A Single-Step Preparation of Thiazolo[5,4-*b*]pyridine- and Thiazolo[5,4-*c*]pyridine Derivatives from Chloronitropyridines and Thioamides, or Thioureas

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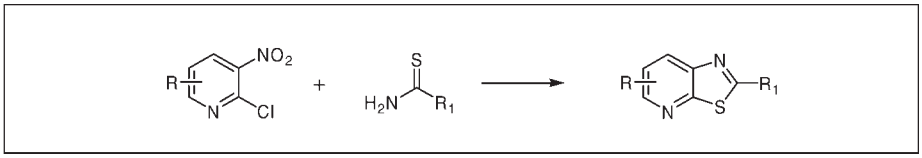

A one-step synthesis of thiazolo[5,4-*b*]pyridines from an appropriately substituted chloronitropyridine and thioamide, or thiourea, is presented. In particular, the reaction was used to prepare a large number of 6-nitrothiazolo[5,4-*b*]pyridine derivatives, bearing hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl, and amine substituents at the 2-position. The reaction could also be extended to produce a thiazolo[4,5-*c*]pyridine derivative and thiazolo[5,4-*b*]pyridines with alternative substituents on the pyridinoid ring.

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INTRODUCTION

The thiazolo[5,4-*b*]pyridine nucleus is of interest to those working in the agrochemical, pharmaceutical, and materials industries [1]. For instance, compounds containing a thiazolo[5,4-*b*]pyridine substructure have been described as ligands, or modulators, of leukotriene A_4 [2], VEGFR-2 [3], p38 MAP kinase [4], CCR3 [5], IAP [6], PPAR [7], D_4 [8], ubiquitin ligase [9], glucokinase [10], JAK3 [11], and sirtuin [12] amongst others [13]. A number of methods to prepare thiazolo[5,4-*b*]pyridines have been documented in the literature [1]. For example, methods that construct the bicycle by formation of a thiazole ring, include condensations of 3-amino-2-halopyridine, or 3-amino-2-pyridone derivatives, with thiocyanates, thioamides, or thioesters [14], the oxidative ring-closure of 3-aminopyridine thioamides or thioureas [15], condensations with 3-aminopyridin-2-thiones [16], and reactions of *N*-(2-pyridone-3-yl)acetamides with phosphorous pentasulfide [17]. Recently, a cross-coupling/cyclization sequence starting from *N*-(2-bromopyridin-3-yl)acetamide was also detailed [18]. In this article, we would like to disclose a new, single-step synthesis of the thiazolo[5,4-*b*]pyridine and thiazolo[4,5-*c*]pyridine nuclei. The approach is based upon the reaction of a thioamide, or thiourea, with an appropriately substituted chloronitropyridine to give a number of interesting thiazolopyridines in up to 60% yield (Fig. 1) [19]. In contrast to many literature methods of thiazolopyridine synthesis, our method does not use reagents such as tin(II) chloride, thiocyanate salts, thiophosgene, organometallics, or bromine [14–18].

RESULTS AND DISCUSSION

Our initial interest in compounds based around thiazolo[5,4-*b*]pyridines was stimulated by an examination of their potential use as modulators of ion-channel activity [20]. Toward this end, we required access to a number of 2-substituted-6-nitrothiazolo[5,4-*b*]pyridines. Our first attempts targeted the preparation of ethyl 6-nitrothiazolo[5,4-*b*]pyridine-2-carboxylate (**3a**). Fusing 2-chloro-3,5-dinitropyridine (**1**) with ethyl 2-amino-2-thioxoacetate (**2a**) in a 1:2 ratio at 70°C, then diluting with xylene and heating at 140°C gave the desired product (**3a**) in a moderate yield after column chromatography (Scheme 1). Subsequently, we found that the reaction could be performed using sulfolane as a solvent without any loss in efficiency (20% isolated yield). Sulfolane was chosen as similar reactions have used this solvent to give benzothiazole derivatives [21].

To investigate the scope of this ring-forming process, a diverse set of thioamides was reacted with 2-chloro-3,5-dinitropyridine to provide a range of thiazolo[5,4-*b*]pyridines that would be of interest to the medicinal chemist (Table 1). For example, it was found that this method could give compounds with substituted alkyl groups at the 2-position. The reaction was tolerant of a number of functional groups in the alkyl side chain,

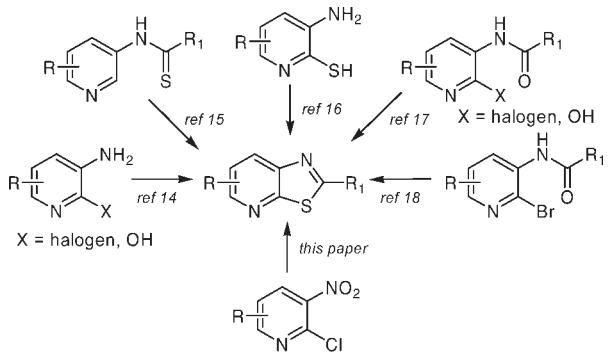
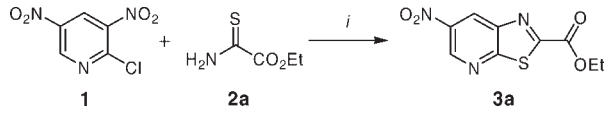


Figure 1. Some approaches to thiazolo[5,4-*b*]pyridines.

such as ester, ether, thioether, nitrile, and sulfone (entries 1–7). Branching on the alkyl chain was also tolerated as demonstrated by the successful reaction to produce compounds (**3i**)–(**3k**) (entries 8–10). 2-Aryl and heteroaryl derivatives were also accessible (entries 11–13), as was the 2-amino thiazolopyridine (entry 14). The parent hydrido compound (**3o**) was also produced (entry 15), although in this instance the final compound was synthesized by reacting 2-chloro-3,5-dinitropyridine with neat *N*,*N*-dimethylthioformamide at 60°C, then diluting with xylenes and refluxing overnight [22]. Yields for the synthesis of 2-substituted-6-nitrothiazolo[5,4-*b*]pyridines ranged from the moderate (*ca*. 40%) to the modest (10–20%). Although the reactions seemed to progress smoothly when followed by analytical techniques such as LC/MS, obtaining material with acceptable purity proved to be problematic in a number of cases. As such, at least part of the lower isolated yield may be attributable to difficulties with purification for many compounds, since preparative high-performance liquid chromatography, or repeated trituration, had to be used. Nevertheless, the above one-step process could be used to make compounds on a gram-scale, without any reduction in yield, for a number of final compounds (*e.g.*, **3b** and **3c**).

Attempts to optimize a model transformation, (**2**–**3k**), by variation in solvent, or additives, did not result in any improvement in conversion as measured by high-performance liquid chromatography (Table 2). For example, changing from sulfolane to a similarly polar solvent such as DMF, DMSO, or NMP resulted in a marked retardation in the formation of desired product (entries 3–5) [23]. The use of diphenylether, ethanol, or 1,4-dioxane (entries 6–8) resulted in a moderate amount of thiazolo[5,4-*b*]pyridine formation, although efficiencies were lower than for sulfolane. We next investigated the influence of a small selection of additives on the amount of product formation (entries 9–14), finding that only the inclusion of scandium(III) triflate (entry 11)

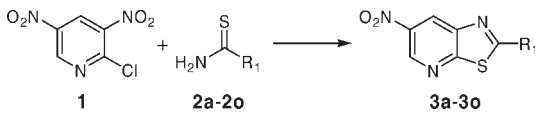
Scheme 1. Synthesis of ethyl 6-nitrothiazolo[5,4-*b*]pyridine-2-carboxylate. *i*. Fuse 70°C, then dilute with xylene and heat to 140°C (20%).



resulted in a comparable conversion compared with the reference transformation (entry 1). Significantly, other model transformations noticed that the use of heating under microwave irradiation resulted in a reduced reaction time, with no loss in isolated yield (Table 3, entry 1). Indeed, the use of 4 equivalents of thioamide starting material, together with microwave irradiation resulted in an enhanced conversion compared to the thermal conditions used previously (Table 3, entries 2–5 *cf*. Table 1 entries 3, 6, 7, and 15, respectively). This improvement in yield was most likely due to a combination of factors, including a rapid initial reaction under microwave conditions, resulting in a transient overshoot in temperature, particularly when reactions were run at high concentrations (*ca*. 1*M*; entry 5). In general, the microwave reactions also gave cleaner mixtures, with fewer by-products, which facilitated the purification process of final compounds.

Table 1

Synthesis of 6-nitrothiazolo[5,4-*b*]pyridines.

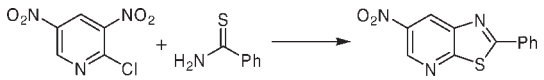


Entry	Product	R_1	% Yield[a]
1	**3a**	CO_2Et	20
2	**3b**	Me	43[b]
3	**3c**	$CH_2OC(O)C(Me)_3$	36
4	**3d**	$CH_2OC_6H_4OMe$ (4-methoxy isomer)	16
5	**3e**	CH_2SPh	14
6	**3f**	CH_2CN	7
7	**3g**	$CH_2SO_2C(Me)_3$	9
8	**3h**	$CH(Me)OC(O)C(Me)_3$	35
9	**3i**	$CH(Ph)_2$	7
10	**3j**	Cyclopropyl	4
11	**3k**	Ph	20
12	**3l**	2-Thienyl	20
13	**3m**	3-Pyridyl	6
14	**3n**	NH_2	15
15	**3o**	H	11[c]

[a] Performed using 1 equiv of compound (**1**) and 2 equiv of thioamide (or thiourea) (**2a**)–(**2n**) in sulfolane at 100−110°C.
[b] Performed using 1 equiv of compound (**1**) and 4 equiv of thioamide (**2b**) in sulfolane at 100°C.
[c] Performed using 1 equiv of compound (**1**) and 4.6 equiv of *N*,*N*-dimethylthioformamide at 60°C and then diluted with xylene and refluxed.

Table 2

Effect of solvent/additives on conversion for a model transformation.



1 **2k** **3k**

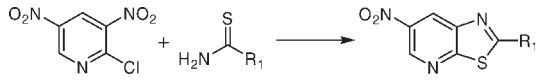
Entry	Solvent	Additive	% Conversion[a]
1	Sulfolane	None	44
2	Sulfolane	None	20[b]
3	DMF	None	10
4	DMSO	None	0
5	NMP	None	4
6	Ph_2O	None	12
7	EtOH	None	12
8	1,4-Dioxane	None	24
9	Sulfolane	^{i}PrNEt	0
10	Sulfolane	DDQ	4
11	Sulfolane	$Sc(OTf)_3$	39
12	Sulfolane	NaOAc	0
13	Sulfolane	K_2CO_3	0
14	Sulfolane	KI	21

[a] Reaction performed using 2 equiv of (**2k**). Conversion to (**3k**) was based upon integration of peak area in LC/MS trace after 4 h at 100°C.
[b] Reaction performed using 1 equiv of (**2k**).

Reactions with 2-chloro-3-nitropyridine. To explore the potential of our method in providing thiazolo[5,4-*b*]pyridines with only hydrogen substituents on the pyridinoid ring, 2-chloro-3-nitropyridine (**4**) was reacted with a representative selection of thioamides (**2b**, **2k**, **2o**) and with thiourea (**2n**) to provide cyclized products (Table 4). Either thermal or microwave conditions could be used to give thiazolo[5,4-*b*]pyridines (**5a**)–(**5d**) in up to 49% yield. As can be seen when comparing the entries in Table 4 to their counterparts in Table 1, the absence of a nitro-group in the pyridinoid ring seemed to be slightly beneficial in terms of isolated yield.

Table 3

Microwave-assisted synthesis of 6-nitrothiazolo[5,4-*b*]pyridines.



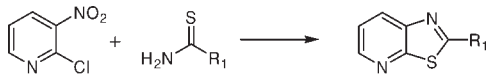
1 **2a**, **2c**, **2f**, **2g**, **2o** **3a**, **3c**, **3f**, **3g**, **3o**

Entry	Product	R_1	% Yield[a]
1	**3a**	CO_2Et	26
2	**3c**	$CH_2OC(O)C(Me)_3$	36[b]
3	**3f**	CH_2CN	16
4	**3g**	$CH_2SO_2C(Me)_3$	18
5	**3o**	H	50

[a] Reaction of (**1**) using 4 equiv of appropriate thioamide at 110–130°C under microwave irradiation.
[b] Reaction performed using 2 equiv of thioamide (**2c**) at 110–130°C under microwave irradiation (4 equiv of (**2c**) not performed).

Table 4

Synthesis of thiazolo[5,4-*b*]pyridines.



4 **2b**, **2k**, **2n**, **2o** **5a-5d**

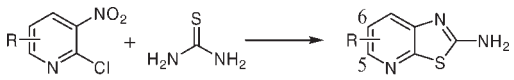
Entry	Thioamide	Product	R_1	% Yield[a]
1	**2b**	**5a**	Me	49
2	**2k**	**5b**	Ph	26
3	**2n**	**5c**	NH_2	46/10[b]
4	**2o**	**5d**	H	26

[a] Reaction of (**4**) using 4 equiv of appropriate thioamide at 135°C under microwave irradiation.
[b] Reaction performed using 2 equiv of thioamide (**2n**) at 130°C (no microwave irradiation).

Reactions with substituted 2-chloro-3-nitropyridines. As a further extension of the reaction, we sought to investigate the use of pyridine starting materials in which a substituent other than nitro, or hydrogen, was present. As can be seen from Table 5, a number of interesting derivatives were prepared. The mildness of the technique was illustrated in the preparation of thiazolo[5,4-*b*]pyridines incorporating a halogen (**7a**)–(**7c**) (entries 1–3). The synthesis of such compounds is somewhat sparse in the chemical literature, and our approach to the bromo- and iodo-analogues (entries 2 and 3) is significant, as some thiazolopyridine syntheses may not be able to provide such compounds (*e.g.*, methods involving metal-mediated approaches). Our methodology is therefore attractive, as halogenated thiazolopyridines are potentially useful building blocks for medicinal chemistry libraries. For instance, compounds (**7b**) and (**7c**) possess a halo- and amine handle for derivatization (*e.g.*, palladium-mediated reactions for halo-substituent;

Table 5

Synthesis of 2-aminothiazolo[5,4-*b*]pyridines.

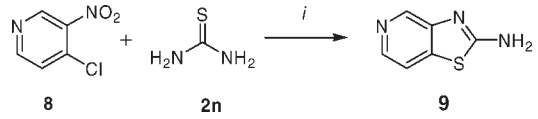


6a-6e **2n** **7a-7e**

Entry	Nitropyridine	Product	R_1	% Yield[a]
1	**6a**	**7a**	6-Cl	48
2	**6b**	**7b**	6-Br	62
3	**6c**	**7c**	6-I	39
4	**6d**	**7d**	6-Me	19
5	**6e**	**7e**	5-OMe	8

[a] Reaction of (**6a**)–(**6e**) using 4 equiv of appropriate thioamide at 135°C under microwave irradiation for 45 min.

Scheme 2. Preparation of 2-amainothiazolo[4,5-*c*]pyridine. *i*. Sulfolane, 135°C, microwave, 75 min (22%).



amide, urea, and reductive alkylation reactions for the amine group). Thus, chemical libraries with two points of diversity could be envisaged around these scaffolds. Compounds with alternative substituents on the pyridinoid ring, such as the 6-methyl and 5-methoxy derivatives (**7d**) and (**7e**) (entries 4–5), were also prepared. However, the reaction to give (**7e**) was particularly low yielding (8%), which may be as a result of the methoxy-group also being activated toward nucleophilic substitution by the thiourea starting material.

Reaction with 4-chloro-3-nitropyridine. As demonstrated, thiazolo[5,4-*b*]pyridines can be synthesized with diverse substituents on both the thiazole and pyridine rings. To probe the utility of the reaction in providing other isomeric thiazolopyridines, a synthesis of 2-aminothiazolo[4,5-*c*]pyridine (**9**) from 4-chloro-3-nitropyridine (**8**) and thiourea (**2n**) was devised (Scheme 2). Heating at 135°C under microwave irradiation gave the desired product (**9**) in 22% yield after column chromatography. Thus, we believe that the reaction may have the potential to access other thiazolo[4,5-*c*]pyridine derivatives, such as those with an alkyl- or aryl-group at the 2-position, or those with substituents other than hydrogen on the pyridinoid ring. However, investigations toward such molecules were beyond the scope of our studies and will await further experimentation. In addition, it would also be desirable to explore the potential of forming thiazolo[5,4-*c*]pyridines from 3-chloro-4-nitropyridine precursors.

The reaction pathway. Currently, we believe that the reaction proceeds by an initial displacement of the chloro-group followed by nitro-group reduction and concomitant cyclization. For example, with 2-chloro-3,5-dinitropyridine (**1**), displacement with an appropriate thioamide gives intermediates (**10a**)–(**10o**) (Fig. 2). Reductive cyclization of (**10a**)–(**10o**), on exposure to excess thioamide in the reaction mixture, provides the desired thiazolopyridines (**3a**)–(**3o**). Although nitro-group reductions with thioamides, or thiourea, have not been detailed extensively in the chemical literature,

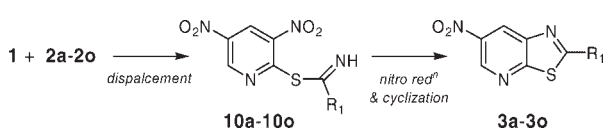
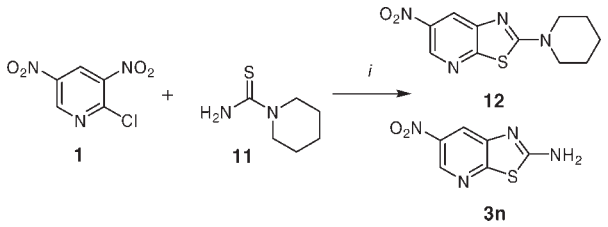


Figure 2. Proposed reaction pathway.

Scheme 3. Reaction with piperidine-1-carbothioamide. *i*. Sulfolane, 100°C (9% **12** and 6% **3n**).



related reductions with sulfur reagents, such as sulfides (Zinin reduction), sodium dithionite, elemental sulfur, and thiourea *S*,*S*-dioxide, have been used frequently [24–27]. Of note in the reduction step is an apparent selectivity in nitro-reduction for the postulated intermediates (**10a**)–(**10o**). Although some low yields encountered in our synthesis meant that we cannot exclude the possibility that both nitro groups in (**10a**)–(**10o**) are reduced, the observed selectivity in reduction of (**10a**)–(**10o**) is consistent with that seen for other 2-substituted-3,5-dinitropyridines, such as the reduction of 2-amino-3,5-dinitropyridine with sodium sulfide [28,29]. Evidence for the type of reaction described earlier, as opposed to one involving displacement of the nitro group from intermediate (**10a**)–(**10o**), is provided in the preparation of parent hydrido derivative (**3o**) using *N*,*N*-dimethylthioformamide (Table 1, entry 15), and the formation of both (**12**) and (**3n**) when 2-chloro-3,5-dinitropyridine (**1**) is reacted with piperidine-1-carbothioamide (**11**) (Scheme 3).

CONCLUSIONS

In conclusion, we have developed an expeditious new single-step synthesis of the thiazolo[5,4-*b*]pyridine and thiazolo[4,5-*c*]pyridine nuclei by condensing an appropriately substituted chloronitropyridine with a thioamide or thiourea. The use of such conditions is complementary to existing techniques to thiazolopyridines and may offer advantages in terms of scope, speed of synthesis, and availability of starting materials. The single-step nature of the reaction is particularly noteworthy, as many established thiazolopyridine syntheses use multistep routes, and frequently resort to toxic reactants, or reagents requiring special handling conditions, to prepare suitable starting materials or final products. Additionally, our method tolerates sensitive functionality in the coupling partners, may be accelerated by the use of microwave irradiation and is operationally simple to perform, giving final products in moderate yield. The synthesis outlined in this article will be of particular interest to those in the medicinal, agrochemical, materials, and heterocyclic fields, where thiazolo[5,4-*b*]- and thiazolo[4,5-*c*]pyridines have found many uses.

EXPERIMENTAL

All reagents except 1-amino-1-thiooxopropan-2-yl pivalate and cyclopropanecarbothioamide were purchased from commercial sources and used without further purification. 1-Amino-1-thiooxopropan-2-yl pivalate (example **3h**) and cyclopropanecarbothioamide (example **3j**) were synthesized by GVK Biosciences Private (Hyderabad, India). All microwave-assisted reactions were performed with a CEM Discover S-Class microwave with 48-position autosampler. Temperature during microwave reactions was monitored by a vertically sensored infrared temperature sensor, which comes as a standard feature of the CEM Discover S-Class system. All NMR spectra are quoted in ppm relative to a tetramethylsilane internal standard, or by referencing on the chemical shift of the deuterated solvent.

General procedure for preparation of thiazolo[5,4-*b*]pyridines under thermal conditions.

Preparation of (6-nitrothiazolo[5,4-b]pyridin-2-yl)methyl pivalate (3c). A mixture of 2-chloro-3,5-dinitropyridine (1) (5.1 g, 25 mmol) and 2-amino-2-thioxoethylpivalate (2c) (8.8 g, 50 mmol) in sulfolane (50 mL) was heated to 100–110°C under a nitrogen atmosphere and stirred for 2 h. After allowing to cool to room temperature, the mixture was poured into EtOAc (150 mL), and the organic layer was washed with H_2O (3 × 200 mL) and brine (1 × 100 mL). The organic layer was dried ($MgSO_4$), filtered, and the solvent removed under vacuum to leave a crude oil. The oil was purified by filtration through a plug of silica eluting with EtOAc/hexanes (1:9–1:4) to give a solid (*ca*. 6–7g). The solid was then triturated with MeOH (*ca*. 20 mL) and filtered to give the desired product (2.17g). Further product was obtained by concentrating the filtrate under vacuum and purifying by column chromatography on silica gel using EtOAc/hexanes (0:1–1:4) as eluent to give a solid (1.1 g). The solid was triturated with MeOH to give further product (0.5g). Total yield 2.67 g (36%). ^{1}H NMR (400 MHz; $CDCl_3$) δ 9.46 (d, J = 2.4 Hz, 1H), 9.00 (d, J = 2.4 Hz, 1H), 5.54 (s, 2H), 1.32 (s, 9H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 177.4, 172.6, 163.6, 145.2, 143.1, 142.3, 125.1, 63.4, 38.9, 27.1; m/z = 296.5 (M + 1).

Ethyl 6-nitrothiazolo[5,4-b]pyridine-2-carboxylate (3a). ^{1}H NMR (400 MHz; $CDCl_3$) δ 9.59 (d, J = 2.4 Hz, 1H), 9.23 (d, J = 2.4 Hz, 1H), 4.62 (q, J = 7.0 Hz, 2H), 1.53 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 164.0, 163.2, 159.4, 145.5, 144.6, 143.5, 127.7, 64.1, 14.2.

2-Methyl-6-nitrothiazolo[5,4-b]pyridine (3b). ^{1}H NMR (400 MHz; d_6-DMSO) δ 9.38 (d, J = 2.3 Hz, 1H), 9.25 (d, J = 2.3 Hz, 1H), 2.91 (s, 3H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 172.4, 164.5, 145.7, 142.9, 141.5, 124.0, 21.4; m/z = 196.2 (M + 1).

2-(4-Methoxyphenoxymethyl)-6-nitrothiazolo[5,4-b]pyridine (3d). ^{1}H NMR (400 MHz; d_6-DMSO) δ 9.45 (d, J = 2.4 Hz, 1H), 9.21 (d, J = 2.4 Hz, 1H), 7.07–7.09 (m, 2H), 6.90–6.92 (m, 2H), 5.64 (s, 2H), 3.71 (s, 3H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 174.9, 163.7, 154.9, 151.4, 145.2, 142.9, 142.1, 124.9, 116.0, 114.8, 68.8, 55.6.

6-Nitro-2-(phenylthiomethyl)thiazolo[5,4-b]pyridine (3e). ^{1}H NMR (400 MHz; d_6-DMSO) δ 9.38 (d, J = 2.0 Hz, 1H), 9.09 (d, J = 2.0 Hz, 1H), 7.42–7.45 (m, 2H), 7.29–7.33 (m, 2H), 7.21–7.23 (m, 1H), 4.89 (s, 2H); ^{13}C NMR (100 MHz; d_6-DMSO) δ 175.7, 163.3, 144.8, 143.3, 142.2, 133.7, 129.3, 129.0, 127.0, 125.0, 35.6; m/z = 302.2 (M – 1).

2-(6-Nitrothiazolo[5,4-b]pyridin-2-yl)acetonitrile (3f). ^{1}H NMR (400 MHz; d_6-DMSO) δ 9.46 (d, J = 2.4 Hz, 1H), 9.27 (d, J = 2.4 Hz, 1H), 4.94 (s, 2H); ^{13}C NMR (100 MHz; d_6-DMSO) δ 165.9, 163.2, 144.4, 143.5, 142.7, 125.5, 115.9, 23.7; m/z = 219.0 (M – 1).

2-(tert-Butylsulfonylmethyl)-6-nitrothiazolo[5,4-b]pyridine (3g). ^{1}H NMR (400 MHz; d_6-DMSO) δ 9.41 (d, J = 2.4 Hz, 1H), 9.28 (d, J = 2.4 Hz, 1H), 5.35 (s, 2H), 1.42 (s, 9H); ^{13}C NMR (100 MHz; d_6-DMSO) δ 163.5, 163.3, 144.1, 143.4, 142.8, 125.8, 60.8, 51.7, 22.8; m/z = 316.3 (M + 1).

1-(6-Nitrothiazolo[5,4-b]pyridin-2-yl)ethyl pivalate (3h). ^{1}H NMR (400 MHz; d_6-DMSO) δ 9.45 (d, J = 2.4 Hz, 1H), 9.21 (d, J = 2.4 Hz, 1H), 6.16–6.21 (q, J = 6.6 Hz, 1H), 1.70 (d, J = 6.6 Hz, 3H), 1.24 (s, 9H); ^{13}C NMR (100 MHz; d_6-DMSO) δ 176.6, 176.3, 162.5, 144.6, 143.4, 142.5, 125.6, 70.0, 38.3, 26.7, 19.9; m/z = 310.4 (M + 1).

2-Benzhydryl-6-nitrothiazolo[5,4-b]pyridine (3i). ^{1}H NMR (400 MHz; d_6-DMSO) δ 9.40 (d, J = 2.0 Hz, 1H), 9.17 (d, J = 2.0 Hz, 1H), 7.37–7.43 (m, 11H), 7.31–7.33 (m, 2H), 6.29 (s, 1H); ^{13}C NMR (100 MHz; d_6-DMSO) δ 179.7, 164.0, 146.1, 144.2, 143.0, 141.6, 129.9, 129.8, 129.0, 128.5, 128.4, 126.2, 56.0; m/z = 348.2 (M + 1).

2-Cyclopropyl-6-nitrothiazolo[5,4-b]pyridine (3j). ^{1}H NMR (400 MHz; d_6-DMSO) δ 9.34 (d, J = 2.4 Hz, 1H), 8.97 (d, J = 2.4 Hz, 1H), 2.66–2.72 (m, 1H), 1.34–1.39 (m, 2H), 1.25–1.29 (m, 2H); ^{13}C NMR (100 MHz; d_6-DMSO) δ 179.2, 162.6, 145.2, 143.2, 141.1, 123.6, 15.8, 12.9; m/z = 222.1 (M + 1).

6-Nitro-2-phenylthiazolo[5,4-b]pyridine (3k). ^{1}H NMR (400 MHz; d_6-DMSO) δ 9.44 (d, J = 2.0 Hz, 1H), 9.22 (d, J = 2.0 Hz, 1H), 8.18–8.21 (m, 2H), 7.65–7.68 (m, 3H); ^{13}C NMR (100 MHz; d_6-DMSO) δ 158.3, 147.9, 142.0, 141.9, 141.5, 132.6, 129.4, 129.4, 127.5, 124.8; m/z = 259.0 (M + 1).

6-Nitro-2-(thiophen-2-yl)thiazolo[5,4-b]pyridine (3l). ^{1}H NMR (400 MHz; $CDCl_3$) δ 9.37 (d, J = 2.0 Hz, 1H), 8.95 (d, J = 2.0 Hz, 1H), 7.78–7.79 (m, 1H), 7.66–7.67 (m, 1H), 7.22–7.23 (m, 1H); ^{13}C NMR (100 MHz; d_6-DMSO) δ 146.4, 141.7, 136.1, 132.0, 131.0, 128.7, 124.0; m/z = 263.0 (M – 1).

6-Nitro-2-(pyridin-3-yl)thiazolo[5,4-b]pyridine (3m). ^{1}H NMR (400 MHz; d_6-DMSO) δ 9.47 (d, J = 2.4 Hz, 1H), 9.36 (dd, J = 2.0 and 0.8 Hz, 1H), 9.27 (d, J = 2.4 Hz, 1H), 8.85 (dd, J = 4.8 and 1.5 Hz, 1H), 8.55 (ddd, J = 8.0, 2.0 and 1.5 Hz, 1H), 7.69 (ddd, J = 8.0, 4.8 and 0.8 Hz, 1H); ^{13}C NMR (100 MHz; d_6-DMSO) δ 154.1, 149.2, 143.6, 136.2, 129.1, 126.4, 125.6, 100.5; m/z = 259.2 (M + 1).

6-Nitrothiazolo[5,4-b]pyridine-2-amine (3n). ^{1}H NMR (400 MHz; d_6-DMSO) δ 8.93 (d, J = 2.5 Hz, 1H), 8.34 (br. s, 2H), 8.26 (d, J = 2.5 Hz, 1H); ^{13}C NMR (100 MHz; d_6-DMSO) δ 168.0, 161.8, 147.0, 143.3, 136.5, 116.7; m/z = 195.1 (M – 1).

6-Nitrothiazolo[5,4-b]pyridine (3o) [22]. A mixture of 2-chloro-3,5-dinitropyridine (**1**) (8.0 g, 39 mmol) and *N*,*N*-dimethylthioformamide (14.5 mL, 178 mmol) was heated at 60°C for 3 h (a yellow precipitate was formed). Xylene (20 mL) was added, and the mixture was heated to reflux for 4 h, then stirred at room temperature for 18 h. The mixture was diluted with EtOH (12 mL), filtered, and the solid recrystallized from EtOH to give the product (800 mg, 11%) as a solid. ^{1}H NMR (400 MHz; d_6-DMSO) δ 9.82 (s, 1H), 9.49 (d, J = 2.4 Hz, 1H), 9.27 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz; d_6-DMSO) δ 162.4, 161.8, 144.7, 143.1, 142.6, 125.8; m/z = 182.2 (M + 1).

6-Nitro-2-piperidin-1-yl-thiazolo[5,4-b]pyridine (12). ^{1}H NMR (400 MHz; d_6-DMSO) δ 8.94 (d, J = 2.3 Hz, 1H), 8.34 (d, J = 2.3 Hz, 1H), 3.66–3.70 (m, 4H), 1.61–1.66 (m, 6H); ^{13}C NMR (100 MHz; d_6-DMSO) δ 166.7, 159.5, 145.3, 141.9, 134.8, 115.7, 23.3, 21.9; m/z = 264.8 (M + 1). Separately, 6-nitrothiazolo[5,4-*b*]pyridin-2-amine (**3n**) (13 mg, 6%) was also isolated.

General procedure for reactions using microwave-assisted synthesis.

Preparation of 6-nitrothiazolo[5,4-b]pyridine (3o). A 5-mL microwave vial was charged with 2-chloro-3,5-dinitropyridine (**1**) (0.41 g, 2.0 mmol), *N*,*N*-dimethylthioformamide (0.69 mL, 8.0 mmol), and sulfolane (2 mL). The mixture was heated under microwave irradiation with a target temperature of 110°C (CARE: the reaction displayed a significant exotherm on heating and reached 130°C within 25 s). After 2 min the mixture had cooled to 110°C, and heating was continued at this temperature for 40 min. After cooling to room temperature, the mixture was diluted with MeOH (5 mL) and EtOAc (60 mL) and then washed with brine (50 mL, 3 × 20 mL) and saturated $NaHCO_3$ (20 mL). The organic layer was dried (Na_2SO_4), filtered, and the solvent removed under vacuum to leave a crude solid (1.08 g). Purification by column chromatography on silica gel (dry-loaded on 4.5 g of silica) using EtOAc/hexanes (1:9–3:2) as eluent gave the product (183 mg, 50%) as a solid.

2-Methylthiazolo[5,4-b]pyridine (5a). ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.54 (d, J = 4.6 Hz, 1H), 8.19 (d, J = 8.2 Hz, 1H), 7.42 (dd, J = 8.2, 4.6 Hz, 1H), 2.87 (s, 3H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 162.3, 159.2, 146.7, 146.6, 129.4, 121.2, 21.1; m/z = 151.2 (M + 1).

2-Phenylthiazolo[5,4-b]pyridine (5b). ^{1}H NMR (400 MHz; d_6-DMSO) δ 8.64 (dd, J = 4.5, 1.5 Hz, 1H), 8.46 (dd, J = 8.2, 1.5 Hz, 1H), 8.15–8.12 (m, 2H), 7.64–7.61 (m, 4H); ^{13}C NMR (100 MHz; d_6-DMSO) δ 167.5, 157.5, 147.6, 146.5, 135.5, 132.0, 130.2, 129.4, 127.3, 122.2; m/z = 213.4 (M + 1).

2-Aminothiazolo[5,4-b]pyridine (5c). ^{1}H NMR (400 MHz; d_6-DMSO) δ 8.09 (dd, J = 1.6, 4.6 Hz, 1H), 7.79 (br. s, 2H), 7.62 (dd, J = 1.6, 7.9 Hz, 1H), 7.24 (dd, J = 4.6, 7.9 Hz, 1H); ^{13}C NMR (100 MHz; d_6-DMSO) δ 165.5, 155.4, 146.8, 141.6, 123.4, 121.1; m/z = 152.2 (M + 1).

Thiazolo[5,4-b]pyridine (5d). ^{1}H NMR (400 MHz; $CDCl_3$) δ 9.18 (s, 1H), 8.66 (m, H), 8.37 (m, 1H), 7.48 (dd, J = 8.3, 4.6 Hz, 1H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 157.4, 155.4, 147.9, 145.8, 131.0, 121.3; m/z = 137.2 (M + 1).

6-Chlorothiazolo[5,4-b]pyridin-2-amine (7a). ^{1}H NMR (400 MHz; d_6-DMSO) δ 8.12 (d, J = 2.2 Hz, 1H), 8.06 (br. s, 2H), 7.74 (d, J = 2.2 Hz, 1H); ^{13}C NMR (100 MHz; d_6-DMSO) δ 167.4, 153.8, 147.9, 139.4, 128.6, 122.8; m/z = 186.2 (M + 1 for ^{35}Cl).

6-Bromothiazolo[5,4-b]pyridin-2-amine (7b). ^{1}H NMR (400 MHz; d_6-DMSO) δ 8.19 (d, J = 2.1 Hz, 1H), 8.06 (br. s, 2H), 7.86 (d, J = 2.1 Hz, 1H); ^{13}C NMR (100 MHz; d_6-DMSO) δ 167.1, 154.1, 148.3, 141.5, 125.4, 117.1; m/z = 230.1/232.1 (M + 1).

6-Iodothiazolo[5,4-b]pyridin-2-amine (7c). ^{1}H NMR (400 MHz; d_6-DMSO) δ 8.27 (d, J = 1.9 Hz, 1H), 8.01 (br. s, 2H), 7.97 (d, J = 1.9 Hz, 1H); ^{13}C NMR (100 MHz; d_6-DMSO) δ 166.5, 154.5, 148.6, 146.4, 130.8, 90.1; m/z = 277.9 (M + 1).

6-Methylthiazolo[5,4-b]pyridin-2-amine (7d). ^{1}H NMR (400 MHz; d_6-DMSO) δ 7.94 (d, J = 1.2 Hz, 1H), 7.74 (br. s, 2H), 7.45 (d, J = 1.2 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz; d_6-DMSO) δ 165.8, 152.4, 146.7, 142.0, 130.4, 124.0, 17.8; m/z = 166.3 (M + 1).

5-Methoxythiazolo[5,4-b]pyridin-2-amine (7e). ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.69 (d, J = 8.6 Hz, 1H), 6.72 (d, J = 8.6 Hz, 1H), 5.52 (br. s, 1H), 5.39 (br. s, 1H), 3.94 (s, 3H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 163.3, 160.6, 151.4, 140.2, 128.7, 108.8, 54.0; m/z = 182.2 (M + 1).

2-Aminothiazolo[4,5-c]pyridine (9). ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.55 (d, J = 0.9 Hz, 1H), 8.13 (d, J = 5.4 Hz, 1H), 7.79 (br. s, 2H), 7.75 (dd, J = 0.9, 5.4 Hz, 1H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 167.0, 149.8, 140.4, 139.5, 138.4, 116.3; m/z = 152.0 (M + 1).

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