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A short and straightforward approach towards 6-amino and 6-aminoalkyl thiazolo[4,5-*c*]pyridazines

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Abstract

A facile and efficient synthesis of 6-amino and 6-aminoalkyl thiazolo[4,5-*c*]pyridazines is reported. The key step for the construction of this novel bicyclic scaffold was the reaction between 3-amino-4-bromopyridazine derivatives and alkylisothiocyanates. The application of this methodology for the synthesis of a small library of thiazolo[4,5-*c*]pyridazines is also described.

Keywords: Thiazolo[4,5-*c*]pyridazine, Isothiocyanates, Privileged structures, Drug-like structures

Heterocyclic structures are of fundamental importance in drug discovery and the development of new strategies for the synthesis of novel heterocyclic scaffolds is an essential field of research in organic and medicinal chemistry.[1] In the last years, there has been a great interest in pyridazine-based structures in medicinal chemistry, as pyridazines can be considered as privileged structures, displaying a plethora of biological activities. The pyridazine moiety has been further fused to other heterocyclic rings, affording fused bi- and tricyclic scaffolds.[2] Several of these pyridazine-containing bicyclic and tricyclic cores show interesting biological activities. For example, the imidazo[1,2-*b*]pyridazine **1** displays activity against human picornaviruses,[3] while pyrrolopyridazine **2** is a novel acyl CoA:diacylglycerol acyltransferase (DGAT1) inhibitor with potential applications in a variety of diseases including obesity, insulin resistance syndrome and type II diabetes.[4] Sulfur-containing pyridazine scaffolds[5] also display interesting pharmacological

activities. For example, thienopyridazinone **3** is a melanine-concentrating hormone I antagonist, which might be developed for the treatment of obesity,[6] while fused thiazolo[4,5-*d*]pyridazine derivative **4** displays antibacterial activity against *S. aureus* and *E. coli*.[7]

Figure 1

The medicinal chemistry community is continuously looking for new heterocyclic scaffolds that can be used in a wide variety of screening campaigns. Based on the interest from our lab in the synthesis and biological evaluation of novel, bicyclic heterocyclic structures, the thiazolo[4,5-*c*]pyridazine scaffold was selected for synthesis. The chemistry of this heterocycle is still very much unexplored as a search on SciFinder revealed only 14 known compounds based on this core structure. Hence, very few reports dealing with the synthesis[8] and biological activity[9] of this novel scaffold are known. To the best of our knowledge, there is no publication describing a general and versatile method for the construction of the thiazolo[4,5-*c*]pyridazine core. Herein, we report a convenient methodology for the synthesis of 6-amino- and 6-aminoalkyl thiazolo[4,5-*c*]pyridazines.
Our strategy for the construction of thiazolo[4,5-*c*]pyridazines is based on a methodology elaborated by Liu and collaborators[10] for the synthesis of 2-aminothiazolo[5,4-*d*]pyrimidines, in which they start from a 4-chloro-5-amino-pyrimidine derivative. Similarly, we envisioned to construct the thiazolo[4,5-*c*]pyridazine scaffold from an appropriate substituted 3-amino-4-bromo-pyridazine analogue.
Starting from the commercially available 3-amino-6-chloropyridazine **5**, a substituted phenyl ring was introduced by a Suzuki cross-coupling reaction, followed by selective C-4 bromination of the pyridazine ring,[11] using bromine in MeOH, in presence of sodium bicarbonate (Scheme 1).

Scheme 1

In order to find the optimal reaction conditions for the construction of the thiazole moiety, the reaction between 3-amino-4-bromo-6-(4-ethylphenyl)pyridazine **7a,** as representative example, and phenyl, as well as alkylisothiocyanates, has been studied, by varying different parameters such as base, solvent, temperature and reaction time (Table 1).

Table 1

From Table 1 it is clear that the desired thiazolo[4,5-*c*]pyridazine was never obtained when aromatic isothiocyanates were used for formation of the thiazole ring. Treatment of pyridazine derivative **7a** with phenylisothiocyanate at 80°C for 12h, in presence of Cs_2CO_3 and CH_3CN as solvent (Entry 1), led mainly to dehalogenation of the starting material, yielding compound **6a**. These results stand in sharp contrast with the results obtained by Liu and coworkers,[10] wherein reaction of 4,6-dichloro-5-amino-pyrimidine and a wide range of phenylisothiocyanates afforded the desired 2-anilino-thiazolo[5,4-*d*]pyrimidines in excellent yields. Other combinations of solvents and bases did not bring any improvement. Using DMF as solvent and Cs_2CO_3 as a base, at 50°C showed only the presence of unreacted starting material (Entry 2), while sodium hydride in THF (at 50°C for 12h, Entry 3) led to debromination of the substrate **7a**. When the reaction was carried out without a base, only starting material **7a** was recovered (Entry 4). In order to investigate if the electronic properties of the aromatic isothiocyanate did have an influence on the reaction outcome, 4-nitrophenylisothiocyanate (as an example of an electron-withdrawing group) and 3,4,5-trimethoxyphenylisothiocyanate (representative for an electron-donating moiety) were selected as coupling partners. When the reaction was performed in toluene as solvent and using DABCO as a base,[12] both reactions failed. No desired product could be isolated, and only reductive removal of the bromine was observed (Entries 6 and 7). Performing the reaction under microwave irradiation (Entry 5), using DMSO as solvent at 150°C for 2 hours, likewise, led to dehalogenation of the pyrazine moiety. All attempts to accomplish the ring closure with aromatic isothiocyanates were unsuccessful and we were not able to prepare 6-anilino-thiazolo[4,5-*c*]pyridazines by this methodology. However, applying this methodology to aliphatic isothiocyanates, the desired thiazolo[4,5-*c*]pyridazines scaffold could be isolated. In particular, performing the reaction with *n*-butylisothiocyanate at 80°C for 12 hours, using CH_3CN as solvent and Cs_2CO_3 (2 eq) as base, allowed the isolation of compound **8a** in 29% yield (Entry 8). Encouraged by this result, further optimization of the reaction parameters, by decreasing the reaction time to 6 hours, lowering the reaction temperature to 60°C and reducing the amount of Cs_2CO_3 to 1.5 eq allowed the isolation of compound **8a** in 56% yield (Entry 9).

To demonstrate that this chemistry was useful for making series of analogues, a small library of thiazolo[4,5-*c*]pyridazines was prepared (Table 2).

Table 2

Four different alkylisothiocyanates (*n*-butyl, cyclohexyl, *n*-propyl and allyl isothiocyanate) were coupled with four different substituted pyridazines **7a-d** bearing various substituents at C-6 position (4-ethylphenyl, 4-fluorophenyl, 4-chlorophenyl and chlorine), leading to a small library of thiazolo[4,5-*c*]pyridazines **8a-p**.

The synthesis of 6-aminothiazolo[4,5-*c*]pyridazine derivatives **9a-d** was also accomplished by reaction of pyridazines **7a-d** with potassium thiocyanate and bromine[13] in acetic acid as solvent (Scheme 2).

Scheme 2

Given the chemical novelty of the thiazolo[4,5-*c*]pyridazine scaffold, the library can be used for screening campaigns in a wide variety of biological assays. Our lab has a main interest in the search for novel antibacterial compounds,[14a-d] either via a phenotypic cell-based assay approach,[14c] or via a target-based approach using SecA as drug target.[14d] Therefore, the thiazolo[4,5-*c*]pyridazine-based compound library was first evaluated in these two assays, both relevant for antibacterial drug discovery. Screening of the compounds for their ability to inhibit the growth of *S. aureus* at a concentration of 64 µg/mL did not reveal any compounds with antibacterial activity. When the thiazolo[4,5-*c*]pyridazines were investigated as potential inhibitors of *S. aureus* secA, none of the analogues displayed any inhibitory activity when tested at a concentration of 200 µM.

In summary, we have developed a short and easy methodology for the synthesis of novel 6-amino and 6-aminoalkyl thiazolo[4,5-*c*]pyridazine derivatives. The key step is the formation of a thiazole moiety starting from a 3-amino-4-bromo-pyridazine derivative and an isothiocyanate. Whereas the reaction proceeds smoothly with aliphatic isothiocyanates, using phenylisothiocyanates did not lead to the expected 6-anilino-thiazolo[4,5-*c*]pyridazines. The methodology presented in this work allows for the rapid synthesis of a wide variety of, hitherto unknown, 3,6-disubstituted thiazolo[4,5-*c*]pyridazines.

Acknowledgments

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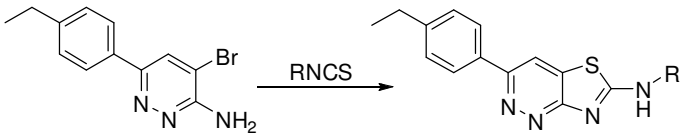
References

1) Dua, R.; Shrivastava, S.; Sonwane, S; K.; Srivastava S. K. *Adv. Biol. Res.***2011**, *5*, 120-144.

2) Wermuth, C. G. *MedChemComm* **2011**, *2*, 935-941.
3) Hamdouchi, C.; Sanchez-Martinez, C.; Gruber, J.; del Prado, M.; Lopez, J.; Rubio, A.; Heinz, B. A. *J. Med. Chem.* **2003**, *46*, 4333-4341.
4) Fox, B. M.; Iio, K.; Li, R.; Choi, R.; Takashi, I.; Jackson, S.; Sagawa, S.; Shan, B.; Tanaka, M.; Yoshida, A.; Kayser, F. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6030-6033.
5) a) Kaji, K.; Nagashima, H.; Nagao, S.; Tabashi, K.; Oda, H. *Chem. Pharm. Bull.* **1984**, *32*, 4437-4446. b) Matsuo, T.; Tsukamoto, Y.; Takagi, T.; Yaginuma, H. *Chem. Pharm. Bull.* **1982**, *30*, 1030-1032. c) Al-Mousawi, S. M.; Moustafa, M. S.; Elnagdi, M. H. *Arkivoc* **2010**, 224-232. d) Bantick, J.; Cooper, M.; Thorne, P.; Perry, M. PCT WO 1999/29695.
6) Dyck, B.; Markison, S.; Zhao, L. R.; Tamiya, J.; Grey, J.; Rowbottom, M. W.; Zhang, M. Z.; Vickers, T.; Sorensen, K.; Norton, C.; Wen, J.; Heise, C. E.; Saunders, J.; Conlon, P.; Madan, A.; Schwarz, D.; Goodfellow, V. S. *J. Med. Chem.* **2006**, *49*, 3753-3756.
7) Makki, M. S. I.; Faidallah, H. M. *J. Chin. Chem. Soc.* **1996**, *43*, 433-438.
8) Fruit, C.; Turck, A.; Ple, N.; Queguiner, G. *J. Heterocycl. Chem.* **2002**, *39*, 1077-1082.
9) Bluth, R. *Pharmazie* **1982**, *37*, 208-212.
10) Liu, J.; Patch, R. J.; Schubert, C.; Player, M. R. *J. Org. Chem.* **2005**, *70*, 10194-10197.
11) Pastor-Fernandez, J.; Bartolome-Nebreda, J. M.; MacDonald, G. J.; Conde-Ceide, S.; Delgado-Gonzalez, O.; Vanhoof, G. C. P.; Van Gool, M. L. M.; Martin-Martin, M. L.; Alonso-De Diego, S. A. PCT WO 2011/051342.
12) Ding, Q. P.; He, X. D.; Wu, J. *J. Comb. Chem.* **2009**, *11*, 587-591.
13) Bernstein, J.; Stearns, B.; Shaw, E.; Lott, W. A. *J. Am. Chem. Soc.* **1947**, *69*, 1151-1158.
14) a) Kögler, M., Vanderhoydonck, B., De Jonghe, S., Rozenski, J., Van Belle, K., Herman, J., Louat, T., Parchina, N., Sibley, C., Lescrinier, E., Herdewijn, P. *J. Med. Chem* **2011**, *13*, 4847-4862. b) Dumbre, S.; Derouaux, A.; Lescrinier, E.; Piette, A.; Joris, B.; Terrak, M.; Herdewijn, P. *J. Am. Chem. Soc.* **2012**, *134*, 9343-9351. c) Stella, A.; Segers, K.; De Jonghe, S.; Vanderhoydonck, B.; Rozenski, J.; Anné; J.; Herdewijn, P. *Chem. Biodiv.* **2011**, *8*, 253-265. d) Yang, M.-Y.; De Jonghe, S.; Segers, K.; Anné, J.; Herdewijn, P. *Bioorg. Med. Chem.* **2011**, *19*, 702-714.
15) *Representative example*: *Synthesis of N-Butyl-3-(4-ethylphenyl)-[1,3]thiazolo[4,5-c]pyridazin-6-amine* **(8a)** To a solution of 3-amino-4-bromo-6-(4-ethylphenyl)pyridazine **7a** (200 mg, 0.719 mmol) in CH_3CN (6 mL), were added Cs_2CO_3 (1.5 eq, 1.08 mmol, 352 mg) and butylisothiocyanate (1.5 eq, 1.08 mmol, 125 µL) and the mixture was stirred at 60°C for 6 hours. The solution was then diluited with AcOEt and brine, organic phase extracted, dried over $MgSO_4$ and evaporated under reduced pressure. The crude mixture was purified by silica gel chromatography using Heptane/AcOEt : 1/1 as mobile phase, affording the title compound in 56% yield. ^{1}H-NMR (300 MHz, (D6)-DMSO): 8.88 (br s, 1H), 8.5 (s, 1H), 7.99 (d, *J* = 7.74 Hz, 2H), 7.35 (d, *J* = 7.74 Hz, 2H), 3.48 (br s, 2H), 2.66 (q, *J* = 7.41 Hz, 2H), 1.62 (m, 2H), 1.38 (m, *J* = 7.14, 2H), 1.22 (t, *J* = 7.35 Hz, 3H), 0.93 (t, *J* = 7.32 Hz, 3H). ^{13}C-NMR (75 MHz, (D6)-DMSO): 168.0, 167.1, 151.2, 144.9, 134.4, 133.2, 128.4, 126.4, 117.0, 44.0, 30,7, 28.0, 19.6, 15.6, 13.8. HRMS: ESI$^+$ calc. for $(C_{17}H_{21}N_4S)^+$ 313.1481, found: 313.1484.

Table 1. Optimization of the reaction conditions

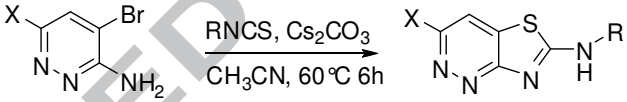


7a

Entry	Isothiocyanate[d]	Base	Solvents	Temperature – Reaction time	Product
1	PhNCS	Cs_2CO_3 (2eq)	MeCN	80°C - 12h	-[a]
2	PhNCS	Cs_2CO_3 (2eq)	DMF	50°C - 4h	-[b]
3	PhNCS	NaH (1.5 eq)	THF	50°C - 12h	-[a]
4	PhNCS	None	MeCN	80°C - 12h	-[b]
5	*p*-NO_2PhNCS	None	DMSO	150°C - 2h[c]	-[a]
6	*p*-NO_2PhNCS	DABCO (2eq)	Toluene	80°C - 12h	-[a]
7	3,4,5-trimethoxyPhNCS	DABCO (2eq)	Toluene	80°C - 12h	-[a]
8	ButylNCS	Cs_2CO_3 (2eq)	MeCN	80°C - 12h	**8a** (29%)
9	ButylNCS	Cs_2CO_3 (1.5eq)	MeCN	60°C - 6h	**8a** (56%)

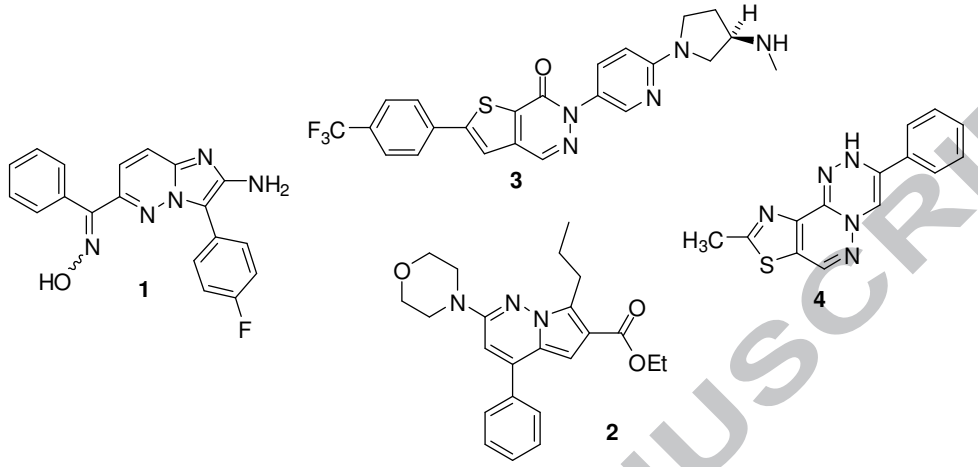
[a]Debromination of the starting material was occurring and compound **6a** was isolated. [b]Starting material was isolated. [C]Reaction performed under microwave irradiation.[d] For all cases, 1.5 eq of isothiocyanates were used.

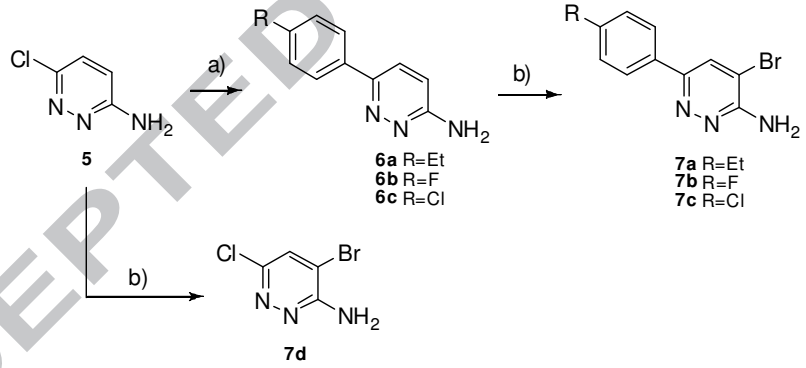
Table 2: Thiazolo[4,5-*c*]pyridazine library



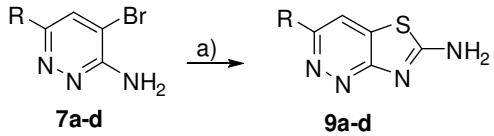
Entry	X	R	Product (Yield)
1	4-Ethylphenyl	Cyclohexyl	**8b** (52%)
2	4-Ethylphenyl	Propyl	**8c** (71%)
3	4-Ethylphenyl	Allyl	**8d** (69%)
4	4-Fluorophenyl	Butyl	**8e** (58%)
5	4-Fluorophenyl	Cyclohexyl	**8f** (49%)
6	4-Fluorophenyl	Propyl	**8g** (76%)
7	4-Fluorophenyl	Allyl	**8h** (47%)
8	4-Chlorophenyl	Butyl	**8i** (53%)
9	4-Chlorophenyl	Cyclohexyl	**8j** (69%)
10	4-Chlorophenyl	Propyl	**8k** (71%)
11	4-Chlorophenyl	Allyl	**8l** (44%)
12	Chlorine	Butyl	**8m** (48%)
13	Chlorine	Cyclohexyl	**8n** (69%)
14	Chlorine	Propyl	**8o** (73%)
15	Chlorine	Allyl	**8p** (62%)

Figure 1: Biologically active pyridazine-fused bi- and tricyclic scaffolds.





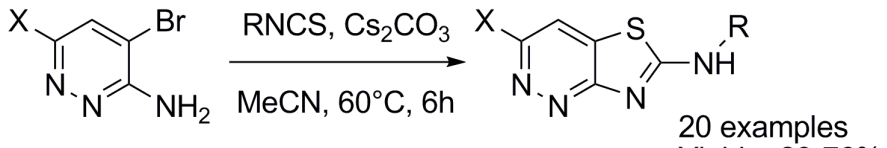
Scheme 1. *Reagents and conditions*: a) Arylboronic acid, $Pd(PPh_3)_4$, Na_2CO_3 2M, Toluene, 90°C, 12h. b) Br_2, $NaHCO_3$, MeOH, rt.



7a R=4-Ethylphenyl
7b R=4-Fluorophenyl
7c R=4-Chlorophenyl
7d R =Chlorine

9a R=4-Ethylphenyl
9b R=4-Fluorophenyl
9c R=4-Chlorophenyl
9d R =Chlorine

Scheme 2. *Reagents and conditions*: a) KSCN, Br_2, AcOH, 70°C.



20 examples
Yield = 28-76%

X = chlorine or substituted phenyl
R = alkyl or cycloalkyl