Novel Syntheses of Variably Substituted Pyrrolo[2,3-*d*]thiazoles

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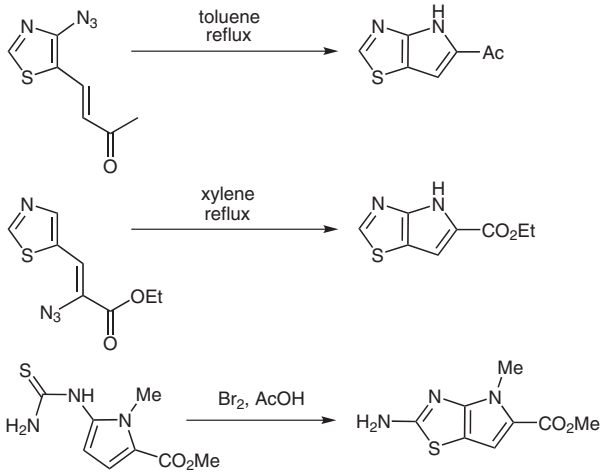
Abstract: Pyrrolo[2,3-*d*]thiazoles are conveniently derived from the corresponding *o*-aminoalkynylthiazoles via microwave assisted 5-*endo*-dig cyclization. Methylene-bridged substituents in the 6-position are directly obtained from 5-*exo*-Heck cyclization based on the same iodoaminothiazole precursor. Further structural variety is accessible via Suzuki reaction of 2-chloroaminothiazoles prior to cyclization or post-cyclization modifications.

Key words: thiazoles, pyrroles, heterocycles, microwave irradiation

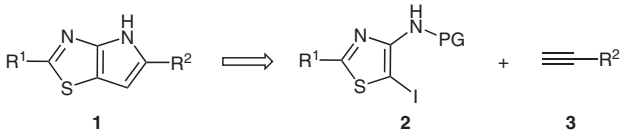
Pyrrolothiazoles represent an important class of heterocyles,[1] particularly useful for new materials,[2] dyes,[3] and pharmacological applications.[4] The rarely described pyrrolo[2,3-*d*]thiazoles **1** are interesting scaffolds suitable even for novel drugs. Until now, their syntheses have always been based on two approaches differing in the construction of the second cycle: formation of the pyrrole moiety by thermally-induced cyclizations of azides[5] or the construction of the thiazole residue by bromine-induced cyclization of pyrrolylthioureas[6] (Scheme 1).



Scheme 1 Currently known synthetic routes to pyrrolo[2,3-*d*]thiazoles

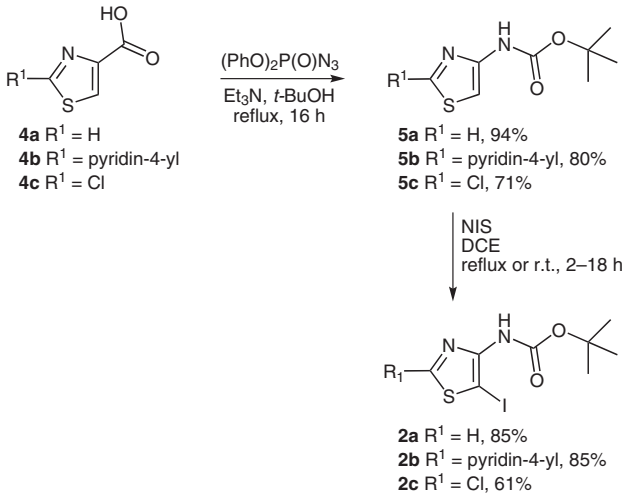
Both approaches yield the bicyclic scaffolds bearing functional groups, either required for further transformations or merely present on account of the synthetic accessibility of the precursors. The functional groups in the latter case need to be removed subsequently, if they are unwanted within the target structure. Therefore, it would be desirable to develop a novel protocol without these drawbacks.

We herein present a straightforward protocol for the construction of variably substituted pyrrolo[2,3-*d*]thiazoles **1** based on palladium-mediated coupling prior to microwave enhanced base-induced 5-*endo*-dig cyclization of the intermediate *o*-aminoalkynylthiazoles. Based on our experiences with the synthesis of pyrrole-fused heterocycles[7] and inspired by numerous publications in the field of indoles[8] we first aimed to build up the pyrrole moiety in a one-step alkynylation/cyclization reaction based on the corresponding *o*-iodoaminothiazoles **2** and alkynes **3**, respectively (Scheme 2).



Scheme 2 Retrosynthesis of pyrrolo[2,3-*d*]thiazoles via alkynylation/cyclization reaction

Due to the common instability of comparable unprotected aminoimidazoles[9] we considered Boc-protected iodoaminothiazoles **2** to be viable precursors with sufficient stability[10] to fulfil the aforementioned task. Their syntheses were based on commercially available thiazole-4-carboxylic acids **4** (Scheme 3).



4a R^1 = H
4b R^1 = pyridin-4-yl
4c R^1 = Cl

5a R^1 = H, 94%
5b R^1 = pyridin-4-yl, 80%
5c R^1 = Cl, 71%

2a R^1 = H, 85%
2b R^1 = pyridin-4-yl, 85%
2c R^1 = Cl, 61%

Scheme 3 Synthesis of precursors **2**

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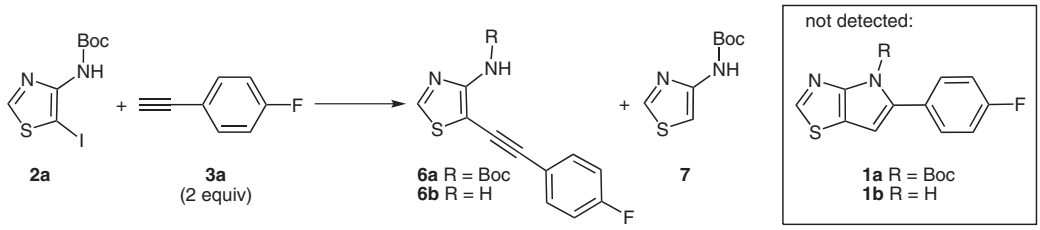
Table 1 Tested Reaction Conditions for the Attempted Direct Synthesis of Pyrrolo[2,3-*d*]thiazoles



Entry	Conditions	Yield (%)[a] or ratio[b] of **6a**, **6b**, and **7**
1	$Pd(OAc)_2$ (5 mol%), Ph_3P (5 mol%), Na_2CO_3 (5 equiv), DMF, 100 °C, 3 h	19%:5%:n.d.
2	$Pd(OAc)_2$ (5 mol%), PB-PPh_3[c] (10 mol%), Na_2CO_3 (3 equiv), DMF, 60 °C, 20 h	38%:0%:10%
3	$Pd(OAc)_2$ (5 mol%), Bu_4NOAc (2.5 equiv), MeCN, reflux, 17 h	5:1:7
4	$Pd(PPh_3)_2Cl_2$ (10 mol%), CuI (10 mol%), Et_3N–MeCN (1:1), r.t., 18 h[d]	1:0:1
5	$Pd(PPh_3)_2Cl_2$ (10 mol%), CuI (10 mol%), TBAF (3 equiv), THF, r.t., 18 h[d]	1:20:1
6	$Pd(PPh_3)_2Cl_2$ (10 mol%), CuI (10 mol%), TBAF (3 equiv), THF, 70 °C mW, 90 min	1:16:3
7	$Pd(dppf)Cl_2 \times CH_2Cl_2$ (5 mol%), CuI (10 mol%), THF, 50 °C, 6 h[e]	85%:0%:trace

[a] Isolated yield.
[b] Product ratio determined by HPLC.
[c] Polymer-bound (PB) Ph_3P was used (diphenylphosphino-polystyrene).
[d] Conversion of **2a** was to an extent of 75%.
[e] Alkyne **3a** used: 1.1 equiv.

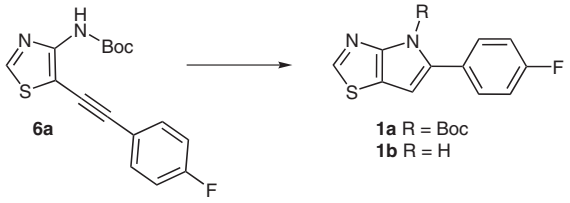
Thiazol-4-carboxylic acids **4** were subjected to Curtius conditions with diphenylphosphoryl azide (DPPA) in *tert*-butyl alcohol directly yielding the corresponding carbamates **5** in high yields.[11] The desired iodothiazoles **2** were thereupon obtained in good yields by treatment with *N*-iodosuccinimide in dichloroethane (DCE).[12]

In a model reaction the Boc-protected iodoaminothiazole **2a** was reacted under various conditions with 4-fluorophenylacetylene (**3a**) to study a putative alkynylation/cyclization reaction (Table 1). However, under the tested reaction conditions, the only products beside the dehalogenated starting material **7** were those derived from alkyne-coupling **6a** and subsequent cleavage of the Boc group **6b**. In a preliminary experiment, standard Pd-catalyzed coupling conditions were used counting on an aminopalladation/reductive elimination mechanism[8g] without addition of a distinct base. The Boc-protected product **6a** was therein obtained in low yields (38% at 60 °C, Table 1, entry 2), beside minor amounts of deprotected product **6b** at higher temperatures (entry 1). When a phosphine ligand was omitted and tetrabutylammonium acetate was employed as base[8b] dehalogenation drastically increased (entry 3). Applying typical Sonogashira conditions (entry 4)[8e] dehalogenation to the thiazole **7** remained a major side reaction. The use of tetrabutylammonium fluoride (TBAF)[8f] as base, thus expecting an in situ 5-*endo*-dig cyclization, led to a nearly quantitatively deprotected alkyne **6b** (entry 5). Even under harsher conditions (entry 6) this side product did not cyclize in situ into the desired pyrrolothiazole **1b**.

Disappointed by these results, we then turned to a directed base-induced 5-*endo*-dig cyclization of the now readily available *o*-aminoalkynylthiazoles **6**. Therefore, their synthesis was finally optimized under previously employed[7] Sonogashira coupling conditions using $Pd(dppf)Cl_2$/CuI as catalyst system yielding **6a** in 85% with only marginal dehalogenation and without any Boc-group cleavage as side reaction (Table 1, entry 7). *O*-Aminoalkynylthiazole **6a** was then subjected to different cyclization conditions (Table 2).

First attempts for the base-induced cyclization were performed with TBAF[8b] in tetrahydrofuran (Table 2, entries 1 and 2) leading to entire deprotection of the starting material. Even under harsh microwave conditions (entry 2) the base strength was insufficient to induce cyclization of the amine **6b**, which happened under these reaction conditions. Further attempts with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in different solvent systems[13] led to rapid decomposition of the reaction mixture (entries 3 and 4), whereas application of sodium hydroxide in *N*,*N*-dimethylformamide[14] resulted in no reaction at 60 °C (entry 5). We then unsuccessfully examined the stronger base *t*-BuOK, first in *t*-BuOH, but outright under microwave irradiation conditions to take advantage of temperature conditions above boiling point (entry 6). Finally, in combination with a polar aprotic solvent, the use of *t*-BuOK[15] led to the formation of 35% of the desired product **1b** after prolonged conventional heating of 46 hours (entry 7). An extension of the reaction time to 62 hours led to full conversion of the starting material **6a** and an increased yield of 53% of **1b** (entry 8). As this long reaction

Table 2 Base-Induced Cyclization of *o*-Aminoalkynylthiazole **6a** to the Corresponding Pyrrolo[2,3-*d*]thiazole **1**



Entry	Conditions	Yield (%)[a]
1	TBAF (3 equiv), THF, reflux, 1.5 h	deprotect. (**6b**)
2	TBAF (3 equiv), THF, 120 °C, mW, 20 min	deprotect. (**6b**)
3	DBN (5 equiv), DMF, 60 °C, 1 h	dec.
4	DBN (5 equiv), MeOH–H_2O, 65 °C, 1 h	dec.
5	NaOH (5 equiv), DMF, 60 °C, 2 h	no reaction
6	*t*-BuOK (1.7 equiv), *t*-BuOH, 110 °C, mW, 20 min	no reaction
7	*t*-BuOK (1.7 equiv), NMP, 90 °C, 46 h	**1a**: 0%; **1b**: 35%[b]
8	*t*-BuOK (1.7 equiv), NMP, 90 °C, 62 h	**1a**: 0%; **1b**: 53%
9	*t*-BuOK (1.7 equiv), NMP, 90 °C, mW, 15 min[c]	**1a**: 0%; **1b**: 55%[b]
10	*t*-BuOK (1.7 equiv), NMP, 90 °C, mW, 20 min[c]	**1a**: 0%; **1b**: 66%

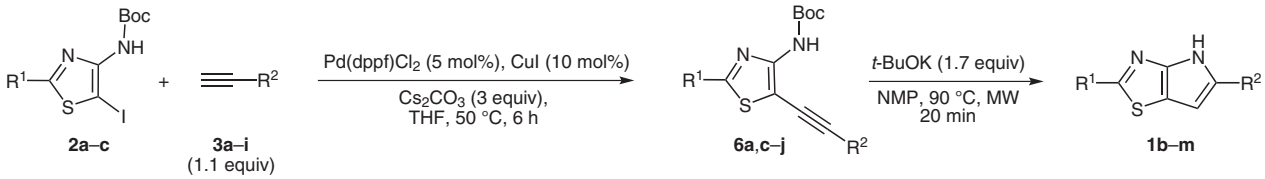
[a] Isolated yield.
[b] Starting material was partially recovered.
[c] Advanced microwave settings were used: 90 °C in combination with constant cooling led to an irradiation of 75 W (see experimental sections for details and the Supporting Information for a full reaction parameter diagram).

time possibly accounted for decomposition processes of either starting material or product, the reaction was conducted with the same reagents in the presence of microwaves. To take full advantage of a high irradiation without risking unwanted side reactions due to overheating, a constant temperature of 90 °C with concurrent nitrogen flow to cool the reaction vessel was tested. This resulted in an irradiation power of approximately 75 W.[16] After 20 minutes, full conversion was achieved and the deprotected pyrrolo[2,3-*d*]thiazole **1b** was isolated in 66% yield as a single product (entry 10).

The methodology was then applied to the synthesis of novel pyrrolo[2,3-*d*]thiazoles **1c**–**m** (Table 3, entries 2–12). Alkynylation of **2a** with benzylalkyne **3b** smoothly led to the benzylated pyrrolo[2,3-*d*]thiazole **1c**. Triethylsilylacetylene was chosen for the alkynylation of **2a** to test the lability of trialkylsilyl groups under the basic cyclization conditions. As anticipated, full cleavage of the triethylsilyl group occurred and **1d** was obtained in 44% (Table 3, entry 3). This is the first reported facile synthesis of an entirely unsubstituted pyrrolo[2,3-*d*]thiazole.[17] 3-Anilinyl- and 4-pyridinylpyrrolothiazoles **1e** and **1f**, respectively, were obtained from commercially available alkynes, under the stated conditions. The 3-hydroxyphenylacetylene (**6g**) could not be cyclized under these conditions: a deprotonation of the more acidic hydroxy group led to a charged species, which appeared to be insusceptible for an intramolecular nucleophilic cyclization. For the synthesis of the benzylated analogue of **1e** and **1h**, an excess of base and a prolonged reaction time were necessary to achieve full conversion (entry 7). The aminopyridinyl-substituted derivative **1i** was derived from the corresponding Boc-protected alkyne **6i**. Treatment of the reaction mixture for 60 minutes under microwave conditions led to a quantitative cleavage of the Boc group within the target molecule (entry 8).[18] Attempts to synthesize the furthermore unsubstituted 2-chloropyrrolothiazole **1j** led to decomposition of the starting material,[19] whereas the 5-(4-fluorophenyl) derivative **1k** proved to be stable and could be isolated in 45% yield (entries 9 and 10). The method further tolerates additional heterocyclic substituents in the 2-position (**1l** and **1m**, entries 11 and 12). Their precursor synthesis is based on Suzuki couplings using commercially available boronic acids (see Scheme 5, vide infra).

Mechanistically, the pyrrole formation most likely involves the deprotonation of the carbamate nitrogen[15] in **6a** and cyclization to the corresponding *N*-Boc-pyrrole derivative **1a**, which can be observed via mass spectrometry of the crude reaction mixtures, but was not isolated due to concomitant deprotection to the desired pyrrolothiazole **1b** (Scheme 4). To verify, whether the carbamate group was essential for an effective cyclization, **6a** was deprotected[20] to **6b** and subjected to the same conditions. As pyrrolothiazole **1b** was isolated in comparable yields from this reaction it could be shown that cyclization is in fact independent of any influence of a carbamate group.

Table 3 Synthesis of Novel Pyrrolo[2,3-*d*]thiazoles **1c–m** by Sonogashira Alkynylation of Thiazoles **2** Followed by 5-*endo*-dig Cyclization



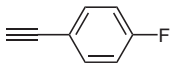
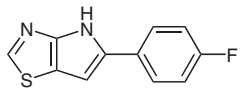
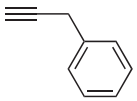
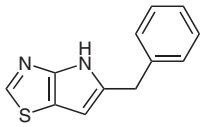
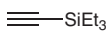
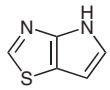
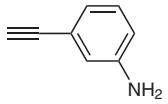
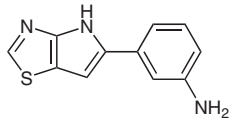
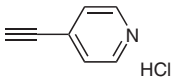
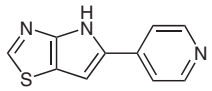
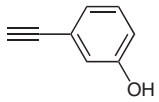
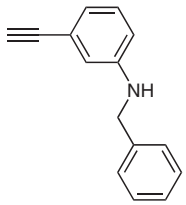
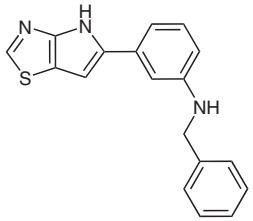
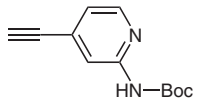
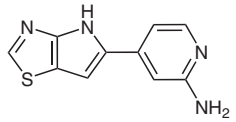
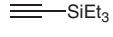
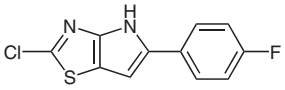
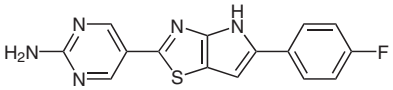
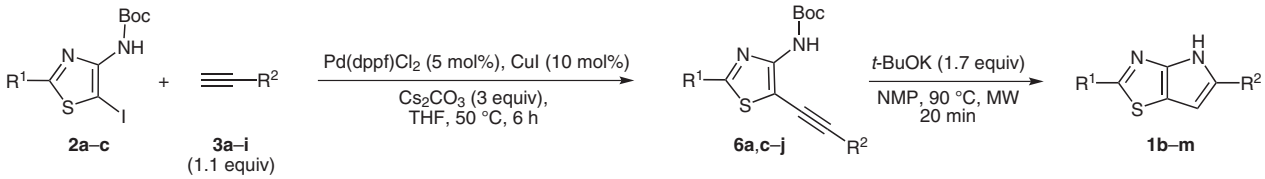
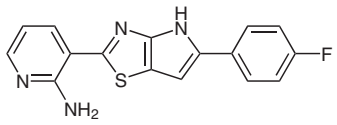
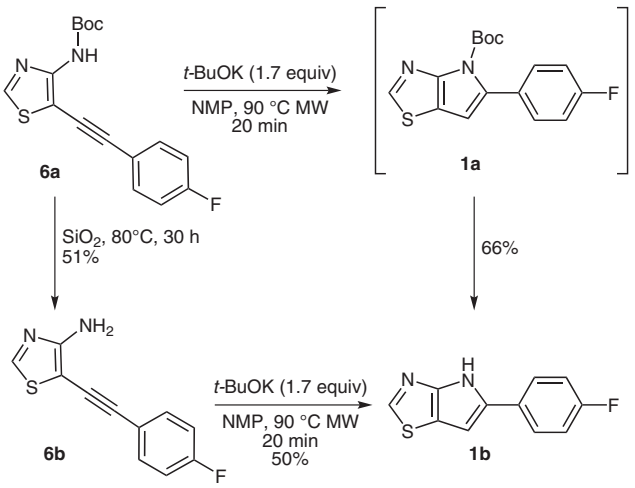
Entry	Thiazole **2**	Alkyne **3**	Amino alkyne **6**	Yield (%)[a]	Pyrrolo[2,3-*d*]thiazole **1**		Yield (%)[b]
1	**2a**	 **3a**	**6a**	85		**1b**	66
2	**2a**	 **3b**	**6c**	92		**1c**	69
3	**2a**	 **3d**	**6d**	92		**1d**	44[c]
4	**2a**	 **3e**	**6e**	66[d]		**1e**	69
5	**2a**	 **3f**	**6f**	97		**1f**	40
6	**2a**	 **3g**	**6g**	80	–	**1g**	0
7	**2a**	 **3h**	**6h**	92[e]		**1h**	52[f]
8	**2a**	 **3i**	**6i**	30		**1i**	20[g]
9	**2c**	 **3d**	**6j**	53	–	**1j**	0
10	**2a**	See Scheme 5	**6k**			**1k**	45[h]
11	**2a**	See Scheme 5	**6l**			**1l**	37[i]

Table 3 Synthesis of Novel Pyrrolo[2,3-*d*]thiazoles **1c–m** by Sonogashira Alkynylation of Thiazoles **2** Followed by 5-*endo*-dig Cyclization



Entry	Thiazole **2**	Alkyne **3**	Amino alkyne **6**	Yield (%)[a]	Pyrrolo[2,3-*d*]thiazole **1**	Yield (%)[b]
12	**2a**	See Scheme 5	**6m**		**1m**	47[j]

[a] Reactions were performed with 1.5 mmol of thiazole **2** in 15 mL of THF; isolated yield.
[b] Reactions were performed with 0.75 mmol of aminoalkyne **6** in 4.5 mL of NMP; isolated yield.
[c] Reaction carried out at 90 °C for 10 min.
[d] Reaction carried out at r.t. for 18 h.
[e] Reaction carried out at 50 °C for 24 h.
[f] Reaction carried out with *t*-BuOK (3 equiv) at 90 °C for 60 min.
[g] Reaction run on a 0.25 mmol scale; 90 °C, 30 min.
[h] Reaction run on a 2 mmol scale; 90 °C, 15 min.
[i] Reaction run on a 0.25 mmol scale; 90 °C, 15 min.
[j] Reaction run on a 0.5 mmol scale; 90 °C, 15 min.



Scheme 4 Influence of the carbamate group on the cyclization

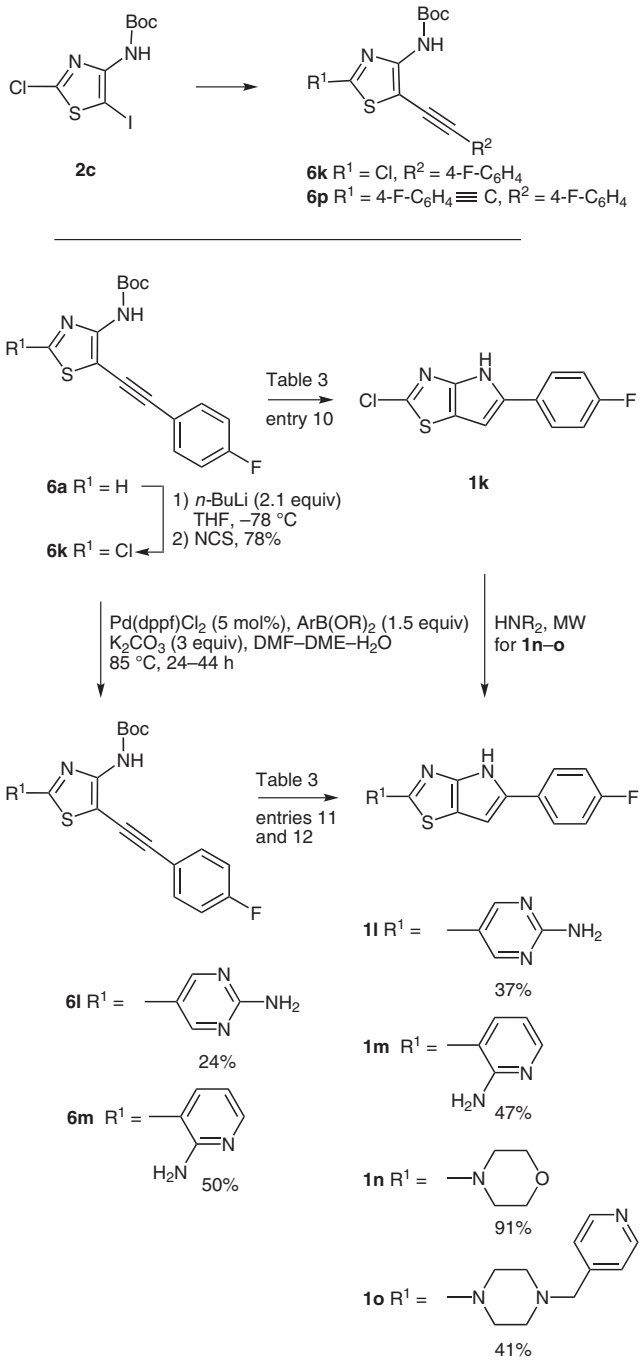
Due to the activated 2-position within the 2-chloro-5-iodothiazole moiety, the alkynylation of **2c** as putative cyclization precursor for **1k** resulted in mono- **6k** and disubstituted **6p** derivatives under various conditions. We therefore introduced the 2-chloro substituent after the alkynylation reaction (Scheme 5). This was achieved in 78% yield by reaction with *N*-chlorosuccinimide (NCS) after lithiation at –78 °C.[21]

A further derivatization prior or after the cyclization reaction then allowed a variable introduction of substituents. For example aryl moieties were introduced in **6k**[22] by Suzuki coupling and the resulting alkynes **6l**,**n** cyclized to the corresponding pyrrolo[2,3-*d*]thiazoles **1l** and **1m** in 37 and 47%, respectively. Furthermore, secondary amines were introduced into the 2-position of pyrrolo[2,3-*d*]thiazole **1k** via nucleophilic substitution to give **1n**,**o** (Scheme 5).

To further access substitutions in the 6-position of the pyrrolo[2,3-*d*]thiazole core a methodology, which was recently published for the synthesis of thieno[2,3-*b*]pyrroles,[23] was adapted to yield benzyl-substituted derivatives **8a**,**b** (Table 4). For this purpose the iodothiazoles **2a** and **2b** were allylated with cinnamyl bromide employing Cs_2CO_3 as base. The reaction mixture was subsequently treated with $Pd(OAc)_2/PPh_3$ to induce 5-*exo*-Heck cyclization[24] followed by rearrangement[23] to the corresponding Boc-protected pyrrolothiazoles. After aqueous workup, the crude mixture was evaporated together with silica gel and heated in vacuo for the indicated time to cleave the Boc group, conveniently yielding **8a**,**b** after subsequent flash chromatography in this overall one-pot procedure in 49 and 53% yield, respectively.

In summary, we have developed a novel synthesis of pyrrolo[2,3-*d*]thiazoles. Employing a base-induced 5-*endo*-dig cyclization or intramolecular Heck reaction as key steps, variable substituents in all positions can be introduced. Particularly, the introduction of residues in the 2-position are easily accessible after expedient halogenation, thus enabling a synthesis of highly functionalized novel heterocycles without the need for potentially dispensable groups due to the synthesis routine. Further studies towards Larock-type reactions of *o*-iodoaminothiazoles with alkynes are currently in progress in our group.

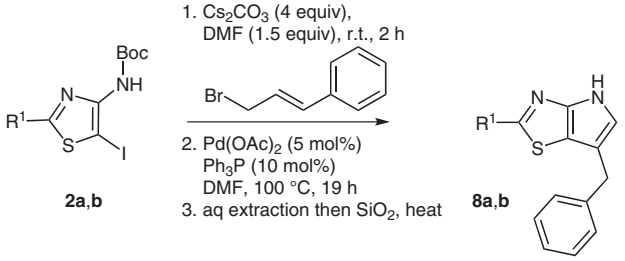
All reagents obtained commercially were used without further purification. DMF and THF were obtained from Aldrich in septum-sealed bottles over molecular sieves under N_2 and handled using syringe/Schlenk techniques. Petroleum ether (PE) used refers to the fraction boiling in the range 50–70 °C. NMP was obtained from



Scheme 5 Derivatization in 2-position of thiazoles and pyrrolo[2,3-*d*]thiazoles

Merck and used without further purification or distillation. TLC analyses were run on precoated silica gel plates (Merck $60F_{254}$) and the spots were visualized using a UV lamp. Flash and gravity chromatography were carried out on columns using silica gel 60 Merck (63–200 μm) as the stationary phase. Microwave-assisted syntheses were carried out in septum-capped glass vials, which were flushed with N_2 prior to closing. Irradiation was carried out in a monomode Biotage EmrysOptimizer microwave with temperature and pressure monitoring. The N_2 cooling stream featured a pressure of 3 bar. NMR spectra were recorded in DMSO-d_6 at 300 K on a Bruker Avance 300 (300 MHz and 75 MHz spectra), Bruker Avance II 400 (400 MHz and 100 MHz spectra) and Bruker Avance DRX 500 (500 MHz spectra), respectively. Chemical shifts are given in ppm relative to TMS as internal standard. EI-MS spectra were obtained with a VG Autospec sector field mass spectrometer. EI-HRMS spectra were acquired with a GCT Premier 95 whereas ESI-HRMS spectra were obtained from a Thermo LTQ XL Orbitrap with ESI interface. ESI-MS spectra were recorded using an Agilent 6110 Quadrupole LC/MS with ESI interface G1946 (positive or negative ionization). The APCI-MS data was acquired with a Finnigan LCQ Deca. Melting points were taken on samples in open capillary tubes employing a HWS SGV500 melting point apparatus and are uncorrected.

Table 4 Synthesis of 6-Substituted Pyrrolo[2,3-*d*]thiazoles **8**



Entry	Thiazole **2**	Boc cleavage	Pyrrolo[2,3-*d*] thiazole **8**	Yield (%)[a]
1	**2a**	5 h, 100 °C	**8a** R^1 = H	49
2	**2b**	19 h, 50 °C	**8b** R^1 = 4-pyridinyl	53

[a] Isolated yield.

tert-Butyl *N*-(1,3-Thiazol-4-yl)carbamates 5; General Procedure

To a solution of the corresponding 4-thiazolecarboxylic acid **4** (37.55 mmol) in *t*-BuOH (180 mL) was added Et_3N (5.80 mL, 41.84 mmol) followed by diphenylphosphoryl azide (9.10 mL, 42.19 mmol) at 0 °C (ice-bath). The mixture was then stirred for 16 h at reflux. After cooling to r.t., the solvent was evaporated in vacuo, the crude residue redissolved in CH_2Cl_2 (100 mL), and washed with brine (2 × 100 mL). The organic layer was dried (Na_2SO_4) and the solvent removed in vacuo. The product was purified by column chromatography on silica gel (cyclohexane–EtOAc).

tert-Butyl *N*-(1,3-Thiazol-4-yl)carbamate (5a)

Yield: 94%; beige crystals; mp 153–155 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.47 (s, 9 H), 7.23 (d, *J* = 2.0 Hz, 1 H), 8.89 (d, *J* = 2.2 Hz, 1 H), 10.15 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 28.0, 79.3, 98.3, 149.4, 151.7, 152.7.

MS (ESI): *m*/*z* (%) = 145 (100, [M – *t*-Bu + 2 H]$^+$), 201 (5, [M + H]$^+$).

Anal. Calcd for $C_8H_{12}N_2O_2S$: C, 47.98; H, 6.04; N, 13.99; S, 16.01. Found: C, 47.90; H, 6.10; N, 14.00; S, 16.60.

tert-Butyl *N*-(2-Pyridin-1,3-thiazol-4-yl)carbamate (5b)

Yield: 80%; white-grey crystals; mp 192–193 °C (PE).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.49 (s, 9 H), 7.45 (s, 1 H), 7.81 (dd, *J* = 4.5, 1.6 Hz, 2 H), 8.70 (dd, *J* = 4.5, 1.6 Hz, 2 H), 10.38 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 28.0, 79.7, 101.6, 119.5, 139.3, 150.0, 150.7, 152.8, 161.2.

MS (EI, 70eV): *m*/*z* (%) = 57 (100, [CCH_3]$^+$), 177 (80, [M – Boc]$^+$), 277 (10, [M]$^+$).

MS (ESI): *m*/*z* (%) = 278 (100, [M + H]$^+$).

Anal. Calcd for $C_{13}H_{15}N_3O_2S$: C, 56.30; H, 5.45; N, 5.15; S, 11.56. Found: C, 56.30; H, 5.50; N, 5.10; S, 12.10.

***tert*-Butyl *N*-(2-Chloro-1,3-thiazol-4-yl)carbamate (5c)**
Yield: 71%; white crystals; mp 118–119 °C (Et_2O).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.46 (s, 9 H), 7.17 (s, 1 H), 10.26 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 28.0, 79.7, 101.3, 146.5, 148.5, 152.5.

MS (ESI): *m*/*z* (%) = 179 (100, [M – *t*-Bu + 2 H]$^+$).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_8H_{11}ClN_2O_2S$: 235.0308; found: 234.9027.

***tert*-Butyl *N*-(5-Iodo-1,3-thiazol-4-yl)carbamates 2; General Procedure**
To a solution of the corresponding carbamate **5** (3.99 mmol) in DCE (40 mL) was added *N*-iodosuccinimide (1033 mg, 4.59 mmol) and the reaction mixture was heated to reflux for 2 h. After cooling to r.t., the organic layer was washed with H_2O (2 × 50 mL) and sat. aq $Na_2S_2O_3$ (50 mL), dried (Na_2SO_4), and the solvent removed in vacuo. The product was purified by flash chromatography on silica gel (cyclohexane–EtOAc, 8:2 to 1:1).

***tert*-Butyl *N*-(5-Iodo-1,3-thiazol-4-yl)carbamate (2a)**
Yield: 85%; white crystals; mp 119–120 °C (Et_2O).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.44 (s, 9 H), 8.99 (s, 1 H), 9.12 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 28.0, 79.0, 152.2 (2 ×), 152.9, 157.2.

MS (EI, 70 eV): *m*/*z* (%) = 57 (95, [CCH_3]$^+$), 226 (100, [M – Boc]$^+$), 326 (17, [M]$^+$).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_8H_{11}IN_2O_2S$: 326.9664; found: 326.9658.

***tert*-Butyl *N*-(2-Pyridin-5-iodo-1,3-thiazol-4-yl)carbamate (2b)**
Yield: 85%; pink solid; mp 197–198 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.46 (s, 9 H), 7.80 (dd, *J* = 4.5, 1.6 Hz, 2 H), 8.72 (dd, *J* = 5.9, 1.5 Hz, 2 H), 9.27 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 27.5, 73.1, 78.9, 118.9, 138.2, 150.3, 152.3, 152.3, 165.4.

MS (EI, 70 eV): *m*/*z* (%) = 57 (100, [CCH_3]$^+$), 303 (80, [M – Boc]$^+$), 403 (10, [M]$^+$).

Anal. Calcd for $C_{13}H_{14}N_3O_2S$: C, 38.72; H, 3.50; N, 10.42; S, 7.95. Found: C, 39.10; H, 3.50; N, 10.40; S, 7.80.

***tert*-Butyl *N*-(2-Chloro-5-iodo-1,3-thiazol-4-yl)carbamate (2c)**
Yield: 61%; pale-yellow crystals; mp 77–78 °C (Et_2O).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.44 (s, 9 H), 9.15 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 28.0, 71.7, 79.5, 149.7, 151.8, 152.7.

MS (ESI): *m*/*z* (%) = 304 (100, [M – *t*-Bu + 2 H]$^+$).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_8H_{10}ClIN_2O_2S$: 360.9274; found: 360.9269.

***tert*-Butyl *N*-[5-(2-Alkynyl)-1,3-thiazol-4-yl]carbamates 6; General Procedure**
Cs_2CO_3 (2.93 g, 9 mmol) was dried in a Schlenk tube and suspended in anhyd THF (50 mL) under N_2. The corresponding carbamate **2** (3 mmol) followed by the corresponding alkyne **3** (3.30 mmol), Pd(dppf)Cl_2·CH_2Cl_2 (122 mg, 0.15 mmol), and CuI (57 mg, 0.30 mmol) were added under N_2. The reaction mixture was heated to 50 °C for 6 h. After cooling to r.t. and filtering over Celite, the solvent was removed in vacuo. The crude residue was redissolved in EtOAc (50 mL) and washed with brine (2 × 50 mL). The organic layer was dried (Na_2SO_4) and the solvent removed in vacuo. The product was purified by column chromatography or flash chromatography on silica gel (cyclohexane–EtOAc).

***tert*-Butyl *N*-{5-[2-(4-Fluorophenyl)ethynyl]-1,3-thiazol-4-yl}carbamate (6a)**
Yield: 85%; pale-yellow solid; mp 139–144 °C (Et_2O).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.45 (s, 9 H), 7.22–7.39 (m, 2 H), 7.50–7.68 (m, 2 H), 8.98 (s, 1 H), 9.62 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 27.4, 78.9, 96.3, 105.6, 115.3 (d, $^2J_{C,F}$ = 22 Hz), 117.9, 117.9, 132.9 (d, $^3J_{C,F}$ = 8 Hz), 150.6, 151.8, 152.1, 161.6 (d, $^1J_{C,F}$ = 246 Hz).

MS (ESI): *m*/*z* (%) = 319 (100, [M + H]$^+$).

Anal. Calcd for $C_{16}H_{15}FN_2S$: C, 60.36; H, 4.75; N, 8.80; S, 10.07. Found: C, 60.20; H, 4.70; N, 8.78; S, 10.19.

***tert*-Butyl *N*-[5-(3-Phenylprop-1-ynyl)-1,3-thiazol-4-yl]carbamate (6c)**
Yield: 92%; pale-yellow solid; mp 121–122 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.41 (s, 9 H), 3.93 (s, 2 H), 7.15–7.45 (m, 5 H), 8.88 (s, 1 H), 9.33 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 25.1, 27.9, 71.6, 79.1, 97.5, 126.6, 127.8, 128.4, 136.0, 150.5, 2 × 151.3, 152.6.

MS (ESI): *m*/*z* (%) = 259 (100, [M – *t*-Bu + 2 H]$^+$), 314 (68, [M]$^+$), 315 (10, [M + H]$^+$).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{18}N_2O_2S$: 315.1167; found: 315.1161.

***tert*-Butyl *N*-{5-[(Triethylsilyl)ethynyl]-1,3-thiazol-4-yl}carbamate (6d)**
Yield: 92%; pale-beige solid; mp 88–90 °C (Et_2O).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.62 (dt, *J* = 8.3, 4.2 Hz, 6 H), 0.98 (t, *J* = 7.8 Hz, 9 H), 1.43 (s, 9 H), 8.91 (s, 1 H), 9.39 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 3.7, 7.3, 27.9, 79.1, 94.9, 101.4, 107.6, 151.4, 152.3, 152.4.

MS (APCI): *m*/*z* (%) = 239 (40, [M – Boc + H]$^+$), 282 (100, [M – *t*-Bu + 2 H]$^+$), 338 (17, [M]$^+$).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{26}N_2O_2SSi$: 339.1562; found: 339.1032.

***tert*-Butyl *N*-{5-[(3-Aminophenyl]ethynyl]-1,3-thiazol-4-yl}carbamate (6e)**
Yield: 66%; dark-white solid; mp 166–177 °C (MeOH).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.45 (s, 9 H), 5.27 (s, 2 H), 6.57–6.71 (m, 3 H), 7.05 (t, *J* = 7.8 Hz, 1 H), 8.95 (s, 1 H), 9.50 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 27.4, 77.1, 78.8, 98.4, 106.7, 114.3, 115.3, 118.0, 121.6, 128.7, 148.3, 150.1, 151.6, 151.9.

MS (EI, 70 eV): *m*/*z* (%) = 215 (100, [M – Boc]$^+$), 315 (20, [M]$^+$).

MS (ESI): *m*/*z* (%) = 316 (100, [M + H]$^+$).

Anal. Calcd for $C_{16}H_{17}N_3O_2S$: C, 60.93; H, 5.43; N, 13.32; S, 10.17. Found: C, 60.90; H, 5.30; N, 13.10; S, 10.10.

***tert*-Butyl *N*-{5-[(Pyridin-4-yl]ethynyl]-1,3-thiazol-4-yl}carbamate (6f)**
Yield: 97%; yellow solid; mp 160–165 °C (Et_2O).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.46 (s, 9 H), 7.45 (dd, *J* = 4.4, 1.6 Hz, 2 H), 8.63 (dd, *J* = 4.4, 1.6 Hz, 2 H), 9.05 (s, 1 H), 9.83 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 27.4, 79.0, 83.3, 94.8, 103.8, 124.2, 129.4, 149.4, 151.6, 151.7, 153.5.

MS (EI, 70 eV): *m*/*z* (%) = 57 (90, $[CCH_3]^+$), 201 (80, $[M – Boc]^+$), 301 (10, $[M]^+$).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{15}N_3O_2S$: 302.0963; found: 302.0959.

***tert*-Butyl *N*-{5-[(3-Hydroxyphenyl)ethynyl]-1,3-thiazol-4-yl}carbamate (6g)**

Yield: 80%; beige solid; mp 170–171 °C (Et_2O).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.44 (s, 9 H), 6.77–6.97 (m, 3 H), 7.21 (t, *J* = 7.9 Hz, 1 H), 8.96 (s, 1 H), 9.53 (s, 1 H), 9.71 (br s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 27.9, 78.5, 79.3, 98.0, 106.7, 116.5, 117.4, 121.9, 122.8, 129.8, 151.0, 152.4 (2 ×), 157.3.

MS (EI, 70 eV): *m*/*z* (%) = 57 (55, $[CCH_3]^+$), 216 (100, $[M – Boc]^+$), 316 (17, $[M]^+$).

Anal. Calcd for $C_{16}H_{16}N_2O_3S$: C, 60.74; H, 5.10; N, 8.85; S, 10.14. Found: C, 60.03; H, 5.10; N, 8.66; S, 10.07.

***tert*-Butyl *N*-(5-{3-[(Benzylamino)phenyl]ethynyl}-1,3-thiazol-4-yl)carbamate (6h)**

Yield: 92%; yellow solid; mp 126–129 °C (Et_2O).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.43 (s, 9 H), 4.28 (d, *J* = 6.0 Hz, 2 H), 6.47 (t, *J* = 6.1 Hz, 1 H), 6.61–6.70 (m, 3 H), 7.04–7.13 (m, 1 H), 7.18–7.31 (m, 1 H), 7.31–7.45 (m, 4 H), 8.94 (s, 1 H), 9.49 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 27.4, 45.6, 77.3, 78.8, 98.4, 106.6, 113.1, 113.2, 118.2, 121.7, 126.1, 126.5, 127.8, 128.7, 139.2, 148.2, 150.2, 151.7, 151.9.

MS (ESI): *m*/*z* (%) = 250 (100, $[M – t\text{-Bu} + 2\ H]^+$), 406 (20, $[M + H]^+$).

Anal. Calcd for $C_{23}H_{23}N_3O_2S$: C, 68.12; H, 5.72; N, 10.36; S, 7.91. Found: C, 67.63; H, 5.80; N, 10.14; S, 8.00.

***tert*-Butyl *N*-(5-{3-[2-(Boc)-aminopyridin-4-ylphenyl]ethynyl}-1,3-thiazol-4-yl)carbamate (6i)**

Yield: 30%; beige solid; mp 250 °C (dec.).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.44 (s, 9 H), 1.48 (s, 9 H), 7.79–7.87 (m, 2 H), 8.37 (d, *J* = 1.1 Hz, 1 H), 8.97 (s, 1 H), 9.62 (s, 1 H), 10.09 (s, 1 H).

MS (ESI): *m*/*z* (%) = 417 (100, $[M + H]^+$).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{24}N_4O_4S$: 417.1596; found: 417.1589.

***tert*-Butyl *N*-{2-Chloro-5-[3-(triethylsilyl)ethynyl]-1,3-thiazol-4-yl}carbamate (6j)**

Yield: 53%; pale-yellow oil.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.58–0.67 (m, 6 H), 0.98 (t, *J* = 7.8 Hz, 9 H), 1.43 (s, 9 H), 9.59 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 3.6, 7.2, 27.8, 79.6, 93.4, 102.9, 109.5, 147.3, 149.0, 152.0.

MS (ESI): *m*/*z* (%) = 317 (100, $[M – t\text{-Bu} + 2\ H]^+$).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{25}ClN_2O_2SSi$: 373.1172; found: 373.1165.

***tert*-Butyl *N*-{2-Chloro-5-[2-(4-fluorophenyl)ethynyl]-1,3-thiazol-4-yl}carbamate (6k)**

A dried Schlenk tube was charged with **6a** (2.63 g, 8.26 mmol) under N_2. After addition of anhyd THF (100 mL), the reaction mixture was cooled to –78 °C and *n*-BuLi (15% in *n*-hexane, 11 mL, 17.34 mmol, 2.1 equiv) was added slowly. After stirring for 20 min at –78 °C, *N*-chlorosuccinimide (1.12 g mg, 8.38 mmol) dissolved in anhyd THF (3 mL) under N_2 was added via a syringe. After stirring for 15 min at –78 °C, the mixture was quenched with *n*-BuOH (10 mL) and warmed to r.t. The solvent was then removed in vacuo and the crude product directly purified via column chromatography on silica gel (cyclohexane–EtOAc, 99:1). After removing the solvent in vacuo, the product was crystallized from PE to yield **6k** (2.3 g, 78%) as a pale beige solid; mp 133–134 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.44 (s, 9 H), 7.25–7.42 (m, 2 H), 7.52–7.62 (m, 2 H), 9.80 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 27.4, 77.2, 79.3, 97.2, 107.4, 115.6 (d, $^2J_{C,F}$ = 22 Hz), 117.4, 133.1 (d, $^3J_{C,F}$ = 9 Hz), 147.2, 148.1, 151.5, 161.8 (d, $^1J_{C,F}$ = 246 Hz).

MS (ESI): *m*/*z* (%) = 296 (100, $[M – t\text{-Bu} + 2\ H]^+$).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{14}ClFN_2O_2S$: 353.0526; found: 353.0522.

***tert*-Butyl *N*-{2-Heteroaryl-5-[2-(4-fluorophenyl)ethynyl]-1,3-thiazol-4-yl}carbamates 6l and 6m; General Procedure**

To a solution of **6k** (705 mg, 2.00 mmol) and the corresponding boronic acid (3 mmol) or the corresponding boronic acid ester, respectively, in DMF (4 mL), H_2O (2 mL) and ethylene glycol dimethyl ether (DME, 8 mL) were added K_2CO_3 (829 mg, 6 mmol) and $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (81 mg, 0.10 mmol). After passing argon through the reaction mixture for 10 min, the reaction vessel was sealed and heated to 85 °C (44 h for 6l; 24 h for 6m). After cooling to r.t., the mixture was extracted with brine (2 × 25 mL) and the combined aqueous layers were extracted with EtOAc (25 mL). The organic layer was dried (Na_2SO_4) and the solvent removed in vacuo. The product was purified by flash chromatography on silica gel (cyclohexane–EtOAc, 1:2; 1% Et_3N).

***tert*-Butyl *N*-{2-(2-Aminopyrimidin-5-yl)-5-[2-(4-fluorophenyl)ethynyl]-1,3-thiazol-4-yl}carbamate (6l)**

Yield: 24%; yellow solid; mp 201–203 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.46 (s, 9 H), 7.23–7.49 (m, 4 H), 7.51–7.70 (m, 2 H), 8.72 (s, 2 H), 9.63 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 27.4, 78.7, 79.0, 96.8, 103.4, 115.6 (d, $^2J_{C,F}$ = 22 Hz), 118.0, 132.8 (d, $^3J_{C,F}$ = 9 Hz), 150.4, 151.7, 155.2, 155.5, 159.5, 161.6 (d, $^1J_{C,F}$ = 247 Hz), 163.4.

MS (ESI): *m*/*z* (%) = 356 (60, $[M – t\text{-Bu} + 2\ H]^+$), 412 (100, $[M + H]^+$).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{18}FN_5O_2S$: 412.1243; found: 412.1242.

***tert*-Butyl *N*-{2-(2-Aminopyridin-3-yl)-5-[2-(4-fluorophenyl)ethynyl]-1,3-thiazol-4-yl}carbamate (6m)**

Yield: 50%; bright-yellow solid; mp 170–172 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.48 (s, 9 H), 6.67 (dd, *J* = 7.7, 4.7 Hz, 1 H), 7.35–7.25 (m, 2 H), 7.58–7.67 (m, 4 H), 7.90 (dd, *J* = 7.7, 1.7 Hz, 1 H), 8.13 (dd, *J* = 4.7, 1.7 Hz, 1 H), 9.89 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 27.4, 78.4, 79.3, 97.2, 100.8, 108.2, 111.7, 115.5 (d, $^2J_{C,F}$ = 23 Hz), 118.0, 132.9 (d, $^3J_{C,F}$ = 8 Hz), 135.6, 149.3, 150.6, 151.4, 155.1, 161.6 (d, $^1J_{C,F}$ = 247 Hz), 163.0.

MS (ESI): *m*/*z* (%) = 411 (100, $[M + H]^+$).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{19}FN_4O_2S$: 411.1291; found: 411.1282.

4*H*-Pyrrolo[2,3-*d*]thiazoles 1; General Procedure

The corresponding alkyne **6** (0.75 mmol) was dissolved in NMP (4.5 mL) in a microwave flask and treated with *t*-BuOK (143 mg, 1.27 mmol) under a blanket of N_2. The vessel was sealed under N_2 and irradiated with microwaves for 20 min at 90 °C (employing a constant stream of N_2). After cooling to r.t., the slurry mixture was diluted with Et_2O (50 mL) and washed with brine (2 × 50 mL). The aqueous layer was extracted with Et_2O (50 mL) and the combined organic layers were dried (Na_2SO_4), and the solvent removed in vacuo. The crude product, which may partially contain remaining traces of NMP, was purified by column chromatography on silica gel (cyclohexane–EtOAc, 1:1).

5-(4-Fluorophenyl)-4*H*-pyrrolo[2,3-*d*]thiazole (1b)

Yield: 66%; grey-white solid; mp 244–245 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.87 (d, *J* = 2.0 Hz, 1 H), 7.20–7.29 (m, 2 H), 7.75–7.83 (m, 2 H), 8.77 (s, 1 H), 12.33 (br s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 96.6, 114.6, 115.8 (d, $^2J_{C,F}$ = 19 Hz), 126.0 (d, $^3J_{C,F}$ = 7 Hz), 129.2, 135.2, 150.8, 153.0, 161.0 (d, $^1J_{C,F}$ = 250 Hz).

MS (ESI): *m*/*z* (%) = 219 (100, $[M + H]^+$).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{11}H_7FN_2S$: 218.0314; found: 218.0312.

5-Benzyl-4*H*-pyrrolo[2,3-*d*]thiazole (1c)

Yield: 69%; brown crystals; mp 117–122 °C (Et_2O).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.99 (s, 2 H), 6.13 (br s, 1 H), 7.17–7.32 (m, 5 H), 8.62 (s, 1 H), 11.78 (br s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 33.9, 96.5, 112.3, 125.6, 127.8, 127.9, 136.0, 139.3, 148.1, 150.9.

MS (APCI): *m*/*z* (%) = 215 (100, $[M + H]^+$).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{12}H_{10}N_2S$: 214.0564; found: 214.0637.

4*H*-Pyrrolo[2,3-*d*]thiazole (1d)

Yield: 44%; dark-white solid; mp 150–151 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.39 (dd, *J* = 3.1, 1.8 Hz, 1 H), 7.11–7.13 (m, 1 H), 8.73 (d, *J* = 1.3 Hz, 1 H), 11.79 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 98.8, 112.9, 122.9, 150.4, 151.9.

MS (APCI): *m*/*z* (%) = 125 (100, $[M + H]^+$).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_5H_4N_2S$: 124.0095; found: 124.0080.

3-(4*H*-Pyrrolo[2,3-*d*]thiazol-5-yl)phenylamine (1e)

Yield: 69%; pale-yellow solid; mp 160–161 °C (Et_2O).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 5.10 (s, 2 H), 6.49 (d, *J* = 7.5 Hz, 1 H), 6.69 (d, *J* = 1.6 Hz, 1 H), 6.98–6.83 (m, 3 H), 7.05 (t, *J* = 8.0 Hz, 1 H), 8.73 (s, 1 H), 12.15 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 95.8, 109.7, 112.3, 112.9, 114.3, 129.2, 133.2, 137.1, 148.8, 150.0, 152.7.

MS (ESI): *m*/*z* (%) = 216 (100, $[M + H]^+$).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{11}H_9N_3S$: 215.0517; found: 215.0520.

5-(Pyridin-4-yl)-4*H*-pyrrolo[2,3-*d*]thiazole (1f)

Yield: 40%; dark crystals; mp 185–187 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.21 (d, *J* = 1.9 Hz, 1 H), 7.73 (dd, *J* = 4.6, 1.6 Hz, 2 H), 8.54 (d, *J* = 6.2 Hz, 2 H), 8.91 (s, 1 H), 12.66 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 99.6, 115.0, 117.9, 113.0, 139.3, 150.0, 153.3, 154.0.

Benzyl[3-(4*H*-pyrrolo[2,3-*d*]thiazol-5-yl)phenyl]amine (1h)

Yield: 52%; yellow solid; mp 169–170 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.34 (d, *J* = 6.1 Hz, 2 H), 6.27 (t, *J* = 6.1 Hz, 1 H), 6.51 (dd, *J* = 8.0, 1.5 Hz, 1 H), 6.71 (d, *J* = 1.9 Hz, 1 H), 6.88–7.01 (m, 2 H), 7.07 (t, *J* = 7.8 Hz, 1 H), 7.22 (t, *J* = 7.3 Hz, 1 H), 7.33 (t, *J* = 7.6 Hz, 2 H), 7.41 (d, *J* = 7.6 Hz, 2 H), 8.74 (s, 1 H), 12.20 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 45.8, 95.4, 107.0, 111.1, 111.7, 113.8, 126.0, 126.7, 127.7, 128.7, 132.6, 136.6, 139.8, 148.4, 149.7, 152.1.

MS (ESI): *m*/*z* (%) = 306 (100, $[M + H]^+$).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{15}N_3S$: 305.0986; found: 306.1051.

4-(4*H*-Pyrrolo[2,3-*d*]thiazol-5-yl)pyridin-2-ylamine (1i)

Yield: 20%; yellow solid; mp 175 °C (Et_2O–MeOH, 99:1; dec.).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 6.05 (s, 2 H), 6.51 (d, *J* = 8.6 Hz, 1 H), 6.66 (d, *J* = 1.9 Hz, 1 H), 7.75 (dd, *J* = 8.6, 2.4 Hz, 1 H), 8.35 (d, *J* = 2.2 Hz, 1 H), 8.68 (d, *J* = 3.5 Hz, 1 H), 12.09 (s, 1 H).

MS (ESI): *m*/*z* (%) = 217 (100, $[M + H]^+$).

2-Chloro-5-(4-fluorophenyl)-4*H*-pyrrolo[2,3-*d*]thiazole (1k)

Yield: 45%; beige solid; mp 150 °C (Et_2O; dec.).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.83 (s, 1 H), 7.13–7.35 (m, 2 H), 7.66–7.90 (m, 2 H), 12.48 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 97.2, 115.8 (d, $^2J_{C,F}$ = 21 Hz), 126.1 (d, $^3J_{C,F}$ = 7 Hz), 128.8, 134.4, 145.9, 147.2, 150.1, 161.2 (d, $^1J_{C,F}$ = 243 Hz).

MS (ESI, –): *m*/*z* (%) = 250 (100, $[M - 2H]^-$), 251 (20, $[M - 1H]^-$), 252 (45, $[M]^-$).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_6ClFN_2S$: 253.0002; found: 252.9998.

5-[5-(4-Fluorophenyl)-4*H*-pyrrolo[2,3-*d*]thiazol-2-yl]pyrimidin-2-ylamine (1l)

Yield: 37%; orange solid; mp 220 °C (PE; dec.).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.89 (d, *J* = 1.9 Hz, 1 H), 7.20 (s, 2 H), 7.21–7.30 (m, 4 H), 8.74 (s, 2 H), 12.37 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 96.6, 113.7, 115.2 (d, $^2J_{C,F}$ = 18 Hz), 117.5, 125.3 (d, $^3J_{C,F}$ = 8 Hz), 128.6, 132.1, 133.9, 154.7, 155.2, 160.3 (d, $^1J_{C,F}$ = 266 Hz), 162.9.

MS (ESI): *m*/*z* (%) = 312 (100, $[M + H]^+$).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{10}FN_5S$: 312.0719; found: 312.0713.

3-[5-(4-Fluorophenyl)-4*H*-pyrrolo[2,3-*d*]thiazol-2-yl]pyridin-2-ylamine (1m)

Yield: 47%; orange solid; mp 300–301 °C (PE–Et_2O, 1:3).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.63–6.74 (m, 1 H), 6.92 (s, 1 H), 7.19–7.35 (m, 2 H), 7.53 (s, 2 H), 7.80 (dd, *J* = 8.8, 5.4 Hz, 2 H), 7.93 (dd, *J* = 7.7, 1.6 Hz, 1 H), 8.06 (dd, *J* = 4.7, 1.6 Hz, 1 H), 12.39 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 97.2, 111.1, 112.3, 114.0, 115.7 (d, $^2J_{C,F}$ = 28 Hz), 125.9, 126.0, 129.0 (2 ×), 134.9, 135.0, 149.1, 151.4, 155.0, 161.0 (d, $^1J_{C,F}$ = 242 Hz), 163.4 ($^3J_{C,F}$ not observed).

MS (ESI): *m*/*z* (%) = 311 (100, $[M + H]^+$).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{11}FN_4S$: 311.0766; found: 311.0757.

5-(4-Fluorophenyl)-2-morpholin-4-yl-4*H*-pyrrolo[2,3-*d*]thiazole (1n)

A microwave flask was charged with **1k** (126 mg, 0.50 mmol), followed by morpholine (2 mL), sealed with a septum, and irradiated with microwaves at 130 °C for 2 h. After cooling to r.t., the reaction mixture was directly purified via column chromatography (cyclohexane–EtOAc, 1:1) to yield **1n** (139 mg, 91%) as beige crystals; mp 240–248 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.35–3.51 (m, 4 H), 3.66–3.81 (m, 4 H), 6.65 (d, *J* = 1.3 Hz, 1 H), 7.16 (t, *J* = 8.9 Hz, 2 H), 7.55–7.69 (m, 2 H), 11.78 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 48.0, 65.3, 97.2, 105.4, 115.5 (d, $^2J_{C,F}$ = 21 Hz), 124.5 (d, $^3J_{C,F}$ = 7 Hz), 128.8, 129.9, 148.6, 160.1 (d, $^1J_{C,F}$ = 240 Hz), 170.6.

MS (ESI): *m*/*z* (%) = 304 (100, [M + H]$^+$).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{14}FN_3OS$: 304.0920; found: 304.0911.

5-(4-Fluorophenyl)-2-(4-pyridin-4-ylmethylpiperazin-1-yl)-4*H*-pyrrolo[2,3-*d*]thiazole (1o)

A microwave flask was charged with **1k** (63 mg, 0.25 mmol), followed by 1-(4-pyridylmethyl)piperazine (443 mg, 2.50 mmol), EtN(*i*-Pr)$_2$ (85 μL, 0.5 mmol), and *i*-PrOH (2 mL). The vessel was sealed and irradiated with microwaves for 1 h at 130 °C, followed by heating to 130 °C for 18 h in an oil bath. After cooling to r.t., the mixture was directly purified by flash chromatography (EtOAc to EtOAc–MeOH, 98:2; 1% Et_3N) to yield **1o** (41 mg, 41%), which was recrystallized as a beige solid (Et_2O–PE); mp 170 °C (dec.).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.52–2.56 (m, 4 H), 3.42–3.49 (m, 5 H), 3.59 (s, 2 H), 6.65 (d, *J* = 1.9 Hz, 1 H), 7.16 (t, *J* = 8.9, 2 H), 7.37 (d, *J* = 5.6 Hz, 2 H), 7.62 (dd, *J* = 8.8, 5.4 Hz, 2 H), 8.53 (d, *J* = 5.3 Hz, 2 H), 11.77 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 47.4, 51.2, 59.9, 96.7, 105.0, 115.0 (d, $^2J_{C,F}$ = 22 Hz), 120.5, 123.2, 123.9 (d, $^3J_{C,F}$ = 8 Hz), 128.1, 129.4, 147.6 (d, $^1J_{C,F}$ = 220 Hz), 148.2, 149.1, 169.8.

MS (ESI): *m*/*z* (%) = 394 (100, [M + H]$^+$).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{20}FN_5S$: 394.1501; found: 394.1447.

6-(Arylmethyl)-4*H*-pyrrolo[2,3-*d*]thiazoles 8; General Procedure

The corresponding *o*-iodocarbamate **2a**,**b** (2 mmol) and 2.6 g (8 mmol) Cs_2CO_3 was dissolved in anhyd DMF (10 mL) in a dried Schlenk tube under N_2 and treated with cinnamyl bromide (622 mg, 3 mmol). After stirring for 2 h at r.t. (TLC monitoring), Pd(OAc)$_2$ (22 mg, 0.10 mmol) and Ph_3P (52 mg, 0.20 mmol) were added and the mixture was stirred for 19 h at 100 °C. After cooling to r.t., the mixture was diluted with brine (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were dried (Na_2SO_4) and the solvent removed in vacuo together with SiO_2 (2 g). The solid was heated in vacuo (10 mbar) at the indicated temperature and time. Subsequently, the product was purified by flash chromatography on silica gel (cyclohexane–EtOAc, 1:1).

6-Benzyl-4*H*-pyrrolo[2,3-*d*]thiazole (8a)

Yield: 49%; white solid; mp 133–135 °C (H_2O–MeCN).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.90 (s, 2 H), 7.01 (dd, *J* = 2.3, 1.3 Hz, 1 H), 7.14–7.34 (m, 5 H), 8.65 (d, *J* = 1.3 Hz, 1 H), 11.58 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 32.1, 111.8, 113.0, 119.8, 125.4, 127.8, 128.0, 140.0, 149.7, 151.3.

MS (APCI): *m*/*z* (%) = 215 (100, [M + H]$^+$).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{12}H_{10}N_2S$: 214.0565; found: 214.0584.

6-Benzyl-2-pyridin-4-yl-4*H*-pyrrolo[2,3-*d*]thiazole (8b)

Yield: 53%; beige solid; mp 185–187 °C (MeOH).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.94 (s, 2 H), 7.08–7.39 (m, 6 H), 7.75 (dd, *J* = 4.5, 1.6 Hz, 2 H), 8.61 (dd, *J* = 4.5, 1.6 Hz, 2 H), 11.86 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 31.9, 113.7, 114.4, 118.5, 122.0, 125.6, 127.9, 128.0, 139.7, 140.4, 150.0, 151.1, 159.1.

MS (ESI): *m*/*z* (%) = 292 (100, [M + H]$^+$).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{17}H_{13}N_3S$: 291.0830; found: 291.0819.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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(18) The low yield can be attributed to decomposition processes due to the considerably intense and long-lasting irradiation of the reaction mixture.

(19) The formation of a black slurry residue is observed, probably due to polymerization..

(20) Several conditions were tested for the Boc cleavage of **6a**: TFA in CH_2Cl_2, ethanolic HCl in CH_2Cl_2 and heating with SiO_2, with the latter being the superior method. In all cases partial decompostion occurred and oxidation of the alkyne appeared as the major side reaction.

(21) All tried standard halogenation conditions for thiazoles affected the alkyne, or led to decomposition: iodination with NIS in CH_2Cl_2, DME, or MeCN with or without addition of K_2CO_3 at ambient or elevated temperatures. Best yields were obtained with *N*-chlorosuccinimide as electrophile compared to CCl_4 and quenching the reaction mixture with *n*-BuOH compared to H_2O, respectively.

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