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Rational multistep synthesis of a novel polyfunctionalized benzo[*d*]thiazole and its thiazolo[5,4-*b*]pyridine analogue

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ABSTRACT

Reliable synthetic routes were studied for an access to a novel polyfunctionalized 6-amino-2-cyanobenzo[*d*]thiazole-5-carboxylate ester (1) and its analogue 5-amino-2-cyanothiazolo[5,4-*b*]pyridine-6-carboxylate ester (2). Both compounds 1 and 2 are functionalized as molecular bricks for the synthesis of innovative molecular systems. Part of the chemistry performed in this study was achieved under microwave irradiation.

1. Introduction

Exploring the synthesis of highly functionalized heterocyclic chemical platforms for the synthesis of C,N,S and C,N,O-containing bioactive molecules is a major challenge of contemporary organic chemistry. As a result, our research group has intensely studied the use of 4,5-dichloro-1,2,3-dithiazolium chloride (Appel salt) for the design of nitrile-bearing heteroarenes with broad applications in biological sciences.[1–3] The overall pharmaceutical interest of various derivatives[4] has encouraged us to reconsider initial strategies and to conceive the synthesis of versatile molecular systems (e.g., **1** and **2** in Fig. 1), which could be used as precursors to various target molecules.

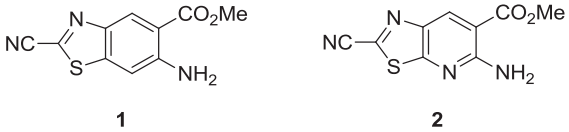

Fig. 1. Structure of the target 6-amino-2-cyanobenzo[*d*]thiazole-5-carboxylate ester (**1**) and its pyrido analogue **2**.

This paper relates the development of reliable synthetic routes allowing access to a novel polyfunctionalized 6-amino-2-cyanobenzo[*d*]thiazole-5-carboxylate ester **1** and its analogue 5-amino-2-cyanothiazolo[5,4-*b*]pyridine-6-carboxylate ester **2**. Both compounds **1** and **2** require to be functionalized enough to open new areas of investigation and prove their utility for the synthesis of innovative molecular systems. Part of the chemistry performed in this study was achieved under microwave irradiation as a continuation of our global strategy, which consists to design adapted reactants and techniques offering operational, economic, and environmental benefits over conventional methods.[5]

2. Results and discussion

The general retrosynthetic pathway depicted in Scheme 1 suggested preparing targets **1** and **2** via a copper-mediated cyclization of *ortho*-brominated aryliminodithiazole intermediates **A**. The latter may be obtained upon condensation of 4,5-dichloro-1,2,3-dithiazolium chloride (Appel salt[6]) with the key N^2-protected brominated aminoanthranilic or nicotinic ester isomers **B**, themselves prepared from nitro- or bromo-derivatives of methyl anthranilate or its nicotinic analogue.[7]

This route was the result of previous experiments demonstrating that: (a) N-protection of anthranilic acid or 2-aminonicotinic precursors is absolutely essential for a convenient access to the

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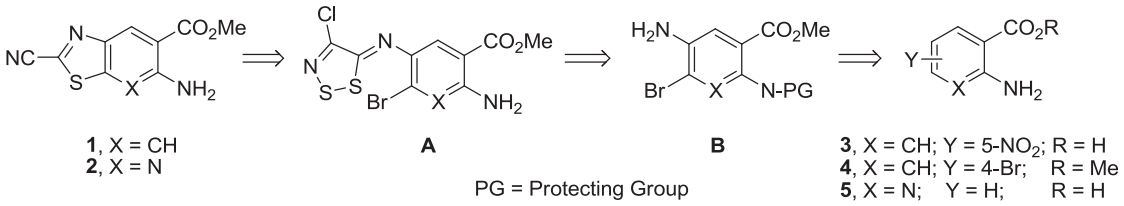
expected compounds. Carboxylic acid should also be converted into an ester analogue (e.g., methyl, ethyl); (b) Regioselective bromination and/or nitrogen insertion (e.g., nitration) of anthranilic and 2-aminonicotinic acid derivatives are crucial steps of the synthesis for the proper orientation of the thiazole ring; (c) benzo[*d*]thiazole or thiazolo[5,4-*b*]pyridine ring and concomitant carbonitrile formation is best achieved via Appel salt chemistry and copper(I)-mediated cyclization. The generated carbonitrile function may be further converted (e.g., amidines, amides, imidates, esters or acids) or cleaved (e.g., hydrolysis and decarboxylation).

both trifluoroacetamide and methyl ester into an original structure: 7-trifluoromethylthiazolobenzoxazinone (**11**) in 89% yield (Scheme 3). This side-cyclisation is most likely the result of an attack of the activated carbonyl of the trifluoroacetamide function on the methyl ester followed by methanol release.

Failure to obtain selectively the expected thiazoloanthranilic ester **12** encouraged us to study the deprotection of the trifluoroacetamide prior to the cyclization of the aryliminodithiazole. Unfortunately, no efficient method led to the clean deprotection of the acetamide function without degrading the iminodithiazole.



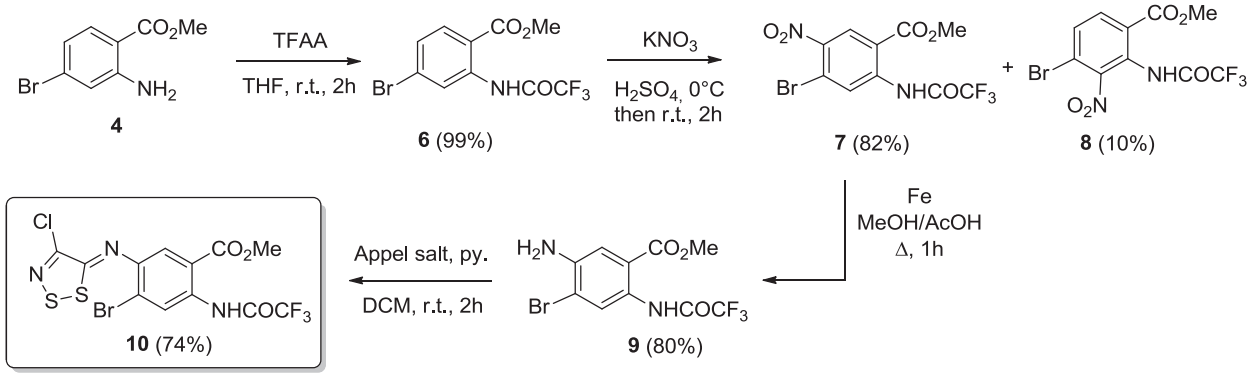
Scheme 1. Retrosynthetic pathway and access to novel linear methyl 6-amino-2-cyanobenzo[*d*]thiazole-5-carboxylate (**1**) and methyl 5-amino-2-cyanothiazolo[5,4-*b*]pyridine-6-carboxylate (**2**) from methyl anthranilate derivatives **3** and **4** and 2-aminonicotinic acid **5**.

In order to obtain intermediate **B** of anthranilic series, 5-nitroanthranilic acid (**3**) was first used as starting material. Despite our efforts and regardless of the synthetic method we were never able to isolate the desired compound from **3**. Instead, the synthesis was alternatively conceived from methyl 4-bromoanthranilate (**4**).

Direct nitration of **4** in usual conditions (concentrated sulfuric acid+potassium nitrate) was infructuous and incited us to first protect the amino group. Methyl ester **4** was treated with trifluoroacetic anhydride (TFAA) in tetrahydrofuran (THF) at room temperature for 2 h to give the trifluoroacylated derivative **6** quantitatively. Its nitration was carried out with a mixture of potassium nitrate and sulfuric acid to give the desired methyl 5-nitro-2-(2,2,2-trifluoroacetamido)benzoate (**7**) in a good 82% yield along with the 3-nitro isomer **8** in 10% yield. Compound **7** was then reduced with iron powder in a refluxing mixture of methanol and acetic acid into its amino-derivative **9** (80%). Addition of Appel salt and pyridine to a solution of **9** in methylene chloride gave the expected *N*-aryliminodithiazole **10** in good yield (74%) (Scheme 2).

Consequently, we investigated smoother conditions for the aryliminodithiazole cyclization. Microwave irradiation of **10** with copper(I) iodide (1 equiv), pyridine (1 equiv) in dry *N*,*N*-dimethylformamide (DMF) at 105 °C provided adduct **12** in good 85% yield. Noticeably, the result of this cyclization was time and scale-dependant, and a short investigation of the reaction time showed that a longer heating (e.g., 30 min instead of 15 min) was sufficient to hydrolyze the carbonitrile-bearing product **12** into its carboxamide derivative **13** (Scheme 3).

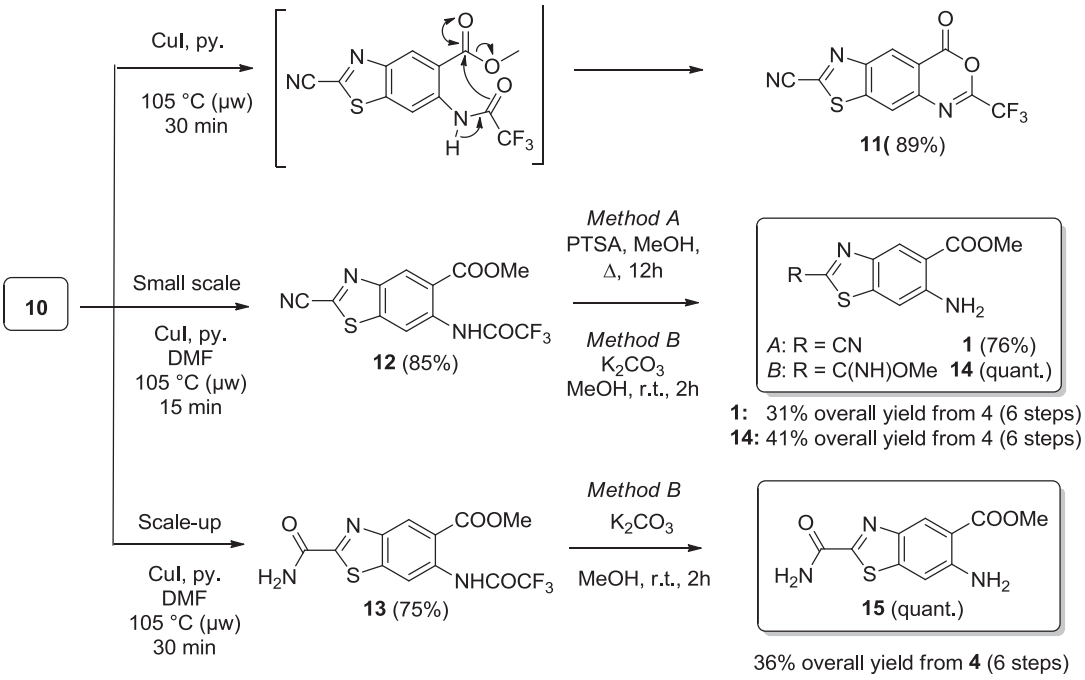
At this stage of the synthesis, deprotection of the amino group was studied in order to generate the target product **1**. Usual conditions (e.g., methanolysis, reduction with sodium borohydride) were experimented but none allowed the cleavage of the trifluoroacetamido group without modifying the carbonitrile function. Thus, methanolysis of **12** led to the methyl carboximidate adduct **14** in quantitative yield. After unsuccessful trials, we found out that refluxing compound **11** and *p*-toluenesulfonic acid (PTSA) in methanol gave the desired methyl 6-aminobenzo[*d*]thiazole-5-carboxylate (**1**) in good 76% yield. In contrast with its cyanated



Scheme 2. Optimized synthetic pathway and access to trifluoroacetylated (*Z*)-methyl 2-amino-4-bromo-5-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)benzoate (**10**) from methyl 2-amino-4-bromobenzoate (**4**).

Iminodithiazole **10** was subjected to copper(I)-mediated cyclisation[8] in order to obtain the thiazole moiety. Unexpectedly, microwave-assisted irradiation of **10** in the presence of copper(I) iodide in pyridine at 115 °C not only led to the rapid formation of the thiazole ring but also provoked the concomitant cyclisation of analogue **12**, compound **13** was quantitatively converted into the adduct **15** by treatment of with potassium carbonate in methanol at room temperature in 2 h.

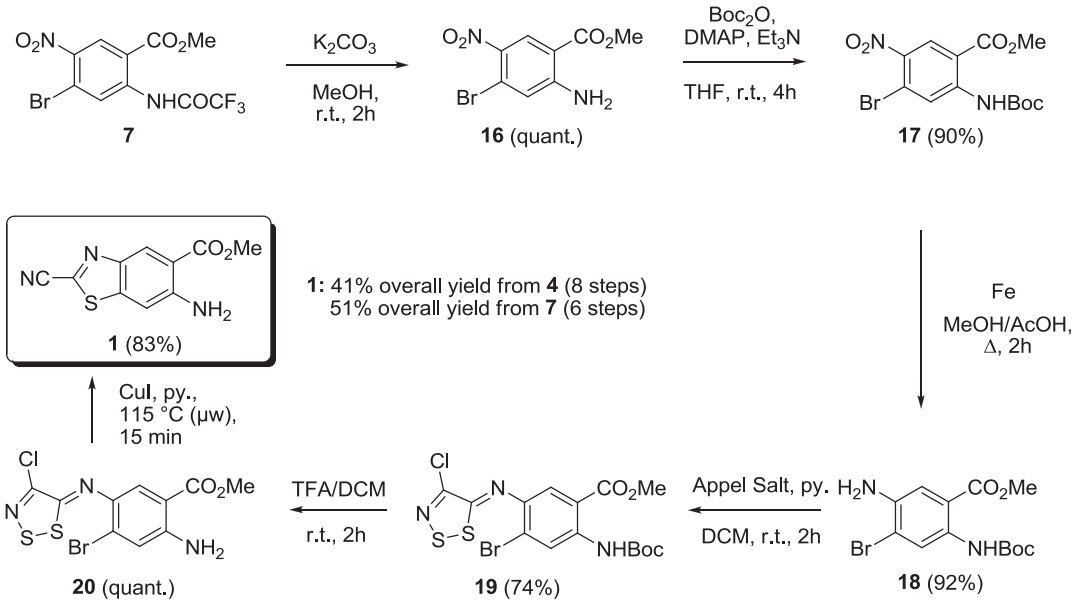
Upon scale-up, the problems encountered during deprotection of **12**, and the growing appearance of product **13** (and incidentally



Scheme 3. Benzoate intermediate **10**: a versatile molecular platform to access 7-trifluoromethylthiazolobenzoxazinone (**11**), methyl 6-amino-2-cyanobenzo[*d*]thiazole-5-carboxylate (**1**), trifluoroacetylated analogues **12** and **13**, methyl carboximidate and carboxamide derivatives **14** and **15**.

15) incited us to reconsider the synthesis. We assumed that the trifluoroacetamide group may be problematic and the synthesis was evaluated again from nitrated derivative **8** using a different protective group. Methanolysis of **7** with potassium carbonate gave methyl 4-bromo-5-nitroanthranilate (**16**) in quantitative yield (Scheme 4). Novel protection of the amino group by a *tert*-butyloxycarbamate (Boc) group was intended. This protective group is normally known for being stable under mild acidic conditions and should therefore withstand iron-mediated reduction. Moreover, Boc should be easily hydrolyzed under strong acidic conditions without affecting aryliminodithiazoles. Therefore, Boc protective group seemed to be the most relevant for this multistep synthesis of **1**.

Accordingly, intermediate **16** was converted in 90% yield into its carbamate analogue **17** using di-*tert*-butylcarbonate, *N*,*N*-dimethylaminopyridine (DMAP), and triethylamine in freshly distilled THF. *N*-protected anthranilic ester **17** was successfully reduced into aminocarbamate **18** with iron powder in a refluxing mixture of acetic acid/methanol in excellent 92% yield. Then, aryliminodithiazole **19** was isolated in good 74% yield upon condensation with Appel salt in usual conditions. As expected, *tert*-butyl carbamate protective group of adduct **18** was readily cleaved in a mixture of trifluoroacetic acid (TFA) and methylene chloride to provide **20** in quantitative yield while sparing the aryliminodithiazole moiety. Copper(I)-mediated cyclization of this *ortho*-bromoiminodithiazole **20** was performed in usual conditions and led to the final methyl 6-



Scheme 4. Optimized sequence for the efficient conversion of trifluoroacetylated methyl 2-amino-4-bromo-5-nitrobenzoate (**6**) into methyl 6-amino-2-cyanobenzo[*d*]thiazole-5-carboxylate (**1**) by a novel deprotection/protection/deprotection sequence.

aminobenzo[*d*]thiazole-5-carboxylate **1** in a good yield of 83%. Compared to the previous synthetic route using trifluoroacetyl as a protective group, this new pathway presents the advantage of avoiding partial hydrolysis of the carbonitrile and side-products such as **13**. This new multi-gram scale route gave the desired molecular scaffold **1** in excellent 41% overall yield in eight steps starting from **4**. In addition to the spectral characterization, the three-dimensional structure of compound **1** was confirmed by single crystal X-ray diffraction.[9–14] A single crystal of **1** was obtained from methylene chloride/diethyl ether/methanol (0.5:0.4:0.1, v/v/v). The ORTEP view is displayed in Fig. 2.

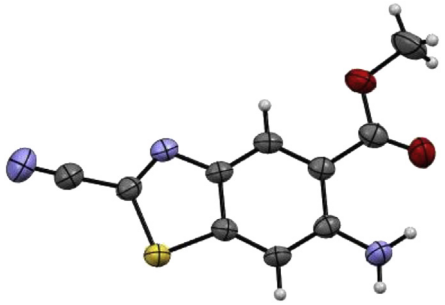
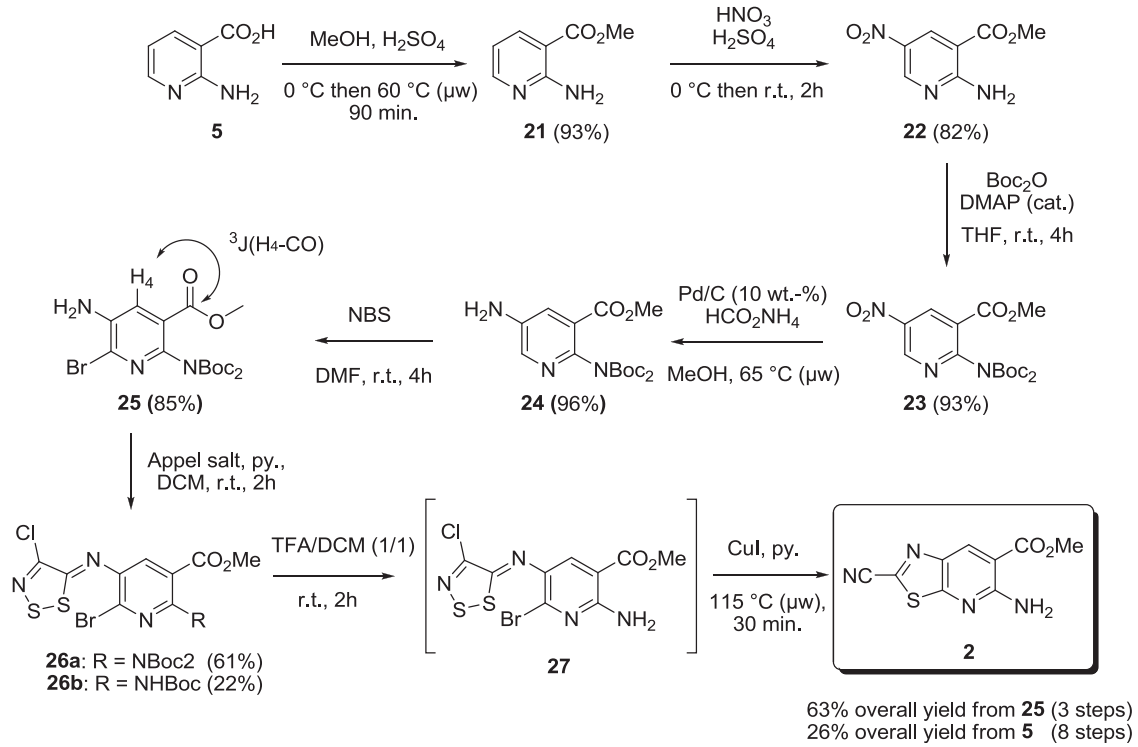


Fig. 2. ORTEP diagram of **1** (for details, see Experimental section and additional data).

In order to achieve different chemo-modulations of these new molecular platforms, we wished to examine the synthesis of a pyridinic analogue of **1**: methyl 5-amino-2-cyanothiazolo[5,4-*b*] pyridine-6-carboxylate **2**. In the absence of commercially available 5-nitro or 4-bromo derivatives, the synthesis was conceived from 2-aminonicotinic acid **5**. The main difficulties of this approach resided in the double regioselective insertion of both bromine and nitro group.

Esterification of **5** was achieved by microwave irradiation in refluxing methanol and concentrated sulfuric acid to provide methyl ester analogue **21** in excellent 93% yield.[15] Regioselective nitration of **21** in a mixture of nitric and sulfuric acid gave methyl 2-amino-5-nitronicotinate **22** in good 82% yield (Scheme 5). ^{1}H NMR analysis of compound **23** in DMSO-d_6 showed two doublets at 9.05 ppm (H^6) and 8.68 ppm (H^4), respectively, with a coupling constant of 2.8 Hz, characteristic of a ^{4}J-coupling constant, hence confirming the regioselectivity of the nitration. Following the improved synthesis of **1** (Scheme 5), adduct **22** was protected and converted into dicarbamate **23** using di-*tert*-butylcarbonate, a catalytic amount of DMAP in THF in excellent 93% yield. Intermediate **23** was efficiently converted in near quantitative yield into aminonicotinate derivative **24** by catalytic hydrogen transfer reduction using palladium on charcoal and ammonium formate in refluxing methanol under microwave irradiation. Regiocontrolled bromination of **24** was accomplished with *N*-bromosuccinimide in DMF to give intermediate **25** in 85% yield. Monobromination was first confirmed by ^{1}H NMR analysis in DMSO-d_6 indicating a singlet at 7.65 ppm (H^{ar}) and a broad singlet at 6.02 ppm (NH_2). Moreover, Heteronuclear Multiple Bond Correlation (HMBC) demonstrated a strong ^3J($\mathbf{H}^{ar}$-CO) correlation between an aromatic hydrogen atom and the carbon atom of the ester's carbonyl. This correlation indicated that bromination proceeded exclusively at position 6. In addition to this spectral characterization, the three-dimensional structure of compound **25** was confirmed by single crystal X-ray diffraction.[9–14] A single crystal of **25** was obtained from methylene chloride/diethyl ether/methanol (0.5:0.4:0.1, v/v/v). The ORTEP view is displayed in Fig. 3.



Scheme 5. Optimized sequence for the efficient conversion of 2-aminonicotinic acid **5** into methyl 5-amino-2-cyanothiazolo[5,4-*b*]pyridine-6-carboxylate (**2**).

The delicate aminodicarbamate 25 was condensed with Appel salt in the usual conditions and gave a mixture of two

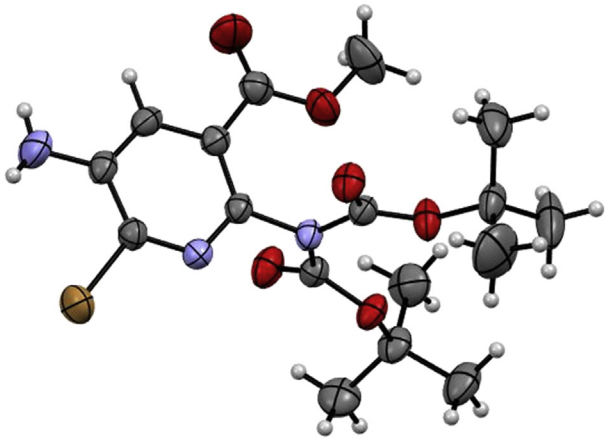


Fig. 3. ORTEP diagram of **25** (for details, see Experimental section and additional data).

aryliminodithiazoles, which can be isolated as **26a** and **26b** in 61% and 22% yield, respectively. This result suggested that the pyridine ring had a deleterious effect on the stability of both dicarbamate and carbamate moieties and provoked a partial hydrolysis of the latter. Consequently we chose to continue the synthesis in a sequential one-pot procedure in order to isolate 2. The mixture of **26a** and **26b** was completely deprotected into 27 (not isolated) using a mixture of trifluoroacetic acid and methylene chloride at room temperature.Copper(I)-mediated cyclisation of *ortho*-bromoiminodithiazole was performed in usual conditions and gave methyl 5-amino-2-cyanothiazolo[5,4-*b*]pyridine-6-carboxylate **2** in 63% yield from **25** (3 steps) and 26% yield from 2-aminonicotinic acid **5** (8 steps).

3. Conclusion

In conclusion the synthesis of novel benzo[*d*]thiazole and thiazolo[5,4-*b*]pyridine derivatives (**1** and **2**, respectively) bearing simultaneously an amino group, a cyano group and an ester function, were described. The difficulty of our work was to manage the presence of three different functions on both heterocyclic scaffolds. Protecting groups were carefully selected to enable the synthesis of the expected product. These new compounds can be considered as versatile molecular platforms, which can be employed in new areas of investigation and prove their utility for the synthesis of innovative molecular systems with potent biological applications.

4. Experimental

4.1. General

All reactions were carried out under inert atmosphere of argon or nitrogen and monitored by thin-layer chromatography with silica gel 60 F_{254} pre-coated aluminium plates (0.25 mm). Visualization was performed with a UV light at 254 and 312 nm. Purifications were carried out on an Armen Instrument Spot 2 Flash System equipped with a dual UV–Vis spectrophotometer (200–600 nm), a fraction collector (192 tubes), a dual piston pump (1–250 mL/min, P_{max}=50 bar/725 psi) allowing quaternary gradients and an additional inlet for air purge.

Melting points of solid compounds were measured on a WME Köfler hot-stage with a precision of ±2 °C and are uncorrected. IR spectra were recorded on a PerkinElmer Spectrum 100 Series FT-IR spectrometer. Liquids and solids were applied on the Single Reflection Attenuated Total Reflectance (ATR) Accessories. Absorption bands are given in cm^{-1}. ^1H, ^{13}C NMR spectra were recorded on a Brucker DXP 300 spectrometer at 300 and 75 MHz, respectively. Abbreviations used for peak multiplicities are s: singlet, d: doublet, t: triplet, q: quadruplet and m: multiplet. Coupling constants *J* are in Hertz and chemical shifts are given in parts per million and calibrated with DMSO-d_6 or $CDCl_3$ (residual solvent signals). Mass spectra analysis was performed by the Mass Spectrometry Laboratory of the University of Rouen. Mass spectra (EI) were recorded with a Waters LCP 1er XR spectrometer.

Dichloromethane was distilled from CaH_2 under argon. NBS was recrystallized in water. Other reagents and solvents were used as provided by chemical companies. Appel salt was prepared according to literature procedure,[6d] see details in SD.

Microwave experiments were conducted in two different commercial microwave reactors especially designed for synthetic chemistry: RotoSYNTH™ (Milestone S.r.l. Italy) for reactions at atmospheric pressure and Anton Paar Monomode 300™ for reactions in pressurized sealed vials (technical details are given in SI) Time indicated in the various protocols is the time measured when the mixtures reached the programmed temperature after a ramp period of 2 min.

The crystal structures were determined from single crystal diffraction on a SMART APEX diffractometer (with $Mo_{K\alpha1}$ radiation: λ=0.71073 Å). The cell parameters and the orientation matrix of the crystal were preliminary determined by using SMART Software.[10] Data integration and global cell refinement were performed with SAINT Software.[11] Intensities were corrected for Lorentz polarization, decay and absorption effects (SAINT and SADABS Softwares) and reduced to F_O.[2] The structures were solved by direct methods (SHEL-XS[12]). Anisotropic displacement parameters were refined for all non-hydrogen atoms using SHEL-XL[13] available with the WinGX[14] package. All hydrogen atoms were located by Fourier-difference synthesis and fixed geometrically according to their environment with a common isotropic factor.

4.2. Synthesis of methyl 6-amino-2-cyanobenzo[*d*]thiazole-7-carboxylate (1)

*4.2.1. Methyl 4-bromo-2-(2,2,2-trifluoroacetamido)benzoate (**6**).* TFAA (25.0 mL, 174 mmol, 2.0 equiv) was added dropwise to a stirred solution of **4** (20.0 g, 86.9 mmol) in dry THF (600 mL) maintained at 0 °C. The reaction mixture was stirred at room temperature for 2 h. Upon completion, the reaction mixture was diluted with water, neutralized with a saturated solution of $NaHCO_3$ and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with a saturated solution of $NaHCO_3$ followed by water and brine, and dried over $MgSO_4$. Evaporation of the solvent gave **6** (28.0 g, 99%) in analytically pure form as a white solid: mp=104–106 °C; IR (cm^{-1}) ν_{max} 3232, 3112, 1728, 1689, 1601, 1583, 1435, 1315, 1252, 1178, 1160, 1139, 1100, 780; ^1H NMR (300 MHz, DMSO-d_6) δ 11.83 (s, 1H, N*H*$COCF_3$), 8.22 (d, *J*=1.8 Hz, 1H, H3), 7.91 (dd, *J*=8.4, 1.8 Hz, 1H, H5), 7.64 (d, *J*=8.4 Hz, 1H, H6), 3.86 (s, 3H, OCH_3); ^{19}F NMR (282 MHz, DMSO-d_6) δ −75.0 (s, 3F, CF_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.6, 154.6 (q, $^2J_{C-F}$=37.5 Hz, C=O_{COCF3}), 137.4, 132.3, 128.8, 127.2, 125.2, 119.3, 117.4 (q, $^1J_{C-F}$=286.5 Hz, CF_3), 52.8; HRMS calcd for $C_{10}H_6{}^{79}BrF_3NO_3$ $[M-H]^-$ 323.9483 found 323.9487, for $C_{10}H_6{}^{81}BrF_3NO_3$ $[M-H]^-$ 325.9463 found 325.9474.

*4.2.2. Methyl 4-bromo-5-nitro-2-(2,2,2-trifluoroacetamido)benzoate (**7**).* KNO_3 (7.44 g, 73.6 mmol, 1.2 equiv) was added portionwise to a mixture of **6** (20.0 g, 61.3 mmol) in concentrated sulfuric acid (260 mL) maintained at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 h. After neutralization to pH=7 with a saturated solution of $NaHCO_3$, the aqueous layer was extracted with AcOEt. The combined organic layers were washed with water and brine, and dried over $MgSO_4$. Evaporation of the solvent provided a crude residue, which was purified by flash

chromatography on silica gel with PE/DCM (2:8, v/v) as eluent to furnish the expected compound **7** (18.7 g, 82%) as a white powder: mp=118–120 °C; IR (cm^{-1}) ν_{max} 3120, 1733, 1705, 1585, 1557, 1441, 1321, 1248, 1163, 1135, 1103, 927, 794; ^1H NMR (300 MHz, DMSO-d_6) δ 12.00 (s, 1H, N*H*COCF$_3$), 8.76 (s, 1H, H6), 8.59 (s, 1H, H3), 3.90 (s, 3H, OCH$_3$); ^{19}F NMR (282 MHz, DMSO-d_6) δ −75.0 (s, 3F, CF$_3$); ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.0, 155.0 (q, $^2J_{C-F}$=37.5 Hz, C=O$_{COCF3}$), 145.7, 139.4, 128.6, 128.0, 121.1, 119.3, 115.3 (q, $^1J_{C-F}$=291.8 Hz, CF$_3$), 53.3; HRMS calcd for $C_{10}H_5{}^{79}BrF_3N_2O_5$ [M−H]$^-$ 368.9334 found 368.9336.

*4.2.3. Methyl 4-bromo-3-nitro-2-(2,2,2-trifluoroacetamido)benzoate (**8**).* Isolated (2.27 g, 10%) as a white solid: mp=112–114 °C; IR (cm^{-1}) ν_{max} 3441, 3267, 3085, 2959, 1715, 1541, 1290, 1246, 1164, 1134, 934, 787, 713; ^1H NMR (300 MHz, DMSO-d_6) δ 11.94 (s, 1H, N*H*COCF$_3$), 8.12 (d, *J*=8.7 Hz, 1H, H6), 8.08 (d, *J*=8.7 Hz, 1H, H5), 3.85 (s, 3H, OCH$_3$); ^{19}F NMR (282 MHz, DMSO-d_6) δ −74.5 (s, 3F, CF$_3$); ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.4, 156.6 (q, $^2J_{C-F}$=38.1 Hz, C=O$_{COCF3}$), 149.7, 134.2, 133.9, 129.1, 128.1, 117.7, 115.5 (q, $^1J_{C-F}$=288.0 Hz, CF$_3$), 53.1; HRMS calcd for $C_{10}H_5{}^{79}BrF_3N_2O_5$ [M−H]$^-$ 368.9334 found 368.9318.

*4.2.4. Methyl 5-amino-4-bromo-2-(2,2,2-trifluoroacetamido)benzoate (**9**).* A stirred mixture of **7** (10.0 g, 26.9 mmol) and iron powder (7.53 g, 135 mmol, 5.0 equiv) in MeOH (130 mL) and AcOH (130 mL) was refluxed for 1 h. The reaction mixture was diluted with water, neutralized with a saturated solution of $NaHCO_3$ and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with a saturated solution of $NaHCO_3$ followed by water and brine, and dried over $MgSO_4$. Evaporation of solvent gave the crude residue, which was purified by flash chromatography on silica gel with DCM/AcOEt (1:0 to 0:1, v/v) as eluent to furnish **9** (7.30 g, 80%) as a white powder: mp=144–146 °C; IR (cm^{-1}) ν_{max} 3443, 3342, 2965, 1719, 1690, 1624, 1597, 1529, 1443, 1334, 1272, 1248, 1226, 1135, 1102, 888, 787, 732; ^1H NMR (300 MHz, DMSO-d_6) δ 11.28 (s, 1H, N*H*COCF$_3$), 7.86 (s, 1H, H3), 7.39 (s, 1H, H6), 5.78 (br s, 2H, NH$_2$), 3.81 (s, 3H, OCH$_3$); ^{19}F NMR (282 MHz, DMSO-d_6) δ −74.7(s, 3F, CF$_3$); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.4, 154.4 (q, $^2J_{C-F}$=37.5 Hz, C=O$_{COCF3}$), 144.6, 128.1, 124.1, 122.7, 115.8, 115.3 (q, $^1J_{C-F}$=291.8 Hz, CF$_3$), 110.9, 52.4; HRMS calcd for $C_{10}H_7{}^{79}BrN_2O_3F_3$ [M−H] 338.9592 found 338.9606, for $C_{10}H_7{}^{81}BrN_2O_3F_3$ [M−H]$^-$ 340.9572 found 340.9590.

*4.2.5. Methyl-4-bromo-5-{[(5E)-4-chloro-5H-1,2,3-dithiazol-5-ylidene]amino}-2-[(trifluoroacetyl)amino]benzoate (**10**).* A suspension of **9** (10.0 g, 29.3 mmol) and 4,5-dichloro-1,2,3-dithiazolium chloride (9.16 g, 35.2 mmol, 1.2 equiv) in DCM (180 mL) was stirred at room temperature under an argon atmosphere. After 1 h of stirring at room temperature, pyridine (4.8 mL, 58.6 mmol, 2.0 equiv) was added and the mixture was stirred again 2 h at room temperature. The resulting solution was concentrated in vacuo to give a crude residue, which was purified by flash chromatography on silica gel with PE/DCM (1:0 to 5:5, v/v) to give **10** (10.3 g, 74%) as an orange solid: mp=174–176 °C; IR (cm^{-1}) ν_{max} 3132, 2963, 1711, 693, 1583, 1489, 1443, 1315, 1181, 1146, 1093, 860, 732; ^1H NMR (300 MHz, DMSO-d_6) δ 11.72 (s, 1H, N*H*COCF$_3$), 8.36 (s, 1H, H3), 7.82 (s, 1H, H6), 3.85 (s, 3H, OCH$_3$); ^{19}F NMR (282 MHz, DMSO-d_6) δ −74.9 (s, CF$_3$); ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.8, 163.5, 154.7 (q, $^2J_{C-F}$=35.8 Hz, C=O$_{COCF3}$), 147.7, 146.1, 133.3, 128.5, 122.6, 120.3, 120.2, 115.6 (q, $^1J_{C-F}$=286.5 Hz, CF$_3$), 52.9; HRMS calcd for $C_{12}H_6{}^{79}BrClF_3N_3O_3S_2$ [M+H]$^+$ 475.8753 found 475.8750.

*4.2.6. 9-Oxo-7-(trifluoromethyl)-9H[1,3]thiazolo[5,4-f][3,1]benzoxazine-2-carbonitrile (**11**).* At atmospheric pressure, a suspension of **10** (0.2 g, 0.53 mmol), CuI (0.2 g, 1.06 mmol, 2.0 equiv), in pyridine (2.0 mL) was irradiated under microwave (power input=300 W) at 105 °C for 15 min. After cooling, the mixture was diluted with AcOEt. The organic layer was washed with a saturated solution of $Na_2S_2O_3$ and dried over $MgSO_4$. The solvent was removed in vacuo and the crude residue was purified by flash chromatography on silica gel with DCM/MeOH (9:1, v/v) as eluent to furnish **11** (0.14 g, 89%) as a white solid: mp >265 °C; IR (cm^{-1}) ν_{max} 2923, 2252, 1723, 1555, 1494, 1370, 1150, 915, 813, 733; ^1H NMR (300 MHz, DMSO-d_6) δ 9.26 (s, 1H, H4), 8.79 (s, 1H, H7); ^{19}F NMR (282 MHz, DMSO-d_6) δ −74.9 (s, CF$_3$); ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.2, 154.5 (q, $^2J_{C-F}$=35.8 Hz, C=O$_{COCF3}$), 147.6, 139.7, 138.2, 136.5, 126.7, 125.5, 116.0 (q, $^1J_{C-F}$=286.5 Hz, CF$_3$), 113.4, 112.0; HRMS calcd for $C_{11}H_3N_3O_3F_3S$ [M+OH]$^-$ 313.9847 found 313.9843.

*4.2.7. Methyl 2-cyano-6-(2,2,2-trifluoroacetamido)benzo[d]thiazole-5-carboxylate (**12**).* At atmospheric pressure, a suspension of **10** (0.2 g, 0.53 mmol), CuI (0.1 g, 0.53 mmol, 1.0 equiv), pyridine (42.4 μL, 0.53 mmol, 1.0 equiv) in DMF (2.0 mL) was irradiated under microwaves (power input=300 W) at 105 °C for 15 min. After cooling, the mixture was diluted in AcOEt. The organic layer was washed with a saturated solution of $Na_2S_2O_3$ and dried over $MgSO_4$. The solvent was removed in vacuo and the crude residue was purified by flash chromatography on silica gel with DCM/AcOEt (1:1, v/v) as eluent to furnish **12** (0.146 g, 85%) as a white solid: mp=174–176 °C; IR (cm^{-1}) ν_{max} 3115, 2962, 2235, 1725, 1696, 1566, 1321, 1285, 1215, 1151, 1127, 752; ^1H NMR (300 MHz, DMSO-d_6) δ 12.04 (s, 1H, N*H*COCF$_3$), 8.97 (s, 1H, H4), 8.76 (s, 1H, H7), 3.93 (s, 3H, OMe); ^{19}F NMR (282 MHz, DMSO-d_6) δ −74.8 (s, CF$_3$); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.4, 154.8 (q, $^2J_{C-F}$=35.8 Hz, C=O$_{COCF3}$), 148.6, 140.4, 139.9, 134.6, 126.8, 122.2, 117.7, 115.5 (q, $^1J_{C-F}$=286.5 Hz, CF$_3$), 113.1, 53.2; HRMS calcd for $C_{12}H_5F_3N_3O_3S$ [M−H]$^-$ 328.0004 found 328.0015.

*4.2.8. Methyl 2-carbamoyl-6-(2,2,2-trifluoroacetamido)benzo[d]thiazole-5-carboxylate (**13**).* According to the procedure described for **12**, product **13** was obtained by irradiation at 105 °C for 30 min of a suspension of **10** (2.0 g, 5.25 mmol), CuI (1.0 g, 5.25 mmol, 1.0 equiv) and pyridine (424 μL, 5.25 mmol, 1.0 equiv) in DMF (20 mL) and was isolated by flash chromatography on silica gel with DCM/AcOEt (1:1, v/v) as eluent to furnish **13** (1.82 g, 75%) as a white solid: mp>265 °C; IR (cm^{-1}) ν_{max} 3457, 3137, 1730, 1681, 1583, 1510, 1430, 1215, 1148, 912; ^1H NMR (300 MHz, DMSO-d_6) δ 11.96 (s, 1H, N*H*COCF$_3$), 8.81 (s, 1H, H4), 8.60 (s, 1H, H7), 8.57 (br s, 1H, N*H*$_{2amide}$), 8.21 (br s, 1H, N*H*$_{2amide}$), 3.92(s, 3H, OMe); ^{19}F NMR (282 MHz, DMSO-d_6) δ −74.9 (s, CF$_3$); ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.6, 166.6, 160.9, 154.7 (q, $^2J_{C-F}$=35.8 Hz, C=O$_{COCF3}$), 150.1, 141.5, 133.3, 126.1, 121.3, 117.8, 115.6 (q, $^1J_{C-F}$=286.5 Hz, CF$_3$), 53.1; HRMS calcd for $C_{12}H_9F_3N_3O_4S$ [M+H]$^+$ 348.0266 found 348.0256.

*4.2.9. Methyl 6-amino-2-[imino(methoxy)methyl]benzo[d]thiazole-5-carboxylate (**14**).* A solution of **12** (0.5 g, 1.52 mmol) and K_2CO_3 (1.05 mg, 7.59 mmol, 5.0 equiv) in MeOH (500 mL) was stirred at room temperature for 2 h. After neutralization with a solution of HCl (2 M), the product was extracted with AcOEt. The combined organic layers were washed with water and brine, and dried over $MgSO_4$. Evaporation of the solvent gave the expected product **14** (0.402 g, quant.) in analytically pure form as a light yellow solid: mp=220–222 °C; IR (cm^{-1}) ν_{max} 3443, 3324, 2955, 1703, 1618, 1436, 1343, 1282, 1239, 1143, 1069, 940, 848, 787; ^1H NMR (300 MHz, DMSO-d_6) δ 9.15 (s, 1H, N*H*$_{imidate}$), 8.40 (s, 1H, H4), 7.32 (s, 1H, H7), 6.95 (br s, 2H, NH$_2$), 3.89(s, 3H, OMe$_{imidate}$), 3.85 (s, 3H, OMe); ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.3, 159.8, 153.7, 149.5, 143.0, 142.7, 126.3, 110.7, 106.5, 53.9, 52.0; HRMS calcd for $C_{11}H_{12}N_3O_3S$ [M+H]$^+$ 266.0599 found 266.0605.

*4.2.10. Methyl 6-amino-2-carbamoylbenzo[d]thiazole-5-carboxylate (**15**).* A solution of **13** (0.5 g, 1.44 mmol) and K_2CO_3 (0.996 g,

7.20 mmol, 5.0 equiv) in MeOH (500 mL) was stirred at room temperature for 2 h. After neutralization with a solution of HCl (2 M), the product was extracted with AcOEt. The combined organic layers were washed with water and brine, and dried over $MgSO_4$. Evaporation of the solvent gave the expected product **15** (0.360 g, quant.) in analytically pure form as a white solid: mp >265 °C; IR (cm^{-1}) ν_{max} 3393, 3301, 3117, 1690, 1617, 1575, 1502, 1445, 1306, 1199, 1111, 834, 792; ^1H NMR (300 MHz, DMSO-d_6) δ 8.39 (s, 1H, H4), 8.28 (br s, 1H, NH_{2amide}), 7.95 (br s, 1H, NH_{2amide}), 7.35 (s, 1H, H7), 6.94 (br s, 2H, NH_2), 3.87 (s, 3H, OMe); ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.4, 161.4, 160.5, 149.5, 143.7, 143.6, 126.5, 110.7, 106.7, 52.1; HRMS calcd for $C_{10}H_{10}N_3O_3S$ $[M+H]^+$ 252.0443 found 252.0447.

*4.2.11. Methyl 2-amino-4-bromo-5-nitrobenzoate (**16**).* According to the procedure described for compound **14**, methanolysis of **7** (10.0 g, 26.9 mmol) was carried out with K_2CO_3 (18.6 g, 134 mmol, 5.0 equiv) in MeOH (500 mL) at room temperature for 2 h to give the expected product **16** (7.32 g, quant.) as a pale yellow solid: mp=192–194 °C; IR (cm^{-1}) ν_{max} 3428, 3343, 1705, 1632, 1551, 1316, 1281, 1254, 1088, 860, 744; ^1H NMR (300 MHz, DMSO-d_6) δ 8.52 (s, 1H, H6), 7.76 (br s, 2H, NH_2), 7.23 (s, 1H, H3), 3.85 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.7, 154.2, 135.0, 131.1, 121.6, 120.5, 107.4, 52.2; HRMS calcd for $C_8H_6{}^{79}BrN_2O_4$ $[M-H]^-$ 272.9511 found 272.9513, for $C_8H_6{}^{81}BrN_2O_4$ $[M-H]^-$ 274.9490 found 274.9488.

*4.2.12. Methyl 4-bromo-5-nitro-2-[(tert-butoxycarbonyl)amino]benzoate (**17**).* DMAP (0.444 g, 3.64 mmol, 0.1 equiv), Boc_2O (15.9 g, 72.8 mmol, 2.0 equiv) and Et_3N (4.90 mL, 36.4 mmol, 1.0 equiv) were successively added to a suspension of **16** (10.0 g, 36.4 mmol) in freshly distilled THF (200 mL). The solution was stirred at room temperature for 4 h and evaporated in vacuo. The crude product was purified by flash chromatography using PE/DCM (1:0 to 0:1, v/v) to give **17** (13.6 g, 90%) as a light yellow solid: mp=170–172 °C; IR (cm^{-1}) ν_{max} 3280, 3251, 3116, 2980, 2923, 1734, 1691, 1559, 1538, 1328, 1249, 1224, 1146, 1099, 885, 707, 657; ^1H NMR (300 MHz, DMSO-d_6) δ 10.37 (s, 1H, N*H*Boc), 8.67 (s, 1H, H6), 8.53 (s, 1H, H3), 3.91 (s, 3H, OCH_3), 1.51 (s, 9H, ^{t}Bu); ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.9, 151.4, 144.3, 141.8, 128.6, 123.6, 120.4, 114.7, 82.0, 53.1, 27.7 (3C); HRMS calcd for $C_{13}H_{14}{}^{79}BrN_2O_6$ $[M-H]^-$ 373.0035 found 373.0043, for $C_{13}H_{14}{}^{81}BrN_2O_6$ $[M-H]^-$ 373.0035 found 373.0043.

*4.2.13. Methyl 5-amino-4-bromo-2-[(tert-butoxycarbonyl)amino] benzoate (**18**).* A stirred mixture of **17** (10.0 g, 26.7 mmol) and iron powder (7.44 g, 133 mmol, 5 equiv) in MeOH (90 mL) and AcOH (90 mL) was refluxed for 2 h. The reaction mixture was diluted with water, neutralized with a saturated solution of $NaHCO_3$ and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with a saturated solution of $NaHCO_3$ followed by water and brine, and dried over $MgSO_4$. Evaporation of solvent gave the crude residue, which was purified by flash chromatography on silica gel with DCM/AcOEt (1:0 to 0:1, v/v) as eluent to furnish **18** (8.46 g, 92%) as a white powder: mp=132–134 °C; IR (cm^{-1}) ν_{max} 3435, 3360, 3307, 2983, 1693, 1584, 1520, 1407, 1249, 1222, 1151, 1102, 1053, 887, 785, 706; ^1H NMR (300 MHz, DMSO-d_6) δ 9.52 (s, 1H, N*H*Boc), 8.11 (s, 1H, H3), 7.38 (s, 1H, H6), 5.32 (br s, 2H, NH_2), 3.82 (s, 3H, OCH_3), 1.46 (s, 9H, ^{t}Bu); ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.4, 152.4, 141.2, 130.0, 123.5, 117.3, 115.8, 113.2, 79.7, 52.4, 27.9 (3C); HRMS calcd for $C_{13}H_{18}{}^{79}BrN_2O_4$ $[M+H]^+$ 345.0450 found 345.0448.

*4.2.14. (Z)-Methyl 4-bromo-2-[(tert-butoxycarbonyl)amino]-5-[(4-chloro-5H-1,2,3-dithiazol-5-ylidene)amino]benzoate (**19**).* According to the procedure described for **10**, reaction of compound **18** (8.0 g, 23.2 mmol) with 4,5-dichloro-1,2,3-dithiazolium chloride (7.20 g, 34.8 mmol, 1.5 equiv) and pyridine (3.75 mL, 46.4 mmol, 2.0 equiv) in DCM (230 mL) at room temperature for 3 h, gave product **19** (9.10 g, 82%) as a yellow solid: mp=208–210 °C; IR (cm^{-1}) ν_{max} 3284, 3126, 2976, 2953, 1719, 1704, 1569, 1497, 1237, 1218, 1151, 1097, 1049, 906, 861, 661; ^1H NMR (300 MHz, DMSO-d_6) δ 10.08 (s, 1H, N*H*Boc), 8.59 (s, 1H, H3), 7.83 (s, 1H, H6), 3.86 (s, 3H, OCH_3), 1.50 (s, 9H, ^{t}Bu); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.8, 162.4, 152.0, 146.4, 143.6, 138.6, 123.5, 122.1, 119.8, 116.3, 80.9, 52.8, 27.8 (3C); HRMS calcd for $C_{15}H_{16}{}^{79}BrClN_3O_4S_2$ $[M+H]^+$ 479.9454 found 479.9457.

*4.2.15. (Z)-Methyl 2-amino-4-bromo-5-[(4-chloro-5H-1,2,3-dithiazol-5-ylidene) amino] benzoate (**20**).* TFA (75 mL) was added dropwise to a stirred solution of **19** (9.0 g, 1.88 mmol) in DCM (75 mL) at room temperature. The mixture was stirred at room temperature for 2 h, then neutralized with a saturated solution of $NaHCO_3$ and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with a saturated solution of $NaHCO_3$ followed by water and brine and dried over $MgSO_4$. Evaporation of the solvent gave a crude residue, which was purified by flash chromatography on silica gel with DCM/AcOEt (1:0 to 0:1, v/v) as eluent to furnish **20** (6.31 g, quant.) as a yellow powder: mp=192–194 °C; IR (cm^{-1}) ν_{max} 3480, 3360, 2953, 1697, 1606, 1433, 1252, 1218, 1132, 1083, 846, 778; ^1H NMR (300 MHz, DMSO-d_6) δ 7.84 (s, 1H, H6), 7.31 (s, 1H, H3), 3.82 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.8, 155.8, 150.2, 147.4, 135.0, 126.3, 120.7, 119.2, 107.6, 51.9; HRMS calcd for $C_{10}H_6{}^{79}BrClN_3O_2S_2$ $[M-H]^-$ 377.8773 found 377.8771.

*4.2.16. Methyl 6-amino-2-cyanobenzo[d]thiazole-7-carboxylate (**1**).*

- PTSA-mediated deprotection of **12**: A solution of **12** (05 g, 1.52 mmol) and PTSA (0.288 g, 1.67 mmol, 1.1 equiv) in MeOH (8 mL) was refluxed overnight at 65 °C and the solvent was removed in vacuo. Purification of the solid residue by flash chromatography on silica gel with DCM/AcOEt (1:1, v/v) as eluent furnished **1** (0.270 g, 76%) as a yellow solid.
- Copper(I)-mediated cyclization of **20**: At atmospheric pressure, a suspension of **20** (6.0 g, 16.5 mmol), CuI (6.30 g, 16.5 mmol, 1.0 equiv) in pyridine (60 mL) was irradiated under microwaves (power input: 300 W) at 115 °C for 15 min. After cooling, the mixture was diluted in AcOEt. The organic layer was washed with a saturated solution of $Na_2S_2O_3$ and dried over $MgSO_4$. The solvent was removed in vacuo and the crude residue was purified by flash chromatography on silica gel with DCM/AcOEt (1:1, v/v) as eluent to furnish **1** (3.19 g, 83%) as a yellow solid: mp=228–230 °C; IR (cm^{-1}) ν_{max} 3487, 3365, 2957, 2218, 1705, 1618, 1472, 1291, 1204, 1128, 1076, 785; ^1H NMR (300 MHz, DMSO-d_6) δ 8.51 (s, 1H, H4), 7.43 (s, 1H, H7), 7.21 (br s, 2H, NH_2), 3.88 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.0, 150.6, 142.2, 142.1, 131.6, 127.5, 113.7, 111.9, 106.1, 52.2; HRMS calcd for $C_{10}H_8N_3O_2S$ $[M+H]^+$ 234.0344 found 234.0353

4.3. Synthesis of methyl 5-amino-2-cyanothiazolo[5,4-*b*]pyridine-6-carboxylate (2)

*4.3.1. Methyl 2-aminonicotinate (**21**).* Concentrated sulfuric acid (96%, 144 mL, 2.69 mol, 18.6 equiv) was added dropwise to a stirred suspension of **5** (20.0 g, 0.145 mol) in MeOH (228 mL, 7.12 mol, 49.2 equiv) maintained at 0 °C. The mixture was irradiated at atmospheric pressure under microwaves (power input=300 W) at 60 °C for 1.5 h. The light brown mixture was poured onto iced water, maintained at 0 °C and carefully quenched by adding solid Na_2CO_3 portionwise until complete neutralization (pH>8). The aqueous layer was extracted three times with AcOEt. The combined organic layers were washed with brine and water and dried over $MgSO_4$. Evaporation of the organic layer yielded the title compound

21 in analytically pure form (21.15 g, 93%) as colourless needles: mp=83–85 °C (Ref. 15, 76–79 °C); spectral data for **21** are consistent with assigned structure, as previously described in Ref. 1; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.20 (dd, J=4.7, 2.0 Hz, 1H, H6), 8.05 (dd, J=7.8, 1.9 Hz, 1H, H4), 7.16 (s, 2H, NH_2), 6.62 (dd, J=7.8, 4.7 Hz, 1H, H5), 3.81 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.9, 159.4, 153.9, 139.6, 111.8, 104.5, 51.8.

*4.3.2. Methyl 2-amino-5-nitronicotinate (**22**).* Concentrated nitric acid (65%, 3.2 mmol, 76 mmol, 1.05 equiv) was added dropwise to a stirred suspension of **21** (10.0 g, 72.4 mmol) in concentrated sulfuric acid (96%, 90.5 mL, 1.69 mol, 23.3 equiv) maintained at 0 °C. The solution was brought back to room temperature and stirred for 2 h. The brown mixture was poured onto iced water and carefully quenched by adding solid Na_2CO_3 portionwise until complete neutralization (pH>8). The aqueous layer was extracted three times with AcOEt. The combined organic layers were washed with brine and water, and dried over $MgSO_4$. Evaporation of the residue in vacuo furnished the title compound **22** in analytically pure form (11.7 g, 82%) as a colourless solid : mp=187–189 °C; IR (cm^{-1}) ν_{max} 3399, 3166, 1706, 1622, 1590, 1501, 1430, 1336, 1306, 1247, 1141, 1082, 803, 711, 619; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.05 (d, J=2.8 Hz, 1H, H6), 8.68 (d, J=2.8 Hz, 1H, H4), 8.67 (br s, 1H, NH), 8.15 (br s, 1H, NH), 3.87 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.4, 161.4, 150.5, 135.4, 133.9, 103.7, 52.6; HRMS calcd for $C_7H_6N_3O_4$ [M–H]$^-$ 196.0358 found 196.0357.

*4.3.3. Methyl 2-[bis(tert-butoxycarbonyl)amino]-5-nitronicotinate (**23**).* DMAP (0.744 g, 6.09 mmol, 0.1 equiv) and Boc_2O (29.2 g, 134 mmol, 2.2 equiv) were successively added portionwise to a suspension of **22** (12.0 g, 60.9 mmol) in freshly distilled THF (200 mL) at room temperature. The solution was stirred at room temperature for 4 h and evaporated in vacuo. The crude product was purified by flash chromatography using PE/DCM/Et_3N (86:13:1, v/v/v) to give **23** (22.5 g, 93%) as a colourless solid: mp=88–90 °C; IR (cm^{-1}) ν_{max} 2984, 1759, 1725, 1606, 1579, 1526, 1484, 1368, 1332, 1282, 1249, 1227, 1150, 1117, 1089, 1021, 911, 859, 784, 745; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.48 (d, J=2.7 Hz, 1H, H6), 8.93 (d, J=2.7 Hz, 1H, H4), 3.90 (s, 3H, CH_3), 1.36 (s, 18H, ^{t}Bu); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.9, 154.0, 149.5, 147.2, 143.1, 135.3, 123.4, 83.5, 53.3, 27.3; HRMS calcd for $C_{17}H_{23}N_3O_8K$ [M+K]$^+$ 436.1122 found 436.1118.

*4.3.4. Methyl 5-amino-2-[bis(tert-butoxycarbonyl)amino]nicotinate (**24**).* Pd/C (10 wt. %, 1.00 g) and ammonium formate (7.93 g, 126 mmol, 5.0 equiv) were successively added portionwise to a suspension of **23** (10.0 g, 25.2 mmol) in MeOH (125 mL). The dark mixture was irradiated under microwaves at 65 °C (power input: 300 W) for 30 min. The cooled solution was filtered on Celite and evaporated in vacuo. The residue was solubilized in AcOEt and washed with brine and water, and dried over $MgSO_4$. The organic layer was concentrated in vacuo to yield the title compound **24** in analytically pure form (8.88 g, 96%) as a colourless solid: mp=188–190 °C; IR (cm^{-1}) ν_{max} 3435, 3342, 3218, 2983, 1783, 1722, 1656, 1595, 1464, 1368, 1280, 1248, 1151, 1092, 850, 784; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.91 (d, J=2.9 Hz, 1H, H6), 7.48 (d, J=2.9 Hz, 1H, H4), 5.77 (s, 2H, NH_2), 3.77 (s, 3H, CH_3), 1.30 (s, 18H, ^{t}Bu); ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.0, 150.7 (2C), 144.7, 139.0, 137.0, 122.9, 122.5, 81.5 (2C), 52.4, 27.5 (6C); HRMS calcd for $C_{17}H_{24}N_3O_6$ [M–H]$^-$ 366.1665 found 366.1683.

*4.3.5. Methyl 5-amino-2-[bis(tert-butoxycarbonyl)amino]-6-bromonicotinate (**25**).* Freshly recrystallized NBS (1.53 g, 8.57 mmol, 1.01 equiv) was added portionwise to a suspension of **24** (3.0 g, 8.17 mmol) in dry DMF (32 mL) at room temperature. The mixture was stirred for 4 h at room temperature and the solvent was removed in vacuo. Purification of the solid residue by flash chromatography using PE/DCM/Et_3N (86:13:1, v/v/v) as eluent gave the title compound **25** (3.11 g, 85%) as a colourless solid : mp=150–152 °C; IR (cm^{-1}) ν_{max} 3458, 3357, 2976, 1721, 1684, 1451, 1367, 1320, 1246, 1162, 1124, 1045, 767; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.65 (s, 1H, H4), 6.02 (br s, 2H, NH_2), 3.79 (s, 3H, CH_3), 1.33 (s, 18H, ^{t}Bu); ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.0, 151.1, 144.0, 138.1, 127.4, 124.1, 123.6, 82.4 (2C), 52.7, 27.4 (6C); HRMS calcd for $C_{17}H_{23}{}^{79}BrN_3O_6$ [M–H]$^-$ 444.0770 found 444.0757.

*4.3.6. (Z)-Methyl 2-[bis(tert-butoxycarbonyl)amino]-6-bromo-5-(4-chloro-5H-1,2,3-dithiazol-5-ylideneamino)nicotinate (**26a**) and (Z)-Methyl6-bromo-2-(tert-butoxycarbonylamino)-5-(4-chloro-5H-1,2,3-dithiazol-5-ylideneamino)nicotinate (**26b**).* 4,5-Dichloro-1,2,3-dithiazolium chloride (Appel salt, 0.888 g, 4.26 mmol, 1.9 equiv) was added portionwise to a suspension of **25** (1.0 g, 2.24.mmol) in DCM (40 mL) and pyridine (362 μL, 4.48 mmol, 2 equiv) at room temperature. The reaction was stirred at room temperature under an argon atmosphere for 4 h. The resulting solution was concentrated in vacuo to give a crude residue, which was purified by chromatography on silica gel with PE/AcOEt (1:0 to 0:1, v/v) to give in the order of elution **26a** (0.791 g, 61%) as an orange solid: mp=64–66 °C; IR (cm^{-1}) ν_{max} 2978, 2938, 1797, 1765, 1729, 1581, 1412, 1368, 1275, 1247, 1151, 1097, 868; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.22 (s, 1H, H4), 3.84 (s, 3H, CH_3), 1.35 (s, 18H, ^{t}Bu); ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.7, 163.3 (2C), 149.6, 147.0, 146.1, 146.0, 135.7, 130.6, 124.0, 83.0 (2C), 53.1, 27.4 (6C); HRMS calcd for $C_{19}H_{22}BrClN_4O_6S_2K$ [M+K]$^+$ 618.9490 found 618.9481; and **26b** (0.236 g, 22%) as an orange solid: mp=189–191 °C; IR (cm^{-1}) ν_{max} 3279, 3257, 2971, 1758, 1702, 1575, 1472, 1307, 1223, 1235, 1147, 1114, 864; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.27 (s, 1H, NH), 8.07 (s, 1H, H4), 3.78 (s, 3H, CH_3), 1.45 (s, 9H, ^{t}Bu); ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.4, 163.9, 152.2, 146.5, 146.3, 142.9, 139.7, 130.5, 118.1, 80.4, 52.5, 27.8; HRMS calcd for $C_{14}H_{14}{}^{79}BrClN_4O_4S_2K$ [M+K]$^+$ 518.8965 found 518.8951.

*4.3.7. Methyl 5-amino-2-cyanothiazolo[5,4-b]pyridine-6-carboxylate (**2**).* TFA (10 ml) was added dropwise to a mixture of **26a** and **26b** (0.81 g, 1.45 mmol[16]) in suspension in DCM (10 ml). After 2 h of stirring, the mixture was neutralized with a saturated solution of $NaHCO_3$ and the aqueous layer was extracted with DCM. The combined organic layers were dried over $MgSO_4$. Evaporation of solvent in vacuo gave the crude deprotected product **27** (0.4 g, 1.05 mmol), which was solubilized in pyridine (0.3 M, 3.5 ml) and CuI (0.2 g, 1.05 mmol, 1 equiv) was added. The reaction mixture was irradiated under microwaves (power input: 300 W) at 100 °C for 30 min. After cooling, the mixture was diluted in AcOEt. The organic layer was washed with a saturated aqueous solution of sodium thiosulfate and dried over $MgSO_4$. The solvent was removed in vacuo and the crude residue was purified by flash chromatography on silica gel with PE/AcOEt (1:0 to 0:1, v/v) to give **2** (0.186 g, 76%) as an orange solid: mp=209–211 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.78 (s, 1H, H4), 8.01 (br s, 2H, NH_2), 3.89 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.1, 162.5, 158.7, 136.9, 136.0, 129.9, 113.4, 107.6, 52.7; IR (cm^{-1}) ν_{max} 3412, 3275, 3183, 2958, 2228, 1693, 1602, 1435, 1411, 1286, 1216, 1146, 800; HRMS calcd for $C_{10}H_7N_3O_2S$ [M–H]$^-$ 233.0133 found 233.0131.

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Supplementary data

^{1}H and ^{13}C NMR spectra of all compounds and ORTEP diagram and crystallographic data of compounds **1** and **25**. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.06.103.

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