**	**9aa**	80	**2aa**[e]	98

[a]Reactions carried out on a 0.2 mmol scale. Lawesson's reagent (2 equiv) is added to a solution of α-amido-β-ketoesters **3** in anhydrous THF (5 mL) and the mixture refluxed until no starting material is detected by TLC. [b]Yields of purified products. [c]Hydrogenolysis carried out by treatment of thiazole **9** with Pd (C) (10%) in AcOEt (5 mL) under atmospheric pressure of hydrogen. [d]$Pd(OH)_2$ was used as catalyst to reduce the nitro group to an amino group simultaneously to the benzyl ester deprotection. [e]Hydrolysis performed by means of treatment of thiazole **9** with LiOH (3 equiv) in THF/H_2O (4:1) (5 mL).

started the synthesis by attaching the Fmoc-glycine to Wang resin and deprotection of the Fmoc group by standard methods (Scheme 11). Next, we again protected the amino group with benzophenonimine to obtain the protected glycine **19**. These three steps were easy, and the corresponding IR spectra showed the expected bands (see Supporting Information). However, it was very difficult to control the first acylation step for the preparation of **20**, and thus a very complex mixture was obtained (as deduced from the IR spectrum). Several different conditions were tested, for example, changing the base used to generate the enolate, the amount of base, the number of equivalents of acid chloride, the addition of other acid derivatives (anhydrides and esters), the temperature of formation of enolate, the temperature of addition of acid chloride, and the reaction time (from 1 h to 2 days). In spite of our efforts, in every case, many new, low intensity bands were observed in the IR spectrum. Moreover, while we also cleaved in every case the material from the beads and analyzed it by means of ^{1}H NMR, we could only observe very complex mixtures that would have been useless in the final synthetic steps. The fluorous synthesis displays the advantages of both solid-phase (which are mainly the purification steps) and solution syntheses; therefore, in view of the difficulties associated with the solid-phase synthesis, we decided to abandon it.

There are some examples of 1,3-azoles that are considered dipeptide mimetics in the literature.[25] For this reason, we thought that an interesting extension of this work would be the addition of an amino acid to the carboxylic moiety in position 4 of the 1,3-oxazoles **1** and 1,3-thiazoles **2** and in this way extend the "peptidic chain". With this purpose in mind, benzyl-protected valine and leucine were condensed to 1,3-azoles **1a** and **1y** and to 1,3-thiazoles **2a** and **2y** by means of standard methods in good yields (64−87%). Palladium-catalyzed deprotection of the benzyl ester gave the desired products **22** in quantitative yield (Scheme 12 and Table 7).

Finally, we tested the antibacterial activity of the 1,3-oxazoles **1** and 1,3-thiazoles **2**. The above-mentioned compounds were evaluated for their antimicrobial activity using a disk diffusion method with 50 μg/disk against *Staphylococcus aureus* ATCC 29213, *Escherichia coli* ATTC 25922, *Micrococcus luteus* ATCC 49732, *Mycobacterium smegmatis* (clinical isolate), and *Candida albicans* ATCC 14053. The initial screening demonstrated promising activities against *S. aureus* (see Table 8) with **1a** (11 mm zone), **1c** (11 mm zone), **1g** (12 mm zone), **1r** (15 mm zone), **2b** (12 mm zone), **2c** (20 mm zone), **2f** (10 mm), **2h** (10 mm zone), **2o** (15 mm), and **2p** (14 mm).

Interestingly, compound **2h** was also active against *M. luteus* (13 mm zone) and methicillin-resistant *S. aureus* (MRSA) ATCC 33591 (13 mm zone). The rest of the assayed compounds were not active against the other studied organisms. For **1s** and **2s**, there was some decreased growth around the disk but not a clear zone of inhibition. These results suggest that further modification of these scaffolds might lead to compounds with enhanced antimicrobial activities. It is unclear why **2a** and **1h** were inactive based on their similarity to the active compounds.

Conclusion

In this paper, we have established a new straightforward and easy methodology to synthesize 2,5-disubstituted

(25) (a) Gordon, T. D.; Singh, J.; Hansen, P. E.; Morgan, B. A. *Tetrahedron Lett.* **1993**, *34*, 1901–1904. (b) Falorni, M.; Dettori, G.; Giacomelli, G. *Tetrahedron: Asymmetry* **1998**, *9*, 1419–1426. (c) Christensen, C.; Schiodt, C. B.; Foged, N. T.; Meldal, M. *QSAR Comb. Sci.* **2003**, *22*, 754–766.

SCHEME 7. Fluorous Synthesis of α-Amido-β-Ketoesters 13

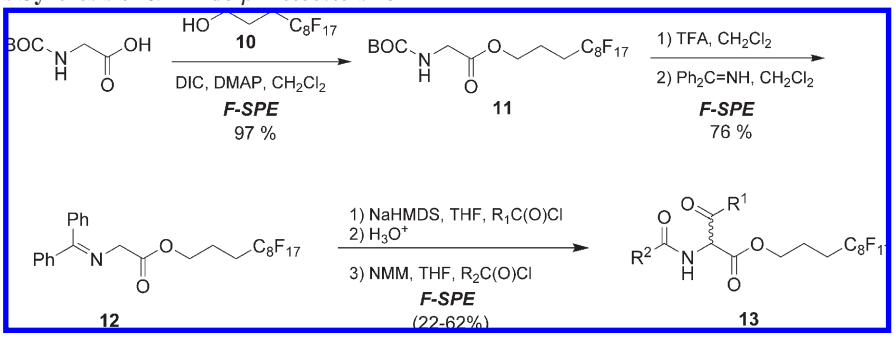


TABLE 4. Fluorous Synthesis of α-Amido-β-Ketoesters 13 from Protected Glycine 12

entry	product	R^1	R^2	yield (%)[a]
1	**13a**	C_6H_5	C_6H_5	60
2	**13b**	C_6H_5	*p*-$MeOC_6H_4$	49
3	**13c**	C_6H_5	*p*-$CF_3C_6H_4$	56
4	**13d**	C_6H_5	Me	56
5	**13e**	C_6H_5	*t*-Bu	54
6	**13f**	*t*-Bu	C_6H_5	53
7	**13g**	*i*-Pr	C_6H_5	22
8	**13h**	Me	C_6H_5	

[a]Reactions carried out on a 1 mmol scale. Yields of purified products after three steps (from compound **12**).

1,3-azoles **1** and 1,3-thiazoles **2**, which starts with inexpensive, commercially available reagents. In this way, a library of more than 50 azoles and thiazoles has been synthesized. We have successfully adapted the strategy to fluorous synthesis. Although the total yields of the fluorous synthesis are slightly lower than in the synthesis in solution, the easy purification by simple fluorous solid-phase extraction (F-SPE) results in substantial time economy. The prepared compounds have shown promising antibacterial activity in preliminary in vitro testing.

Experimental Section

General Procedure for the Synthesis of α-Amido-β-Ketoesters 3 and 13: A solution of **5** or **12** (1 equiv) in anhydrous THF (5 mL) was cooled to −78 °C under argon atmosphere, and a 1 M solution of sodium bis(trimethylsilyl)amide in THF (1 equiv) was slowly added while maintaining the reaction temperature at −78 °C. After 30 min, the red solution of the Schiff base anion was added via cannula to a stirred solution of the acyl chloride (1 equiv) in anhydrous THF (3 mL) at −78 °C, and the mixture was stirred for 2 h. The reaction mixture was quenched with 1 M HCl solution (3 mL) and concentrated to dryness under reduced pressure. The residue was suspended in ether (5 mL) and filtered to remove benzophenone. The intermediate β-ketoester hydrochloride salt was obtained as a white solid and used in the next reaction without any additional purification. *N*-Methyl morpholine (1.5 equiv) was added to a cooled solution (−20 °C) of β-ketoester hydrochloride salt (1 equiv) in anhydrous THF (5 mL) under argon atmosphere. Acyl chloride (1 equiv) was slowly added while maintaining the reaction mixture at −20 °C, and the bath was removed after stirring for 15 min. The reaction mixture was stirred for an additional 2 h, and the solvent was removed under reduced pressure. The residue was partitioned between ethyl acetate (3 mL) and water (3 mL). The aqueous layer was extracted with AcOEt (3 × 5 mL), and the organic layers were dried over anhydrous sodium sulfate and the solvents removed under reduced pressure to yield the crude product, which was then purified by flash chromatography on silica gel for compounds **3** and fluorous chromatography for compounds **13**.

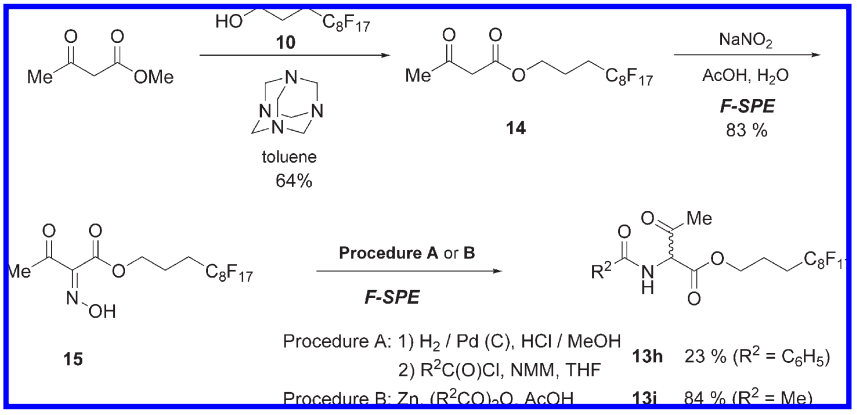
Benzyl 2-(2-methoxybenzamido)-3-oxo-3-phenylpropanoate (3c): Yield 87%; colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 9.28 (d, J = 7.4 Hz, 1H), 8.09 (dd, J_1 = 1.8 Hz, J_2 = 7.8 Hz, 1H), 8.03 (d, J = 7.2 Hz, 2H), 7.48 (tt, J_1 = 1.1 Hz, J_2 = 1.8 Hz, J_3 = 7.5 Hz, 1H), 7.34 (t, J = 7.7 Hz, 3H), 7.09−7.16 (m, 3H), 6.98−7.05 (m, 2H), 6.94 (dt, J_1 = 0.9 Hz, J_2 = 7.7 Hz, 1H), 6.86 (d, J = 8.1 Hz, 1H), 6.36 (d, J = 6.9 Hz, 1H), 5.08 (d, J = 12.3 Hz, 1H), 5.01 (d, J = 12.3 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 191.5 (C), 166.5 (C), 164.7 (C), 157.9 (C), 134.6 (C), 134.3 (C), 134.1 (CH), 133.3 (CH), 132.1 (CH), 129.4 (CH), 128.6 (CH), 128.3 (CH), 128.1 (CH), 127.8 (CH), 121.0 (CH), 120.1 (C), 111.4 (CH), 67.7 (CH_2), 59.1 (CH), 55.9 (CH_3); HRMS (EI) m/z calcd for $C_{24}H_{21}NO_5$ 403.1420, found 403.1425.

3-(Perfluorooctyl)propyl 2-(benzamido)-3-oxo-3-phenylpropanoate (13a): Yield 60%; yellowish solid; mp 91−93 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.94 (d, J = 8.1 Hz, 2H), 7.65 (d, J = 8.1 Hz, 2H), 7.41 (d, J = 6.9 Hz, 2H), 7.17−7.36 (m, 4H), 6.21 (dd, J_1 = 1.2 Hz, J_2 = 7.2 Hz, 1H), 3.89−4.11 (m, 2H), 1.55−1.83 (m, 4H); ^{19}F NMR (282 MHz, $CDCl_3$) δ ppm −81.31 (t, J = 9.6 Hz, 3F), −114.96 (t, J = 13.8 Hz, 2F), −122.34 (br s, 6F), −123.19 (s, 2F), −123.79 (s, 2F), −126.60 (s, 2F); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 191.4 (C), 167.0 (C), 166.5 (C), 134.7 (CH), 134.0 (C), 132.9 (C), 132.1 (CH), 129.5 (CH), 128.8 (CH), 128.6 (CH), 127.3 (CH), 64.8 (CH_2), 58.6 (CH), 27.5 (t, J = 22.4 Hz), 19.7 (CH_2); HRMS (FAB) m/z calcd for $C_{27}H_{18}F_{17}NO_4$ (M + 1) 744.1043, found 744.1038.

Reduction/Acylation of Oximes 7 and 15. Procedure A: Reduction with Pd/AcOH. Pd/C (25% w/w, 0.1 equiv) was added to a solution of oxime **7** or **15** (1 equiv) in a 1 M solution of HCl in MeOH (3 mL) and stirred at rt under atmospheric pressure of hydrogen for 24 h. The reaction mixture was filtered through Celite, and the solid residue was washed with MeOH (3 × 2 mL). The combined filtrates were concentrated under reduced pressure to yield a yellowish solid, which was dissolved in THF (5 mL). *N*-Methyl morpholine (1.5 equiv) and acyl chloride (1 equiv) were slowly added to the previous solution, and the reaction mixture was stirred for an additional 5 h. The solvent was removed under reduced pressure, and the residue was partitioned between ethyl acetate (3 mL) and water (3 mL). The aqueous layer was extracted with AcOEt (3 × 5 mL), and the organic layers were dried over anhydrous sodium sulfate and the solvents removed under reduced pressure to yield the crude product, which was then purified, when necessary, by means of flash chromatography on silica gel.

Methyl 2-(4-nitrobenzamido)-3-oxobutanoate (3z): Yield 42%; yellowish solid; mp 103−105 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.31 (d, J = 9.0 Hz, 2H), 8.01 (d, J = 9.0 Hz, 2H), 7.40 (d, J = 5.4 Hz, 1H), 5.44 (d, J = 6.3 Hz, 1H), 3.87 (s, 3H), 2.48 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 197.8 (C), 166.1

SCHEME 8. Alternative Fluorous Synthesis of α-Amido-β-Ketoesters 13h and 13i



SCHEME 9. Fluorous Cyclization and Deprotection of α-Amido-β-Ketoesters 13

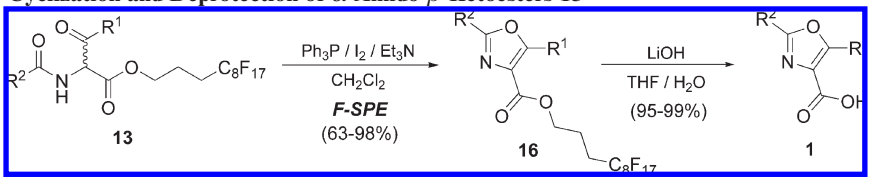


TABLE 5. Fluorous Synthesis of 2,5-Disubstituted Oxazoles 16 and 1

entry	13	16[a]	yield (%)[b]	1[d]	yield (%)[b]
1	**13a**	**16a**	98	**1a**	99
2	**13b**	**16b**	95	**1b**	95
3	**13c**	**16c**	98	**1c**	97
4	**13d**	**16d**[c]	63	**1d**	99
5	**13e**	**16e**[c]	73	**1e**	99
6	**13f**	**16f**	71	**1f**	99
7	**13g**	**16g**	76	**1g**	99
8	**13h**	**16h**	72	**1h**	98
9	**13i**	**16i**	82	**1i**	97

[a]Reactions carried out on a 0.2 mmol scale. A solution of α-amido-β-ketoesters **13** in CH_2Cl_2 (2 mL) is added to a solution of triphenylphosphine (2 equiv) and iodine (2 equiv) in CH_2Cl_2 (4 mL) and stirred at rt until the reaction is finished (TLC). [b]Yields of purified products. [c]Cyclization carried out by addition of concentrated H_2SO_4. [d]Hydrolysis performed by treatment of 1,3-oxazoles **16** with LiOH (3 equiv) in THF/H_2O (4:1) (5 mL).

TABLE 6. Fluorous Synthesis of 2,5-Disubstituted Thiazoles 17 and 2

entry	13	17[a]	yield (%)[b]	2[c]	yield (%)[b]
1	**13a**	**17a**	54	**2a**	99
2	**13b**	**17b**	79	**2b**	95
3	**13c**	**17c**	74	**2c**	97
4	**13d**	**17d**	79	**2d**	99
5	**13e**	**17e**	73	**2e**	99
6	**13f**	**17f**	82	**2f**	99
7	**13g**	**17g**	78	**2g**	99
8	**13h**	**17h**	86	**2h**	99
9	**13i**	**17i**	80	**2i**	98

[a]Reactions carried out on a 0.2 mmol scale. Lawesson's reagent (2 equiv) is added to a solution of α-amido-β-ketoesters **13** in anhydrous THF (5 mL) and the mixture refluxed until no starting material is detected by TLC. [b]Yields of purified products. [c]Hydrolysis performed by treatment of thiazole **17** with LiOH (3 equiv) in THF/H_2O (4:1) (5 mL).

(C), 164.8 (C), 150.0 (C), 138.4 (C), 128.5 (CH), 123.9 (CH), 63.5 (CH), 53.6 (CH_3), 28.1 (CH_3); HRMS (EI) *m*/*z* calcd for $C_{12}H_{12}N_2O_6$ 280.0695, found 280.0697.

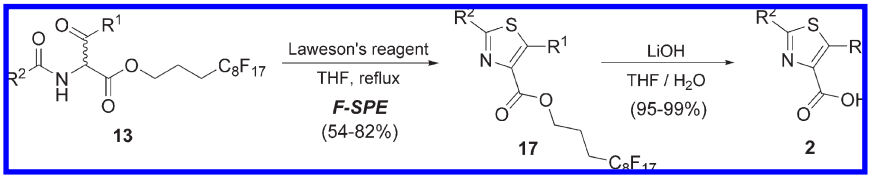
Reduction/Acylation of Oximes 7 and 15. Procedure B: Reduction with Zn/AcOH. Zn powder was slowly added (addition for 1 h) to a solution of oxime **7** or **15** (1 equiv) and anhydride (2.5 equiv) in glacial AcOH (4 mL), and the mixture was stirred for 18 h at rt. The reaction mixture was quenched with 4 mL of H_2O, filtrated over Celite, and the solid residue washed with dichloromethane (3 × 5 mL). The layers were separated, and the aqueous mixture was extracted with dichloromethane (3 × 5 mL). The organic layers together were washed with aqueous saturated $NHCO_3$ solution and dried over anhydrous sodium sulfate, and the solvents were removed under reduced pressure. The crude product was purified, when necessary, by means of flash chromatography on silica gel for compounds **7** and fluorous chromatography for compounds **15**.

Benzyl 2-acetamido-3-oxobutanoate (3y): Yield 99%; white solid; mp 100−102 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.29−7.40 (m, 5H), 6.78 (d, J = 5.4 Hz, 1H), 5.29 (d, J = 6.6 Hz, 1H), 5.24 (d, J = 12.3 Hz, 1H), 5.18 (d, J = 12.0 Hz, 1H), 2.29 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 198.3 (C), 169.8 (C), 166.0 (C), 134.5 (C), 128.6 (CH), 128.3 (CH), 68.1 (CH_2), 63.1 (CH), 28.0 (CH_3), 22.5 (CH_3); HRMS (EI) *m*/*z* calcd for $C_{13}H_{15}NO_4$ 249.1001, found 249.1004.

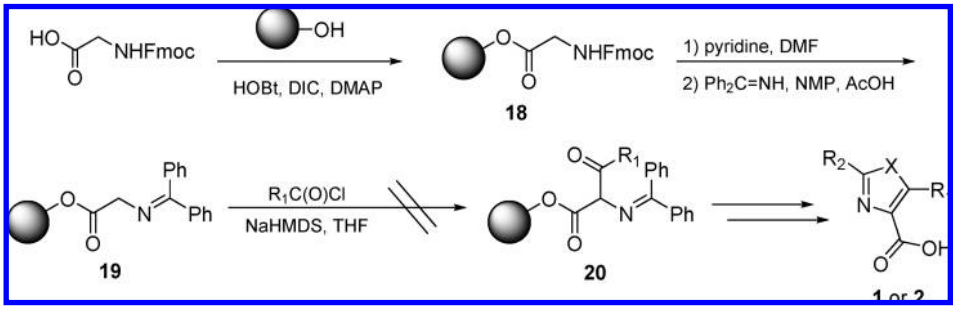
General Procedure for the Synthesis of 1,3-Oxazoles 8 and 16: Triethylamine (4 equiv) was added to a solution of triphenylphosphine (2 equiv) and iodine (2 equiv) in dry dichloromethane (6 mL) and stirred for 5 min. Then a solution of the α-amido-β-ketoester (1 equiv) in dry dichloromethane (4 mL) was added and the reaction mixture stirred until completion of reaction (followed by TLC). The solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel for compounds **8** and fluorous chromatography for compound **16**.

Benzyl 2-(3-(trifluoromethyl)phenyl)-5-phenyloxazole-4-carboxylate (8f): Yield 92%; white solid; mp 130−132 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.30 (s, 1H), 8.22 (d, J = 7.8 Hz, 1H), 7.93 (d, J = 7.5 Hz, 1H), 7.93 (s, 1H), 7.63 (d, J = 7.8 Hz, 1H), 7.50 (t, J = 7.8 Hz, 1H), 7.30−7.40 (m, 5H), 7.18−7.30 (m, 3H), 5.33 (s, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ ppm −63.29 (s, 3F); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 161.8 (C),

SCHEME 10. Fluorous Synthesis of Thiazoles 2 from α-Amido-β-Ketoesters 13



SCHEME 11. Solid-Phase Synthesis of 1,3-Oxazoles 1 and 1,3-Thiazoles 2



SCHEME 12. Addition of Benzyl-Protected Amino Acid to 1,3-Oxazoles 1a and 1y and to 1,3-Thiazoles 2a and 2y

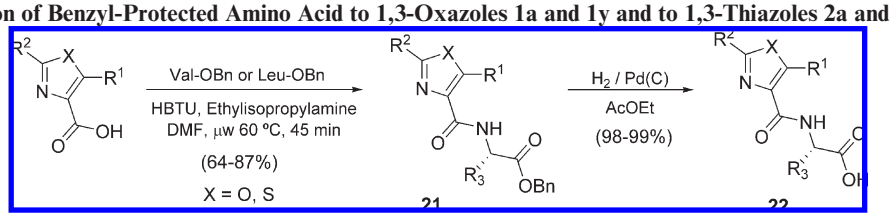


TABLE 7. Addition of Benzyl-Protected Amino Acid to 1,3-Oxazoles 1a and 1y and 1,3-Thiazoles 2a and 2y and Deprotection

entry	R^1	R^2	R^3	X	**21**[a]	yield (%)[b]	**22**[c]	yield (%)[b]
1	C_6H_5	C_6H_5	*i*-Pr	O	**21a**	76	**22a**	99
2	Me	Me	*i*-Bu	O	**21b**	87	**22b**	99
3	C_6H_5	C_6H_5	*i*-Pr	S	**21c**	64	**22c**	98
4	Me	Me	*i*-Bu	S	**21d**	85	**22d**	99

[a]Reactions carried out on a 0.5 mmol scale. **1** or **2**, *O*-Bn-amino acid (1.5 equiv), HBTU (3 equiv), and *N*-ethylisopropylamine (3 equiv) in anhydrous DMF (5 mL) are stirred at 60 °C under microwave irradiation for 45 min. [b]Yields of purified products. [c]Hydrogenolysis carried out by treatment of **21** with Pd(C) (10%) in AcOEt (5 mL) under 1 atm of H_2.

158.3 (C), 155.8 (C), 135.4 (C), 131.4 (q, ^2J = 32.7 Hz), 130.5 (CH), 129.8 (CH), 129.4 (CH), 128.6 (CH), 128.5 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 128.2 (C), 127.4 (q, ^3J = 3.7 Hz), 127.1 (C), 126.6 (C), 123.6 (q, ^3J = 3.8 Hz), 123.6 (q, ^1J = 270.8 Hz), 67.0 (CH_2); HRMS (EI) *m*/*z* calcd for $C_{24}H_{16}F_3NO_3$ 423.1082, found 423.1076.

3-(Perfluorooctyl)propyl 2-(4-(trifluoromethyl)phenyl)-5-phenyloxazole-4-carboxylate (16c): Yield 98%; yellowish solid; mp 53−55 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.27 (d, *J* = 8.1 Hz, 2H), 7.98−8.16 (m, 2H), 7.75 (d, *J* = 8.1 Hz, 2H), 7.66−7.87 (m, 3H), 4.46 (t, *J* = 5.9 Hz, 2H), 3.87 (s, 3H), 1.99−2.37 (m, 4H); ^{19}F NMR (282 MHz, $CDCl_3$) δ ppm −63.51 (s, 3F), −81.30 (t, *J* = 9.6 Hz, 3F), −114.78 (t, *J* = 13.8 Hz, 2F), −122.17 (s, 2F), −122.36 (s, 4F), −123.18 (s, 2F), −123.83 (s, 2F), −126.60 (s, 2F); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 161.8 (C), 158.5 (C), 156.1 (C), 132.7 (q, ^2J = 32.3 Hz), 130.7 (CH), 129.5 (C), 128.7 (CH), 128.5 (CH), 128.2 (C), 127.1 (CH), 126.7 (C), 125.9 (q, ^3J = 3.2 Hz), 123.7 (q, ^1J = 270.8 Hz), 63.9 (CH_2), 27.9 (t, *J* = 22.1 Hz), 20.0 (CH_2); HRMS (FAB) *m*/*z* calcd for $C_{28}H_{15}F_{20}NO_3$ 793.0733, found 793.0727.

TABLE 8. Antimicrobial Activity of 1,3-Oxazoles 1 and 1,3-Thiazoles 2 against *S. aureus* ATCC 29213

entry	compound[a]	activity (mm)[b]
1	**1a**	11
2	**1c**	11
3	**1g**	12
4	**1r**	15
5	**2b**	12
6	**2c**	20
7	**2f**	10
8	**2h**	10
9	**2o**	15
10	**2p**	14
11	oxacillin[d]	20
12	blank experiment[c]	0

[a]Fifty micrograms of compound per disk spotted from a 5 mg/mL DMSO solution. [b]Bacterial growth inhibition halo against *S. aureus* ATCC 29213. [c]Only DMSO was added. [d]Fifty micrograms of compound per disk spotted from a 5 mg/mL DMSO solution for the tested compounds, while only 1 microgram was used for the oxacillin used as reference.

General Procedure for the Hydrogenation of 8a−y: Pd/C (25% w/w, 0.1 equiv) was added to a solution of 1,3-oxazole **8** (1 equiv) in dry ethyl acetate (5 mL) and stirred at rt under atmospheric pressure of hydrogen overnight. The catalyst was filtered off and washed with methanol (2 mL). The combined filtrates were concentrated under reduced pressure to yield the pure product.

2-(2-Fluorophenyl)-5-phenyloxazole-4-carboxylic acid (1b): Yield 99%; white solid; mp 176−178 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 8.03−8.17 (m, 3H), 7.37−7.69 (m, 6H); ^{19}F NMR (282 MHz, DMSO-d_6) δ ppm −111.76 (s, 1F); ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 162.9 (C), 159.3 (d, ^1J = 254.0 Hz), 155.1 (d, ^3J = 3.8 Hz), 153.8 (C), 133.3 (d, ^3J = 8.3 Hz), 130.2

(CH), 129.6 (CH), 128.7 (C), 128.4 (CH), 128.2 (CH), 126.7 (C), 125.1 (d, ^3J = 2.9 Hz), 117.0 (d, ^2J = 20.8 Hz), 114.1 (d, ^2J = 10.9 Hz); HRMS (EI) m/z calcd for $C_{16}H_{10}FNO_3$ 283.0645, found 283.0649.

General Procedure for the Hydrolysis of 8z-aa and 16: A stirred solution of ester **8** or **16** (1 equiv) in THF/H_2O 4:1 (5 mL) was chilled in an ice bath. Then lithium hydroxide monohydrate (3 equiv) was added, the ice bath was allowed to reach rt, and the mixture stirred until completion of the reaction (followed by TLC). The reaction mixture was then evaporated under reduced pressure, and the residue suspended in 1 M HCl solution (1 mL) and extracted with ethyl acetate to yield the pure product.

5-Methyl-2-(3,4,5-trimethoxyphenyl)oxazol-4-carboxylic acid (1aa): Yield 99%; white solid; mp 224−226 °C; ^{1}H NMR (300 MHz, 0.6 mL $CDCl_3$ + 0.1 mL MeOD) δ ppm 7.27 (s, 2H), 3.91 (s, 6H), 3.87 (s, 3H), 2.69 (s, 3H); ^{13}C NMR (75 MHz, 0.6 mL $CDCl_3$ + 0.1 mL MeOD) δ ppm 164.3 (C), 159.5 (C), 156.5 (C), 153.4 (C), 140.3 (C), 128.5 (C), 121.7 (C), 103.8 (CH), 60.9 (CH_3), 56.3 (CH_3), 12.1 (CH_3); HRMS (EI) m/z calcd for $C_{14}H_{15}NO_6$ 293.0899, found 293.0908.

General Procedure for the Synthesis of 1,3-Thiazoles 9 and 17: A solution of the α-amido-β-ketoester **3** or **13** (1 equiv) and Lawesson's reagent (2 equiv) in dry THF (5 mL) was heated to reflux until completion of reaction (followed by TLC). The reaction mixture was then evaporated under reduced pressure and purified by flash chromatography on silica gel for compounds **9** and fluorous chromatography for compound **17** to yield the product.

Benzyl 2-(3-methoxyphenyl)-5-phenylthiazole-4-carboxylate (9e): Purification by means of flash chromatography on silica gel (hexane/AcOEt 4:1): yield 98%; white solid; mp 106−108 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.35−7.50 (m, 4H), 7.23−7.33 (m, 4H), 7.06−7.23 (m, 5H), 6.92 (dd, J_1 = 2.6 Hz, J_2 = 8.3 Hz, 1H), 5.20 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 166.0 (C), 162.1 (C), 160.0 (C), 146.0 (C), 141.2 (C), 135.3 (C), 134.0 (C), 130.4 (C), 130.0 (CH), 129.8 (CH), 129.1 (CH), 128.3 (CH), 128.2 (CH), 128.2 (CH), 128.0 (CH), 119.4 (CH), 116.9 (CH), 111.4 (CH), 66.8 (CH_2), 55.5 (CH_3); HRMS (EI) m/z calcd for $C_{24}H_{19}NO_3S$ 401.1086, found 401.1076.

3-(Perfluorooctyl)propyl 2-(4-methoxyphenyl)-5-phenylthiazole-4-carboxylate (17b): Yield 79%; yellowish solid; mp 129−131 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.93 (d, J = 9.0 Hz, 2H), 7.38−7.54 (m, 5H), 6.96 (d, J = 9.0 Hz, 2H), 4.28 (t, J = 5.3 Hz, 2H), 3.86 (s, 3H), 1.79−1.94 (m, 4H); ^{19}F NMR (282 MHz, $CDCl_3$) δ ppm −81.26 (t, J = 9.9 Hz, 3F), −114.85 (t, J = 11.5 Hz, 2F), −122.37 (br s, 6F), −123.19 (s, 2F), −123.73 (s, 2F), −126.58 (s, 2F); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 166.3 (C), 162.1 (C), 161.7 (C), 145.1 (C), 140.9 (C), 130.7 (C), 129.7 (CH), 129.2 (CH), 128.3 (CH), 128.2 (CH), 125.5 (C), 114.3 (CH), 63.6 (CH_2), 55.4 (CH_3), 27.8 (t, J = 22.3 Hz), 19.7 (CH_2); HRMS (FAB) m/z calcd for $C_{28}H_{18}F_{17}NO_3S$ 771.0736, found 771.0761.

Hydrogenolysis or Hydrolysis of Compounds 9 and 17 To Furnish Thiazoles 2: The procedures are the same as those for compounds **8** and **16**.

2-(4-Methoxyphenyl)-5-phenylthiazole-4-carboxylic acid (2g): Yield 99%; white solid; mp 160−162 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.88 (d, J = 8.7 Hz, 2H), 7.61−7.69 (m, 2H), 7.40−7.48 (m, 3H), 6.98 (d, J = 8.7 Hz, 2H), 3.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 165.3 (C), 161.9 (C), 161.7 (C), 146.5 (C), 138.8 (C), 130.0 (CH), 129.6 (CH), 129.3 (C), 128.3 (CH), 128.1 (CH), 124.8 (C), 114.5 (CH), 55.5 (CH_3); HRMS (EI) m/z calcd for $C_{17}H_{13}NO_3S$ 311.0616, found 311.0608.

General Procedure for the Synthesis of Compounds 21: A solution of **1** or **2** (1 equiv), OBn-protected amino acid (1.5 equiv), HBTU (3 equiv), and *N*-ethyldiisopropylamine (1 equiv) in anhydrous DMF (5 mL) was irradiated with microwaves at 60 °C for 45 min. The reaction mixture was then evaporated under reduced pressure, and the residue was dissolved in AcOEt, washed with 10% citric acid solution and saturated solution of $NaHCO_3$, dried with Na_2SO_4, and concentrated under reduced pressure to yield the crude product. Purification was performed by flash chromatography on silica gel.

(*S*)-Benzyl 2-(2,5-dimethylthiazole-4-carboxamido)-4-methylpentanoate (21d): Yield 85%; yellowish oil; $[\alpha]^{25}_D$ = +2.11 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.75 (d, J = 8.7 Hz, 1H), 4.74−4.86 (m, 5H), 5.21 (d, J = 12.3 Hz, 1H), 5.15 (d, J = 12.6 Hz, 1H), 4.74−4.85 (m, 1H), 2.75 (s, 3H), 2.58 (s, 3H), 1.61−1.80 (m, 3H), 0.96 (d, J = 1.8 Hz, 3H), 0.94 (d, J = 3.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 172.7 (C), 162.3 (C), 160.9 (C), 141.7 (C), 140.9 (C), 135.5 (C), 128.4 (CH), 128.1 (CH), 128.0 (CH), 66.8 (CH_2), 50.4 (CH), 41.5 (CH_2), 24.8 (CH), 22.7 (CH_3), 21.8 (CH_3), 18.7 (CH_3), 12.4 (CH_3); HRMS (EI) m/z calcd for $C_{19}H_{24}N_2O_3S$ 360.1508, found 360.1521.

Hydrogenolysis of Compounds 21: The procedure is the same as that for compounds **8a**−**y**.

In Vitro Evaluation of Various Compounds: A disk diffusion method was utilized to evaluate the in vitro antibacterial activity of various 2,5-disubstituted 1,3-azoles against *S. aureus* ATCC 29213. Culture plates were prepared using polystyrene 100 mm tissue culture dishes (Corning Glass Works, Corning, NY) with BBL Mueller Hinton II agar (Becton, Dickinson and Company, Sparks, MD). The compounds were diluted with DMSO to yield a final concentration of 5 mg/mL. The solutions were spotted on 6 mm blank paper disks (Becton, Dickinson and Company, Sparks, MD) to deliver 50 μg per disk. The disks were placed on lawns of *S. aureus* spread with cotton swabs from 0.5 McFarland unit turbidometric standard cell suspensions (Scientific Device Lab. Inc., Des Plaines, IL). The culture plates were incubated at 37 °C for 18−24 h prior to reading.

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Supporting Information Available: Characterization data and ^{1}H and ^{13}C NMR spectra for all of the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.