A straightforward approach towards 5-substituted thiazolylpeptides *via* the thio-Ugi-reaction†

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A wide range of 5-substituted thiazoles are easily accessible *via* cross coupling of thiazolyl triflates. These activated thiazoles can be obtained by Ugi reactions using thioacids (thio-Ugi-reaction) and subsequent cyclisation of the *endo* thiopeptides formed with triflic anhydride. In addition, cyclisations with acyl halides give rise to 5-acyloxysubstituted derivatives.

Introduction

Natural products are an important source not only for pharmaceutically relevant compounds such as antibiotics, but also as lead structures for the development of natural product based drugs.[1] While many classes of natural products can directly be used as drugs, peptides especially are critical candidates based on their moderate proteolytic stability. In nature, as well as in medicinal chemistry this problem can be solved by incorporation of nonproteinogenic amino acids into the peptides, which are not accepted by hydrolytic enzymes.[2] This explains the wide range of unusual amino acids found in secondary metabolites and in drugs.[1] One interesting option to increase proteolytic stability of a peptide is the replacement of a peptide bond by a hydrolytically more stable thioamide bond.[3] If such a thioamide is located at the N-terminus of a serine, subsequent ring closure to the thiazoline[4] and oxidation to the corresponding thiazole amino acid is possible.[5] Thiazole amino acids are also found widespread in nature, especially as secondary metabolites of marine organisms or bacteria.[6] Typical examples are dolastatin 3,[7] the tubulysins[8] (Fig. 1) or the large group of thiopeptides,[9] to name only a few.

Biosynthetically, these structures are formed by cyclisation of cysteine peptides and subsequent oxidation.[10] If an enzymatic decarboxylation occurs after the oxidation step,[11] the corresponding unsubstituted thiazole structure is located at the C-terminus of the peptide chain, as found in bottromycin (Fig. 1),[12] dolastatin 10[13] or the lyngbyabellins.[14] The origin of the thiazole moiety from cysteine explains why in natural products the 5-position of the thiazole ring in general is unsubstituted. On the other hand, for the development of natural product based drugs, modifications at the 5-position are an interesting issue, and several 5-substituted thiazole derivatives have made their way into clinical trials, such as BMS-18725[15] (Fig. 1) or CP-619700.[16]

For the synthesis of 4-substituted thiazoles, the 4-thiazole carboxylic acid is a suitable precursor,[17] and for the additional introduction of 5-substituents the corresponding ester can be deprotonated and subsequently alkylated or acylated.[18] In principle, this approach is also suitable to introduce substituents into the 5-position of unsubstituted thiazoles, but here very strong bases such as BuLi are required,[19] conditions which are not compatible with peptides.

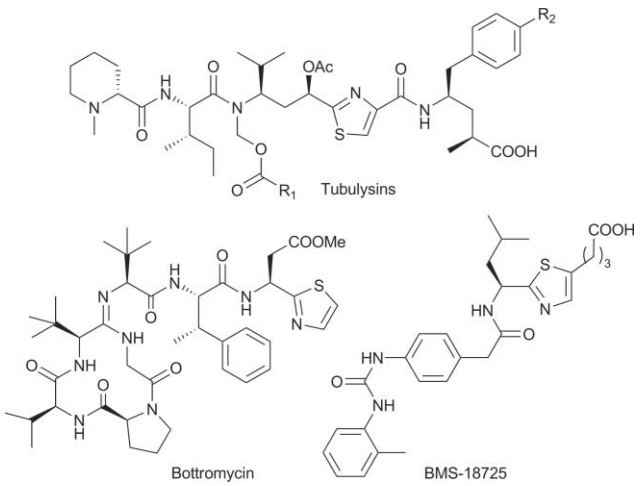
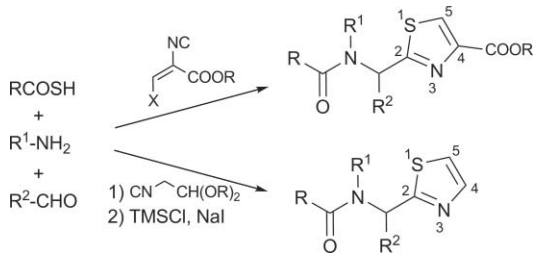


Fig. 1 Thiazolylpeptides as natural products and drugs.

Herein, we describe a straightforward protocol towards 5-substituted thiazole peptides based on Ugi-reactions as a key step. The Ugi-reaction has become an extremely useful tool for the construction of unusual peptides,[20] and by using thioacids and suitable isonitriles, this multicomponent reaction can also be used for the synthesis of peptidic thiazole carboxylic acids (Scheme 1).[21] Very recently, Thompson *et al.* reported on the synthesis of 5-aminothiazoles by Ugi-reaction and subsequent thionation/cyclisation.[22] During our long-term interest in the Ugi-reactions and their application,[23] we also developed a protocol suitable for the synthesis of terminal unsubstituted thiazole amino acids.[24]



Scheme 1 Thiazolylpeptides *via* thio-Ugi-reaction.

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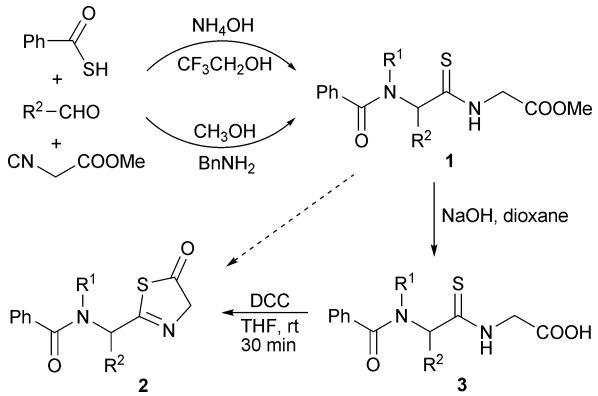
In the reaction of the acetal of isocyanoacetaldehyde in combination with thioacids the corresponding endothiopeptide acetals are obtained, which undergo cyclisation under Lewis acidic conditions (Scheme 1).

Results and discussion

Based on this protocol, we developed a route towards 5-substituted thiazole peptides. As a standard thiobenzoic acid was used in combination with isocyanoacetates. As aldehydes we used the sterically demanding isobutyraldehyde (providing valine peptides) and pivaldehyde (*tert*-leucine peptides). As amine component we used benzylamine as a representative for the synthesis of N-alkylated peptides and ammonia, or ammonium hydroxide respectively, for the unsubstituted peptides. Although Ugi-reactions with ammonia are critical candidates because of several possible side reactions,[25] the yields obtained were good in all cases (Table 1). It is recommended to use CF_3CH_2OH as solvent in the ammonia reactions to avoid participation of the solvent in the Ugi-reaction, as is observed in CH_3OH as solvent.[25] In some reactions we observed the formation of the 5-thiazolone **2** as side product from nucleophilic attack of the thiocarbonyl group on the ester moiety. In principle, this thiazolone should be a good precursor for the synthesis of 5-substituted thiazoles. Unfortunately, all attempts to cyclise the thiopeptides **1** directly to the thiazolone **2** *e.g.* by refluxing overnight, gave no synthetically useful yields. Therefore, we decided to saponify the ester to obtain the thiazolones *via* activation/cyclisation. The free peptide acids **3** were obtained quantitatively in all cases. And indeed, on addition of DCC the corresponding thiazolones **2** were formed in good to excellent yields.

Interestingly, a complete different reaction behavior was observed if the peptide acids were activated as mixed anhydrides (Table 2). With one equivalent of acetyl chloride around 50% conversion was observed, but not towards the corresponding thiazolone **2**, but the acylated thiazole derivatives **4**. Probably, the thiazolone was formed as an intermediate, and under the basic conditions used, the deprotonated thiazolone reacts faster with the acyl halide than the peptide acid.[26]

Table 1 Thio-Ugi-reactions and applications

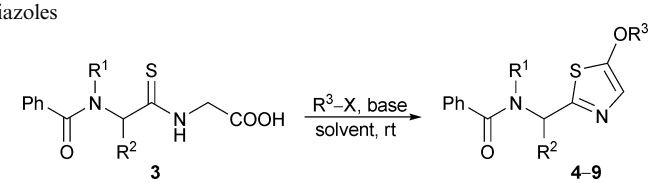


R^1	R^2	**1**	Yield (%)	**3**	Yield (%)	**2**	Yield (%)
H	*i*Pr	**1a**	69	**3a**	99	**2a**	65
H	*t*Bu	**1b**	60	**3b**	99	**2b**	97
Bn	*i*Pr	**1c**	75	**3c**	99	n.i.	
Bn	*t*Bu	**1d**	80	**3d**	99	n.i.	

n.i.: not investigated.

Therefore, unreacted peptide could be recovered. But by using two equivalents of acyl halide the corresponding acylated hydroxy thiazoles were formed in excellent yield, independent of the halide used. Both, acyl halides (entries 1 and 2) as well as chloroformates (entries 3 to 7) can be used with comparable success. Even with inorganic halides such as phosphoryl chlorides (entry 8) the corresponding thiazolylphosphate **8** was obtained, although the yield was somewhat lower in this case. This forced us to investigate the synthesis of thiazolyl triflates directly from the peptide acids by using triflic anhydrides. This would be a straightforward approach towards a wide range of thiazole derivatives *via* subsequent cross coupling. With triflic anhydride the reaction behaved slightly different compared to the other acyl halides investigated. In THF as a solvent, the yields were only moderate (10–15%), and therefore we had to switch to other solvents, such as CH_2Cl_2.

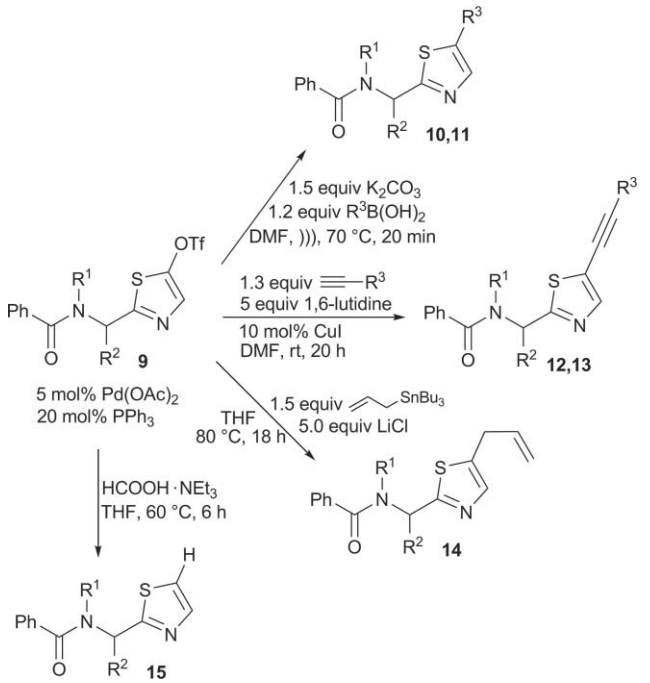
Table 2 Synthesis of 5-substituted thiazoles



Entry	Peptide	R^1	R^2	R^3X (equiv)	Base (equiv)	Solvent	Product	Yield (%)
1	**3d**	Bn	*t*Bu	MeCOCl (2.0)	NEt_3 (3.0)	THF	**4d**	92
2	**3d**	Bn	*t*Bu	PhCOCl (2.0)	NEt_3 (3.0)	THF	**5d**	93
3	**3b**	H	*t*Bu	EtOCOCl (2.0)	NEt_3 (3.0)	THF	**6b**	91
4	**3d**	Bn	*t*Bu	EtOCOCl (2.0)	NEt_3 (3.0)	THF	**6d**	94
5	**3b**	H	*t*Bu	*i*BuOCOCl (2.0)	NEt_3 (3.0)	THF	**7b**	95
6	**3c**	Bn	*i*Pr	*i*BuOCOCl (2.0)	NEt_3 (3.0)	THF	**7c**	92
7	**3d**	Bn	*t*Bu	*i*BuOCOCl (2.0)	NEt_3 (3.0)	THF	**7d**	98
8	**3b**	H	*t*Bu	$(EtO)_2POCl$ (2.0)	NEt_3 (3.0)	THF	**8b**	69
9	**3c**	Bn	*i*Pr	$(CF_3SO_2)_2O$ (2.0)	NMM (2.0)	CH_2Cl_2	**9c**	50
10	**3d**	Bn	*t*Bu	$(CF_3SO_2)_2O$ (2.0)	NMM (2.0)	CH_2Cl_2	**9d**	48
11	**3d**	Bn	*t*Bu	$(CF_3SO_2)_2O$ (1.0)	NMM (2.0)	CH_2Cl_2	**2d**	68
12	**2a**	H	*i*Pr	$(CF_3SO_2)_2O$ (1.0)	—	CH_2Cl_2	**9a**	55
13	**2b**	H	*t*Bu	$(CF_3SO_2)_2O$ (1.0)	—	CH_2Cl_2	**9b**	60

In this solvent the yields could be increased to 50% and 48% respectively (entries 9 and 10). Although this is not outstanding, the short reaction sequence still makes this approach attractive. Interestingly, if only one equivalent of Tf_2O was used, the formation of the thiazolyl triflate **9** was not observed, but thiazolone **2** was formed (entry 11). This clearly supports the idea, that **2** is the intermediate in this domino cyclisation/acylation process. Unfortunately, this direct interconversion of **3** into the triflates **9** works only with the *N*-substituted peptides **3c** and **3d**, because **3a** and **3b** are insoluble in CH_2Cl_2. But in this case the thiazolones **2a** and **2b** obtained by the DCC-coupling can be used as substrates (entries 12 and 13). This reaction does not require *N*-methylmorpholine (NMM) as an additional base and makes the triflates of all different substituted thiazoles accessible.

With these thiazolyl triflates in hand we next investigated a range of cross coupling reactions, starting with Suzuki couplings (Scheme 2). To evaluate the scope and limitations of this protocol we subjected all four triflates **9** to a coupling with phenylboronic acid. The reactions were carried out under microwave irradiation.[27] After 20 min all reactions were complete and the coupling products **10** were obtained in 73–76% yields, independent of the substitution pattern of the thiazoles **9** (Table 3, entries 1–4). With another *p*-methoxyphenyl boronic acid the yield was even better under the same reaction conditions (entry 5).



Scheme 2 Cross coupling reactions of thiazolyl triflates **9**.

With phenylacetylene we were able to get excellent yields in the corresponding Sonogashira coupling with both types of thiazolyl peptides (entries 6 and 7). Even unprotected propargylic alcohol could be coupled under the same reactions conditions,[28] although the yield was lower in this case (entry 8). A similar result was also obtained in a Stille coupling using allylstannane (entry 9).[29] Last, but not least, we investigated the direct reduction of the triflate towards the unsubstituted thiazole. An excellent yield was obtained in a Pd-catalyzed hydride transfer using formic acid as reducing agent.[30]

Table 3 Cross coupling reactions of thiazolyltriflates **9**

Entry	Triflate	R^1	R^2	Product	R^3	Yield (%)
1	**9a**	H	*i*Pr	**10a**	Ph	73
2	**9b**	H	*t*Bu	**10b**	Ph	73
3	**9c**	Bn	*i*Pr	**10c**	Ph	76
4	**9d**	Bn	*t*Bu	**10d**	Ph	76
5	**9a**	H	*i*Pr	**11a**	*p*-MeOPh	85
6	**9b**	H	*t*Bu	**12b**	Ph	95
7	**9c**	Bn	*i*Pr	**12c**	Ph	95
8	**9c**	Bn	*i*Pr	**13c**	CH_2OH	58
9	**9c**	Bn	*i*Pr	**14c**	allyl	51
10	**9a**	H	*i*Pr	**15a**	H	94

Conclusion

In conclusion, we have shown that thio Ugi reactions are a straightforward approach towards 5-substituted thiazolyl peptides. The primarily formed *endo* thiopeptides can be cyclised with a wide range of organic and inorganic acid chlorides and anhydrides. The especially interesting thiazolyl triflates can be obtained either from the peptide acid or from the corresponding thiazolone, and they are excellent substrates for subsequent cross couplings or reductions. Further investigations concerning synthetic applications are currently in progress.

Experimental

General remarks

All reactions were carried out in oven-dried glassware (100 °C) under nitrogen. All solvents were dried before use: THF was distilled from $LiAlH_4$ and CH_2Cl_2 from CaH_2. The products were purified by flash chromatography on silica gel (0.063–0.2 mm). Mixtures of ethyl acetate and hexanes were generally used as eluents. Analysis by TLC was carried out on commercially precoated Polygram SIL-G/UV 254 plates (Machery-Nagel, Dueren). Visualization was accomplished with UV light, $KMnO_4$ solution or iodine. ^{1}H- and ^{13}C-NMR spectroscopic analysis was performed on a Bruker Avence II 400 MHz spectrometer. Chemical shifts are reported on the δ (ppm) scale and the coupling constants are given in Hz. HRMS were measured with Finnigan MAT 95S mass spectrometer. Elemental analyses were carried out at the Department of Chemistry at Saarland University.

2-[1-(*N*-Benzoylamino)-2-methylpropyl]-4*H*-5-thiazolone (2a). Carboxylic acid **3a**[31] (100 mg, 0.34 mmol) was dissolved in THF (3 mL) before a solution of DCC (70 mg, 0.34 mmol) in THF (3 mL) was added. After stirring for 30 min at room temperature the solvent was removed *in vacuo*. The residue was dissolved in ether and filtered. After evaporation of the solvent **2a** was obtained as pale brown solid (60 mg, 0.22 mmol, 65%), which was crystallized from CH_2Cl_2–Et_2O, mp. 110–111 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.02 (d, J = 6.8 Hz, 3H), 1.10 (d, J = 6.8 Hz, 3H), 2.32 (dqq, J = 6.8, 6.8, 6.8 Hz, 1H), 4.61 (dd, J = 23.6, 2.0 Hz, 1H), 4.67 (dd, J = 23.6, 2.0 Hz, 1H), 5.15 (m, 1H), 6.88 (d, J = 8.0 Hz, 1H), 7.45 (m, 2H), 7.52 (m, 1H), 7.81 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 17.0, 19.5, 31.6, 58.5, 71.7,

127.0, 128.6, 131.9, 133.9, 167.4, 171.6, 205.6; HRMS (CI) calcd for $C_{14}H_{17}N_2O_2S$ $[M + H]^+$: 277.1011. Found; 277.0997.

2-[1-(*N*-Benzoylamino)-2,2-dimethylpropyl]-4*H*-5-thiazolone (2b). Thiazolone **2b** was obtained according to **2a** from acid **3b**[31] (500 mg, 1.62 mmol) and DCC (334 mg, 1.62 mmol) as a pale yellow solid (457 mg, 1.57 mmol, 97%), mp. 106–109 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 1.12$ (s, 9H), 4.61 (d, $J = 23.8$ Hz, 1H), 4.68 (d, $J = 23.8$ Hz, 1H), 5.02 (d, $J = 8.8$ Hz, 1H), 6.93 (d, $J = 8.8$ Hz, 1H), 7.44 (m, 2H), 7.52 (m, 1H), 7.79 (d, $J = 7.2$ Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): $\delta = 26.9$, 35.5, 61.3, 71.9, 127.0, 128.7, 131.8, 133.9, 167.0, 170.8, 205.7. Anal. calcd for $C_{15}H_{18}N_2O_2S$ (290.38): C, 62.05; H, 6.25; N, 9.66. Found: C, 62.13; H, 6.32; N, 9.53%.

2-[1-(*N*-Benzoyl-*N*-benzylamino)-2,2-dimethylpropyl]-4*H*-5-thiazolone (2d). Carboxylic acid **3d**[31] (100 mg, 0.25 mmol) was dissolved in CH_2Cl_2 (5 mL) under Ar before 2,6-di-*tert*-butyl-4-methyl-pyridine (103 mg, 0.50 mmol) and triflic anhydride (72 mg, 0.25 mmol) was added slowly. After stirring for 4 h at room temperature, the solvent was removed *in vacuo* and the residue was purified by flash chromatography (silica, hexanes/EtOAc, 7 : 3) to give **2d** in 68% yield (65 mg, 0.17 mmol) as an orange solid, mp. 107–111 °C. Major rotamer: ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta =$ 1.29 (s, 9H), 4.02 (d, $J = 24.2$ Hz, 1H), 4.50 (d, $J = 24.2$ Hz, 1H), 4.80 (d, $J = 16.4$ Hz, 1H), 5.06 (d, $J = 16.4$ Hz, 1H), 5.77 (bs, 1H), 6.88–7.53 (m, 10 H); ^{13}C-NMR (100 MHz, $CDCl_3$): $\delta = 28.1$, 38.6, 51.9, 63.2, 72.9, 126.3, 126.6, 126.8, 128.3, 128.6, 129.5, 136.7, 138.4, 167.7, 174.0, 206.4. Selected signals of the minor rotamer: ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 1.08$ (s, 9H), 4.40 (m, 1H), 4.62 (m, 1H), 4.73 (bs, 1H), 4.88 (m, 1H), 5.23 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): $\delta = 49.3$. HRMS (CI) calcd for $C_{22}H_{25}N_2O_2S_2$ $[M + H]^+$: 381.1637. Found; 381.1630.

General procedure for the synthesis of 5-thiazolyl esters. The carboxylic acid **3** (*n* mmol) was dissolved in abs. THF (10 *n* mL) under N_2. Subsequently NEt_3 (3.0 *n* mmol) and the corresponding acid chloride (2.0 *n* mmol) was added slowly. The reaction mixture was allowed to stir overnight at room temperature before it was hydrolyzed. After washing with brine, drying and evaporation of the solvent, the crude product was purified by flash chromatography.

2-[1-(*N*-Benzoyl-*N*-benzylamino)-2,2-dimethylpropyl]-5-thiazolyl ethyl carbonate (6d). According to the general procedure for the synthesis of 5-thiazolyl esters carbonate **6d** was obtained from carboxylic acid **3d**[31] (500 mg, 1.25 mmol) and ethyl chloroformate (277 mg, 2.50 mmol) in 94% yield (530 mg, 1.17 mmol) as pale orange solid, mp. 87–89 °C. Major rotamer: ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 1.26$ (s, 9H), 1.40 (t, $J = 6.4$ Hz, 3H), 4.37 (m, 2H), 4.62 (d, $J = 16.4$ Hz, 1H), 5.37 (d, $J = 16.4$ Hz, 1H), 6.08 (bs, 1H), 6.37–7.56 (m, 11H); ^{13}C-NMR (100 MHz, $CDCl_3$): $\delta = 14.1$, 28.1, 38.8, 51.7, 61.1, 66.1, 125.9, 126.1, 126.3, 126.9, 127.9, 128.9, 129.4, 137.4, 138.8, 148.9, 151.8, 158.9, 173.6. Selected signals of the minor rotamer: ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 1.05$ (s, 9H), 5.01–5.05 (m, 2H), 5.14 (d, $J = 13.6$ Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): $\delta = 48.5$, 67.6; HRMS (CI) calcd for $C_{25}H_{29}N_2O_4S$ $[M + H]^+$: 453.1848. Found; 453.1845; Anal. calcd for $C_{25}H_{28}N_2O_4S$ (452.58): C, 66.35; H, 6.24; N, 6.19. Found: C, 66.13; H, 6.37; N, 6.23%.

2-[1-(*N*-Benzoylamino)-2-methylpropyl]-5-thiazolyl triflate (9a). Triflic anhydride (69 mg, 0.24 mmol) was added to a solution of thiazolone **2a** (60 mg, 0.22 mmol) in CH_2Cl_2 (3 mL) under N_2. After stirring for 30 min at room temperature the solvent was removed *in vacuo* and the crude product was purified by flash chromatography (silica, hexanes–EtOAc, 7 : 3) to give **9a** in 55% yield (50 mg, 0.12 mmol) as an orange solid, mp. 119–121 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 1.03$ (d, $J = 6.4$ Hz, 6H), 2.44 (m, 1H), 5.32 (m, 1H), 6.89 (d, $^3J_{NH,6} = 8.0$ Hz, 1H), 7.44–7.57 (m, 4H), 7.82 (d, $J = 7.6$ Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): $\delta = 17.8$, 19.3, 33.3, 57.0, 118.6 (q, $J_{C,F} = 320$ Hz), 127.1, 128.7, 132.0, 133.2, 133.8, 145.8, 167.0, 167.1. HRMS (CI) calcd for $C_{15}H_{16}N_2O_4F_3S_2$ $[M + H]^+$: 409.0504. Found; 409.0502.

2-[1-(*N*-Benzoylamino)-2,2dimethylpropyl]-5-thiazolyl triflate (9b). According to triflate **9a**, **9b** was obtained from thiazolone **2b** (88 mg, 0.30 mmol) and triflic anhydride (95 mg, 0.33 mmol) as a pale orange solid (76 mg, 0.18 mmol, 60%), mp. 82–84 °C (dec.). ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 1.09$ (s, 9H), 5.26 (d, $J = 9.2$ Hz, 1H), 7.01 (d, $J = 9.2$ Hz, 1H), 7.46 (m, 2H), 7.53 (m, 1H), 7.58 (s, 1H), 7.81 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): $\delta = 26.6$, 36.0, 59.2, 118.6 ($J = 320$ Hz), 127.0, 128.7, 131.9, 133.1, 133.9, 145.6, 165.1, 166.9. HRMS (CI) calcd for $C_{16}H_{18}N_2O_4F_3S_2$ $[M + H]^+$: 423.0660. Found; 423.0632.

2-[1-(*N*-Benzoyl-*N*-benzylamino)-2-methylpropyl]-5-thiazolyl triflate (9c). Carboxylic acid **3c** (100 mg, 0.26 mmol) was dissolved in CH_2Cl_2 (3 mL) under N_2 before *N*-methylmorpholine (53 mg, 0.52 mmol) and triflic anhydride (135 mg, 0.47 mmol) were added. After stirring for 30 min at room temperature the solvent was removed *in vacuo* and the crude product was purified by flash chromatography (silica, hexanes–EtOAc, 7 : 3) to give **9c** in 50% yield (64 mg, 0.13 mmol) as a pale orange solid, mp. 80–84 °C. Major rotamer: ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta =$ 0.88 (d, $J = 4.0$ Hz, 3H), 1.15 (d, $J = 4.8$ Hz, 3H), 3.02 (m, 1H), 4.52 (d, $J = 15.8$ Hz, 1H), 4.68 (d, $J = 15.8$ Hz, 1H), 4.78 (d, $J =$ 9.6 Hz, 1H), 6.81–7.53 (m, 11H); ^{13}C-NMR (100 MHz, $CDCl_3$): $\delta =$ 19.8, 20.3, 29.8, 53.4, 66.9, 118.7 (q, $J_{C,F} = 320$ Hz), 126.8, 127.2, 127.4, 128.3, 128.5, 129.9, 131.7, 136.2, 136.4, 147.5, 164.7, 172.8. Selected signals of the minor rotamer: ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta =$ 0.78 (bs, 3H), 0.98 (bs, 3H), 2.73 (bs, 1H), 5.10 (bs, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): $\delta = 45.2$. HRMS (CI) calcd for $C_{22}H_{22}N_2O_4F_3S_2$ $[M + H]^+$: 499.0973. Found: 499.0909.

2-[1-(*N*-Benzoyl-*N*-benzylamino)-2,2-dimethylpropyl]-5-thiazolyl triflate (9d). According to triflate **9c**, **9d** was obtained from carboxylic acid **3d** (1.00 g, 2.51 mmol) as a pale red solid (620 mg, 1.21 mmol, 48%), mp. 105–107 °C. Major rotamer: ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta =$ 1.25 (s, 9H), 4.63 (d, $J = 16.0$ Hz, 1H), 5.24 (d, $J = 16.0$ Hz, 1H), 5.91 (bs, 1H), 6.43–7.62 (m, 11H); ^{13}C-NMR (100 MHz, $CDCl_3$): $\delta = 28.2$, 38.8, 52.1, 67.9, 118.6 ($J = 320$ Hz), 125.9, 126.5, 128.1, 128.2, 129.4, 130.0, 133.3, 136.8, 138.2, 146.5, 162.5, 173.7. Selected signals of the minor rotamer: ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta =$ 1.07 (s, 9 H, H-17), 5.01–5.09 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): $\delta = 48.3$. HRMS (CI) calcd for $C_{23}H_{24}N_2O_4F_3S_2$ $[M + H]^+$: 513.1130. Found: 513.1067.

General procedure for microwave assisted Suzuki couplings of triflates 9. A solution of triflate **9** (*n* mmol), the corresponding boronic acid (1.1 *n* mmol), $Pd(OAc)_2$ (5 mol%), PPh_3 (0.2 *n* mmol) and K_2CO_3 (1.5 *n* mmol) in DMF (12 *n* mL) was placed in a

microwave oven and heated to 70 °C for 20 min (200 Watt). After cooling to room temperature the solution was diluted with ethyl acetate and the organic layer was washed twice with H_2O, brine and was dried (Na_2SO_4). After evaporation of the solvent, the crude product was purified by flash chromatography.

2-[1-(*N*-Benzoyl-*N*-benzylamino)-2,2-dimethylpropyl]-5-phenyl-thiazole (10d). According to the general procedure for microwave assisted Suzuki couplings thiazole **10d** was obtained from triflate **9d** (80 mg, 0.156 mmol), phenylboronic acid (22 mg, 0.172 mmol), $Pd(OAc)_2$ (3.6 mg, 0.008 mmol), PPh_3 (8.3 mg, 0.031 mmol) and K_2CO_3 (32.3 mg, 0.234 mmol) in 76% yield (52.0 mg, 0.118 mmol) as a pale red solid, mp. 144–148. Major rotamer: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.34 (s, 9H), 4.70 (d, J = 16.4 Hz, 1H), 5.50 (d, J = 16.4 Hz, 1H), 6.33 (s, 1H), 6.42–7.97 (m, 16H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 28.1, 38.8, 51.6, 60.6, 126.0, 126.3, 126.8, 127.7, 127.9, 128.1, 128.3, 128.5, 129.0, 131.1, 132.3, 138.4, 138.9, 139.3, 164.8, 173.7. Selected signals of the minor rotamer: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.13 (s, 9H), 5.11 (d, J = 13.6 Hz, 1H), 5.22–5.26 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 48.5, 67.5; HRMS (CI) calcd for $C_{28}H_{29}N_2OS$ [M + H]$^+$: 441.2001. Found: 441.2020.

2-[1-(*N*-Benzoylamino)-2-methylpropyl]-5-(*p*-methoxyphenyl)-thiazole (11a). According to the general procedure for microwave assisted Suzuki couplings thiazole **11a** was obtained from triflate **9a** (50 mg, 0.122 mmol), *p*-methoxyphenylboronic acid (22.9 mg, 0.146 mmol), $Pd(OAc)_2$ (2.9 mg, 0.006 mmol), PPh_3 (6.5 mg, 0.025 mmol) and K_2CO_3 (25.4 mg, 0.184 mmol) in 85% yield (38.0 mg, 0.104 mmol) as a pale yellow solid, mp. 135–137 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.03 (d, J = 6.8 Hz, 3H), 1.06 (d, J = 6.8 Hz, 3H), 2.45 (dqq, J = 6.8, 6.8, 6.4 Hz, 1H), 5.41 (dd, J = 8.4, 6.4 Hz, 1H), 6.91 (m, 2H), 7.08 (d, J = 8.4 Hz, 1H), 7.43–7.46 (m, 3H), 7.51 (m, 1H), 7.77 (s, 1H), 7.85 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 18.2, 19.2, 33.8, 55.3, 56.5, 114.5, 123.7, 127.1, 128.0, 128.6, 131.6, 134.3, 136.7, 139.1, 159.7, 166.9, 167.9; HRMS (CI) calcd for $C_{21}H_{23}N_2O_2S$ [M + H]$^+$: 367.1480. Found: 367.1450.

2-[1-(*N*-Benzoyl-*N*-benzylamino)-2-methylpropyl]-5-phenylethynyl-thiazole (12c). Triflate **9c** (100 mg, 0.20 mmol), CuI (3.8 mg, 0.02 mmol), $Pd(OAc)_2$ (4.7 mg, 0.01 mmol) and PPh_3 (10.6 mg, 0.04 mmol) were dissolved in DMF (2 mL) under argon. 2,6-lutidine (109 mg, 1.00 mmol) and phenylacetylene (27.4 mg, 0.26 mmol) were added dropwise and the mixture was allowed to stir overnight at room temperature. After evaporation of the solvent, the crude product was purified by flash chromatography (silica, hexanes–EtOAc, 7 : 3) to give **12c** in 95% yield (85.0 mg, 0.19 mmol) as pale yellow, highly viscous oil. Major rotamer: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.91 (bs, 3H), 1.16 (bs, 3H), 3.03 (bs, 1H), 4.70–4.75 (m, 1H), 4.99 (d, J = 14.0 Hz, 1H), 5.14 (d, J = 8.8 Hz, 1H), 6.79–7.82 (m, 16H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 19.8, 20.3, 30.2, 45.3, 66.1, 79.1, 96.2, 120.1, 122.2, 126.5, 127.1, 127.4, 128.1, 128.4, 128.8, 129.5, 129.7, 130.1, 131.4, 136.6, 136.9, 145.1, 146.1, 168.6, 172.7. Selected signals of the minor rotamer: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.76 (bs, 3H), 0.97 (bs, 3H), 2.74 (bs, 1H), 4.55 (d, J = 15.6 Hz, 1H), 4.70–4.75 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 30.8, 52.1, 64.5, 78.5, 96.6, 119.6, 145.1 146.1, 167.6; HRMS (CI) calcd for $C_{29}H_{27}N_2OS$ [M + H]$^+$: 451.1844. Found; 451.1846.

2-[1-(*N*-Benzoyl-*N*-benzylamino)-2-methylpropyl]-5-allyl-thiazole (14c). Triflate **9c** (100 mg, 0.20 mmol), LiCl (42.4 mg, 1.00 mmol), $Pd(OAc)_2$ (4.7 mg, 0.01 mmol) and PPh_3 (10.6 mg, 0.04 mmol) were dissolved in abs. THF (2 mL) under N_2. Allytributylstannane (102 mg, 0.30 mmol) was added dropwise and the mixture was allowed to stir at 60 °C overnight. After evaporation of the solvent, the crude product was purified by flash chromatography (silica, hexanes–EtOAc, 7 : 3) to give **14c** in 51% yield (40.0 mg, 0.102 mmol) as pale yellow, highly viscous oil. Major rotamer: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.72 (bs, 3H), 0.90–0.97 (m, 5 H), 1.24–1.40 (m, 3H), 2.75 (bs, 1H), 4.72 (m, 1H), 4.85 (d, J = 9.6 Hz, 1H), 4.98 (d, J = 14.4 Hz, 1H), 6.60–7.71 (m, 11H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 13.5, 17.5, 19.7, 20.2, 26.8, 30.9, 45.3, 66.1, 119.3, 119.9, 126.4, 127.4, 127.9, 128.2, 128.6, 129.7, 136.6, 138.3, 141.9, 142.6, 167.2, 167.7, 172.8. Selected signals of the minor rotamer: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.97 (bs, 3H), 1.17 (bs, 3H), 1.64 (m, 1H), 2.98 (bs, 1H), 4.54 (d, J = 15.6 Hz, 1H), 4.72 (m, 1H), 5.46 (d, J = 9.6 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 27.8, 30.3, 50.9, 62.8, 119.3, 119.9, 141.9, 142.6, 167.2, 167.7; HRMS (CI) calcd for $C_{21}H_{21}N_2OS$ [M – allyl + H]$^+$: 351.1523. Found; 351.1530.

2-[1-(*N*-Benzoylamino)-2-methylpropyl]-thiazole (15a). A solution of triflate **9a** (50 mg, 0.122 mmol), $Pd(OAc)_2$ (2.8 mg, 0.006 mmol) and PPh_3 (6.5 mg, 0.025 mmol) in abs. THF (0.5 mL) was heated to 60 °C under N_2, before a solution of NEt_3 (24.7 mg, 0.244 mmol) and formic acid (11.5 mg, 0.244 mmol) in THF (0.5 mL) was added dropwise. The solution was stirred for 6 h at this temperature and after evaporation of the solvent, the crude product was purified by flash chromatography (silica, hexanes–EtOAc, 7 : 3) to give **15a** in 94% yield (30.0 mg, 0.115 mmol) as pale yellow solid, mp. 97–100 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.98 (d, J = 6.8 Hz, 3H), 1.02 (d, J = 6.8 Hz, 3H), 2.43 (m, 1H), 5.45 (dd, J = 7.6, 6.8 Hz, 1H), 7.08 (d, J = 7.6 Hz, 1H), 7.26 (d, J = 3.2 Hz, 1H), 7.44 (m, 2H), 7.50 (m, 1H), 7.74 (d, J = 3.2 Hz, 1H), 7.83 (d, J = 7.2 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 18.1, 19.1, 34.0, 56.3, 118.6, 127.1, 128.6, 131.6, 134.3, 142.3, 166.9, 169.8; HRMS (CI) calcd for $C_{14}H_{17}N_2OS$ [M + H]$^+$: 261.1062. Found; 261.1024.

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