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Synthesis of polyfunctionalized benzo[*d*]thiazoles as novel anthranilic acid derivatives

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ABSTRACT

A small library of valuable novel polyfunctionalized benzo[*d*]thiazole derivatives was prepared in a straightforward and convenient manner. Here again, 4,5-dichloro-1,2,3-dithiazolium chloride (Appel salt) proved to be an efficient agent for merging a 2-cyanothiazole ring to an arene counterpart.

The design and synthesis of new C,N,S-containing polyfunctionalized heterocycles has become a major challenge for medicinal chemists in search of new bioactive molecules. In this context, our group has extensively studied the reactivity of 4,5-dichloro-1,2,3-dithiazolium chloride (Appel salt)[1] for the synthesis of nitrile-bearing heteroarenes[2] with broad applications in biological science.[3] In the course of our work, the multistep synthesis of angular thiazolo[5,4-*f*] and [4,5-*h*]quinazolin-4-one isomers (**I** and **II** in Scheme 1) was described.[4] More recently their synthesis was revisited and the access to their linear thiazolo[4,5-*g*] and [5,4-*g*]quinazolin-4-ones analogues was also published (**III** and **IV** in Scheme 1).[5]

The reported strategies consisted of the construction of N^3-substituted quinazolines.[4,5] Modifications of the substituents at N^3 were done at the beginning of the multistep processes (six or seven steps) and involved generation of at least three intermediates for which synthetic and biological interest were judged limited.[4] The thiazole moiety of these 6,6,5-tricyclic heterocyclic systems was then built via a copper-mediated cyclization of *ortho*-brominated [(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)amino]quinazoline intermediates.[6] The recent significant therapeutic interest of the final derivatives (e.g., type **I** in Scheme 1)[7] has encouraged us to reconsider the synthetic pathway and to envision the synthesis of smaller molecular platforms (e.g. **1** and **2** in Scheme 1) as versatile precursors to our target molecules.[8] In this way, a 6-aminobenzothiazole-2,7-dicarbonitrile derivative (**3** in Scheme 1) was recently built, providing a convenient route to novel and efficient inhibitors of the DYRK's kinases family (Scheme 1).[3a,b] Pursuing our efforts, this Letter relates the development of reliable synthetic routes allowing extension of novel methyl amino-2-cyanobenzothiazole-carboxylate derivatives (**4**, **5** and **6** in Scheme 2) considered as versatile molecular platforms for the synthesis of potentially active kinase inhibitors. As a continuation of our global strategy, heating of the reaction mixtures was performed under microwaves with special attention to the development of efficient and adapted conditions.[9]

The general retrosynthetic pathway depicted in Scheme 2 was inspired by our recent work with anthranilonitrile as starting material.[3] It suggests preparing the target molecules (**4**, **5** and **6**) via a copper-assisted cyclization of the ortho-brominated aryliminodithiazole intermediates (**A**) themselves obtained by condensation of 4,5-dichloro-1,2,3-dithiazolium chloride (Appel salt) with the appropriate N^2-protected brominated aminoanthranilic ester (**B**). These latter can be prepared from nitro-derivatives of methyl 4- or 5-nitroanthranilates.[10] Another difficulty of this work consists of managing the presence of different functional groups on both heterocyclic scaffolds. In this sense, appropriate protective groups need to be carefully chosen for efficient syntheses of the required products.

The route suggested in Scheme 2 was the result of various trials and previous experiments[3,5,8] which demonstrated that: (a) a convenient access to the expected compounds was facilitated when the acid function was transformed into its methyl ester analogue; (b) protection of the amino group of the anthranilic precursor was absolutely necessary and may dramatically influence the key step

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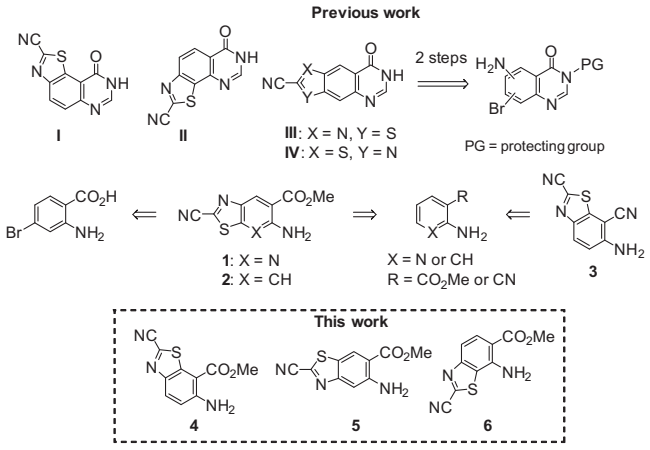


Scheme 1. Previous work on the synthesis thiazolo[4,5-*g* or -*h*] and [5,4-*f* or -*g*]quinazolin-4-ones isomers (**I**–**IV**), polyfunctionalized methyl 5-amino-2-cyanothiazolo[5,4-*b*]pyridine-6-carboxylate (**1**), methyl 6-amino-2-cyanobenzo[*d*]thiazole-5-carboxylate (**2**) and 6-amino-2-cyanobenzo[*d*]thiazole-7-carbonitrile (**3**). In the framed areas, general description of the target molecules of this work is displayed.

of this synthesis: a regiocontrolled bromination at the desired position of the anthranilic acid derivatives; (c) coupling of the thiazole ring to the benzenic part via Appel salt chemistry and copper(I)-assisted cyclization was preferred to generate a versatile cyano group on the target structures.[1,2] This carbonitrile function can be easily eliminated (hydrolysis + decarboxylation) or transformed into amidines, amides, imidates, esters, or acids.[3]

Our study started from methyl 5-nitroanthranilate (**7**);[10] its selective bromination in position 4 or 6 should generate key intermediate precursors of benzothiazole **2** and its isomer **4** (Scheme 3).

As described above, the first challenge of our approach was to find a protective group of the starting aromatic amine, which would be sufficiently stable to withstand the various stages of the synthesis.[8] Since *tert*-butylcarbamate (Boc) is stable under reductive conditions and is easily hydrolyzed under acidic conditions, it was chosen as the most versatile protective group for this multi-step synthesis. Also, *N*-arylimino-1,2,3-dithiazoles derived from the condensation of Appel salt with anilines are, in most cases, stable in strongly acidic conditions.[5,8]

Methyl 2-(*tert*-butoxycarbonylamino)-5-nitrobenzoate (**8**) was synthesized in very good yield (90%) by stirring of the starting ester **7** with di-*tert*-butyl carbonate (Boc_2O, 2.0 equiv), *N*,*N*-dimethylaminopyridine (DMAP, 0.1 equiv) and triethylamine (TEA, 1 equiv) in dry tetrahydrofuran (THF) at room temperature for 4 h. Reduction of the NO_2 group on *N*-protected anthranilic ester **8** was successfully performed by using ammonium formate (HCO_2NH_4, 5.0 equiv) and palladium on charcoal (Pd/C, 10%) for catalytic transfer hydrogenation in refluxing methanol (μw) to give **9** in an excellent yield of 98%. According to previous strategies, compound **9** was treated with bromine (Br_2) in acetic acid to give the *ortho*-brominated amines (e.g., **10** and **11** in Scheme 2). Unfortunately, the reaction afforded a complex mixture that was difficult to separate. This suggested that *N*-deprotected 1,4-diamines were obtained but were difficult to isolate, probably due to iminoquinonic forms generated. Bromination of **8** with *N*-bromosuccinimide (NBS) in DMF also failed.

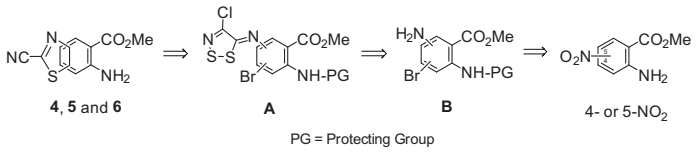
Back to the preceding steps the amino group of compound **7** was protected as a dicarbamate. Methyl 2-[di(*tert*-butoxycarbonyl)amino]-5-nitrobenzoate (**12**) was prepared from **7** according to the procedure described for **8**. The quantity of Boc_2O was slightly increased (2.2 equiv), and one equivalent of DMAP allowed the synthesis of the *N*-di-Boc derivative **12** in very good yield (96%). The latter was successfully reduced as described above for **9** to give **13** quantitatively. Bromination of **13** was tested in the conditions described above (Br_2/AcOH or NBS/DMF). The procedure involving bromine led to a complex mixture while the method using NBS in DMF revealed to be most regioselective and gave methyl 3-amino-2-bromo-6-[di-(*tert*-butoxycarbonyl)amino]benzoate (**14**) in very good yield (90%), along with 10% of its 4-bromo-substituted isomer **15**.[8] Despite our efforts, attempts to separate both isomers by column chromatography only yielded modest amounts of pure derivative **14** (30%), while recrystallization was tested without success.

Taking in account these results, the crude mixture of **14** and **15** was directly condensed with Appel salt (1.2 equiv) in dichloromethane at room temperature. After 3 h of stirring, pyridine was added and both isomers of the corresponding imino-1,2,3-dithiazoles (**16** and **17**, respectively) were easily separated and purified. Major compound **16** was obtained in a good overall 56% yield for both steps, while its isomeric partner **17** was purified in a low 5% yield.

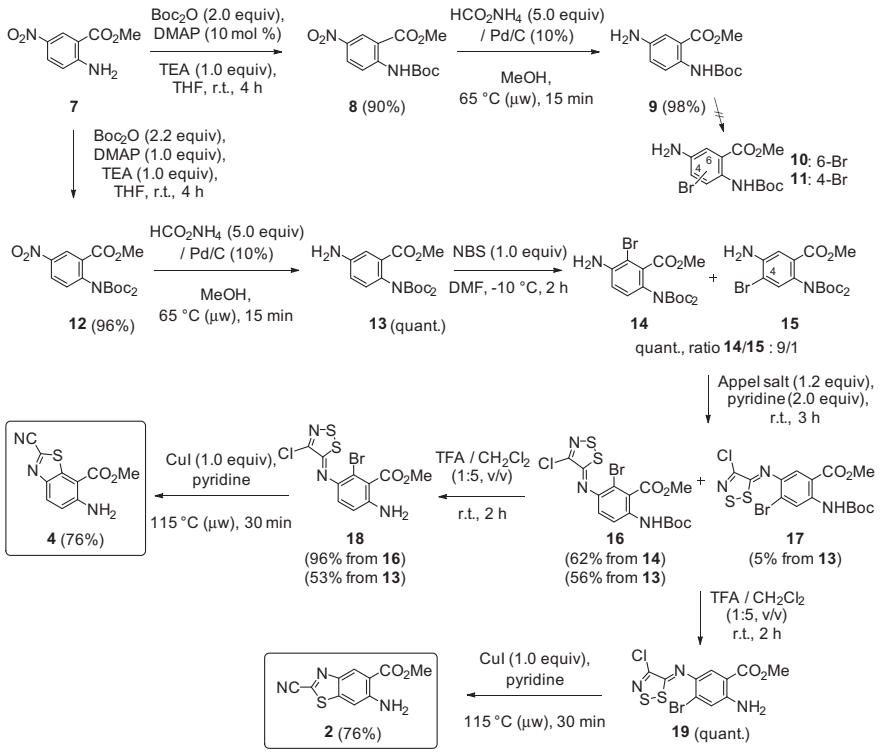
Analysis of the spectral data obtained for both imines **16** and **17** revealed that the di-Boc protective group was partially hydrolyzed during the reaction. This expected result suggests that the release of hydrogen chloride during the process with Appel salt and/or the final work-up on an acidic silica gel has induced a partial hydrolysis of the N^2-protecting group leading to a drastic decrease in the yields. The residual *N*-Boc group of imine **16** was cleaved by trifluoroacetic acid (TFA) in dichloromethane to furnish **18** in quantitative yield.

Cyclization procedure of **18** was performed in the presence of copper(I)-iodide (CuI, 1 equiv) in refluxing pyridine under microwave heating. The final methyl 6-amino-2-cyanobenzo[*d*]thiazole-7-carboxylate (**4**) was purified in a good yield (76%). In an identical strategy, methyl 6-amino-4-bromo-3-([(5*E*)-4-chloro-5*H*-1,2,3-dithiazol-5-ylidene]amino)-benzoate (**19**) was obtained quantitatively from its imino-1,2,3-dithiazole precursor **17** and was converted into methyl 6-aminobenzo[*d*]thiazole-5-carboxylate (**2**). Although this route gave access to a valuable and highly functionalized benzothiazole, product **2**, it was only isolated as side-product of this synthetic sequence. Our group reported a more efficient method to synthesize **2** starting from methyl 4-bromoanthranilate.[8]

Syntheses of methyl 5-amino-2-cyanobenzo[*d*]thiazole-6-carboxylate (**5**) and methyl 7-amino-2-cyanobenzo[*d*]thiazole-6-carboxylate (**6**) were inspired by the results described above. Although reaction conditions and steps' order were similar to the preceding work, the stability of the Boc group introduced in N^3 is closely related to the position of the nitro group.



Scheme 2. Retrosynthetic pathway and access to novel linear methyl 6-amino-2-cyanobenzo[*d*]thiazole-7-carboxylate (**4**), methyl 5-amino-2-cyanobenzo[*d*]thiazole-6-carboxylate (**5**) and methyl 7-amino-2-cyanobenzo[*d*]thiazole-6-carboxylate (**6**) from methyl 4- or 5-nitroanthranilate derivatives.



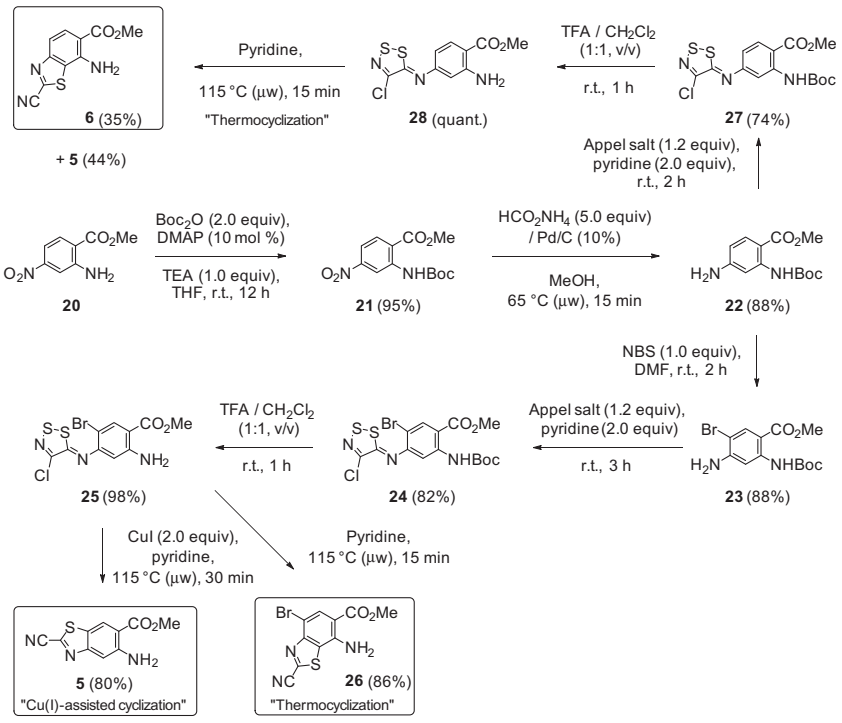
Scheme 3. Synthetic route to methyl 6-amino-2-cyanobenzo[*d*]thiazole-7-carboxylate (**4**) and secondarily to methyl 6-aminobenzo[*d*]thiazole-5-carboxylate (**2**).

The synthetic pathway is depicted in Scheme 4 and describes usual conditions. It started from methyl 4-nitroanthranilate (**20**)[10] which was treated for 12 h at room temperature with di-*tert*-butyl carbonate (2.0 equiv) to give **21** (95%) which was reduced into its amino derivative **22** (88%). The latter was selectively brominated in position 5 of the aromatic ring with NBS in DMF at room temperature to give **23** in very good yield (88%). Methyl 5-bromo-4-nitroanthranilate (**23**) was then stirred with Appel salt in conditions described above to afford the corresponding imino-1,2,3-dithiazole **24** (82%) which was quantitatively deprotected into **25**, before microwave-assisted heating in the presence of CuI (1.0 equiv) and in pyridine as solvent. Purification of the crude mixture gave the target methyl 5-amino-2-cyanobenzo[*d*]thiazole-6-carboxylate (**5**) in 80% yield, accompanied by 10% of a new derivative identified as the methyl 7-amino-4-bromo-2-cyanobenzo[*d*]thiazole-6-carboxylate (**26**). This brominated benzothiazole **26** was the result of the thermal cyclization process described in preceding works.[11] A short exploration study was performed, varying reaction time and stoichiometric parameters (e.g., CuI: 0, 1.0, 1.5 or 2.0 equiv). Results obtained demonstrated that heating the starting imino-1,2,3-dithiazole **25** with 2.0 equiv of CuI led to **5** in an excellent yield of 80%, without any traces of **26**. In contrast, copper-free microwave-assisted heating of **25** in refluxing pyridine exclusively led to **26** in a very good yield (86%), confirming the competition between the thermocyclization and the copper-assisted cyclization processes. Kinetically, the thermocyclization seemed to occur faster than the copper-mediated cyclization. This result may explain the presence of **26** in the preceding experiment; it was partially formed until the copper-assisted phenomenon was involved.

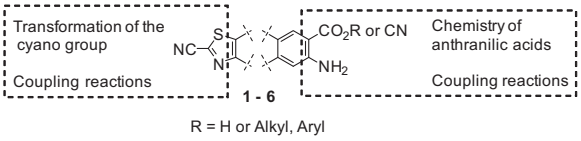
In order to prepare the methyl 7-amino-2-cyanobenzo[*d*]thiazole-6-carboxylate (**6**) another route was envisioned. It started from methyl 4-amino-2-[(*tert*-butoxycarbonyl)amino]benzoate (**22**) which was treated with Appel salt in the usual conditions to afford methyl 2-[(*tert*-butoxycarbonyl)amino]-4-[(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)amino]benzoate (**27**) and then deprotected into **28** in a good overall yield (74% for the two steps). Microwave-assisted thermocyclization of **28** in refluxing pyridine for 15 min provided complete conversion of the starting material into a mixture of the benzothiazole-2-carbonitrile (**5**) and the novel methyl 7-amino-2-cyanobenzo[*d*]thiazole-6-carboxylate (**6**) in a ratio of 3:2 (estimated by ^{1}H NMR).[11] The mixture was purified by column chromatography on silica gel to furnish **5** and its regioisomer **6** in 44% and 35% yield, respectively.

As depicted in Scheme 5, these molecular polyfunctionalized heterocyclic systems were conceived as efficient precursors to various target molecules. On the one side of compounds **1**–**6**, the versatile carbonitrile function in position 2 of the thiazole ring may provides an easy access to various functions or can be functionalized via modern coupling methods. On the other side, the 2-aminobenzonitrile or 2-aminocarboxylic ester or acid moieties offer a large panel of possibilities for extension of the aromatic structure with heterocyclic cores, for example, via anthranilic acids chemistry and coupling methods.

In conclusion, this synthetic work allowed the preparation a short library of valuable novel polyfunctionalized benzo[*d*]thiazole derivatives in a straightforward and sustainable manner. Here again, Appel salt proved to be an efficient agent for fusing the 2-cyanothiazole ring to arene or heteroarene parts. This work concludes a series of papers[4,5,8] describing the construction of a library of versatile benzothiazoles. Very relevant and highly functionalized molecular platforms which can be employed for the exploration of new chemical spaces were presented, and hence prove their utility for the synthesis of innovative heterocyclic systems with potent biological applications.



Scheme 4. Synthetic route to methyl 5-amino-2-cyanobenzo[*d*]thiazole-6-carboxylate (**5**), methyl 7-amino-2-cyanobenzo[*d*]thiazole-6-carboxylate (**6**) and methyl 7-amino-4-bromo-2-cyanobenzo[d]thiazole-6-carboxylate (**26**).



Scheme 5. Description of the amino-2-cyanobenzothiazole-carboxylic acid derivatives for new areas in molecular diversity.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures, ^{1}H and ^{13}C NMR spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.05.018.

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10. Methyl 2-amino-5-nitrobenzoate (**7**) and methyl 2-amino-4-nitrobenzoate (**20**) are commercially available but quite expensive. Both products can be efficiently synthesized according to our previous works[8] from the cheaper 5-nitro- and 4-nitroanthranilic acids which were treated by dimethylformamide-dimethylacetal (DMF-DMA, 2.5 equiv) in dimethylformamide (DMF) at 100 °C for 15 min under microwaves to afford **5** and **20** in excellent yields (92% and 95%, respectively) after acidic work-up.
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