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A concise synthesis of 7-chloro-2-methylsulfanyl-thiazolo-[4,5-*b*]pyridine-6-carbonitrile, a versatile intermediate for substituted 6-cyanothiazolopyridines

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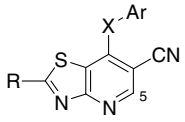
Abstract—We describe the development of a simple route for the preparation of the novel title intermediate thiazolo[4,5-*b*]pyridine. This intermediate was particularly well suited for derivatization at the C-2 and C-7 positions of the bicyclic ring system.

In support of kinase target directed projects we sought to synthesize substituted 6-cyanothiazolopyridines devoid of substitution on the C-5 position, **1**. Surprisingly, there are no published literature procedures for making such compounds. Furthermore, there are few examples of 6-cyanothiazolo[4,5-*b*]pyridines with substitution on the C-5 position. Common synthetic routes involve pyridine ring formation through either intramolecular cyclization onto one of the cyano groups of a malonitrile derivative leaving an amine on the C-5 position,[1] or reaction of 2-thiazolin-4-ones with 2-cyanoacryl amides and thioamides resulting in, respectively, oxygen or sulfur on the C-5 position.[2] In either case removal of the C-5 substituent, if possible, would lengthen the synthetic route. More importantly for our purposes, the nature of these convergent syntheses would limit SAR development around the C-2 and C-7 positions. As a consequence we desired an alternative route.



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One possible approach would be to build the thiazolo ring system by the method outlined in Scheme 1. Potassium methyl cyanoiminodithiocarbonate, **2**, underwent alkylation and cyclization with methyl chloroacetate to generate the thiazole ring, **3**.[3] Condensation of **3** with DMF dimethylacetal gave the amidine **4**. Displacement of the dimethyl amino group using lithium acetonitrile, a sequence used for the synthesis of quinoline-3-carbonitriles,[4] proved to be a low yielding reaction. We subsequently abandoned this route after several attempts to cyclize **5** to the fused thiazolopyridine ring system, **6**, gave extensive decomposition under both acidic and basic conditions. The only appreciable product isolated from these reactions was the precursor **3**.

As an alternate route, we contemplated incorporating the nitrile group as a substituent at the C-5 position of the thiazole ring as depicted retrosynthetically in Scheme 2. This had proven successful both in the literature and in our hands for making the ethyl ester analog, **12b**, of our desired intermediate, **12a**.[5] The most direct route for synthesizing the thiazole ring **10a** would require using the previously unpublished alkylating agent 1-chloro-3-cyanoacetone. While the synthesis of this reagent from cyanoacetone offers one potential methodology, the instability of cyanoacetone could be problematic.[6] To circumvent polymerization, cyanoacetone can be handled as the more stable enolate salt generated from ring-opening of 5-methylisoxazole.[7] With this as precedent, we felt a *t*-butylcarboxylate derivative of 1-chloro-3-cyanoacetone, **7**, would be more readily available (Scheme 3). The intermediate **7**, formed by acylation of *t*-butyl cyanoacetate, was cleanly isolated by acid–base extraction.[8] Alkylation with **7** on the sulfur anion **2** followed by cyclization gave the thiazole ring,

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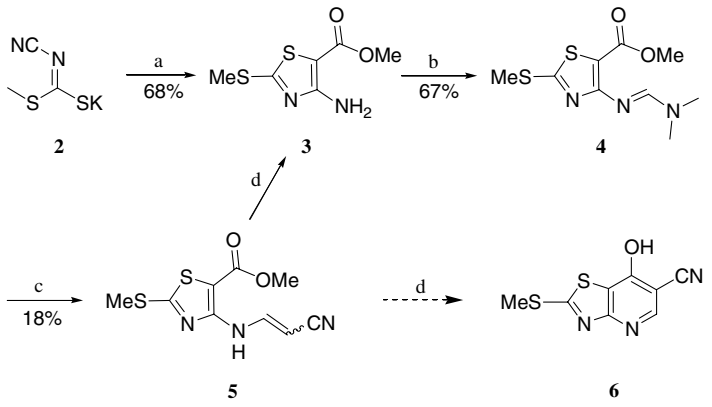
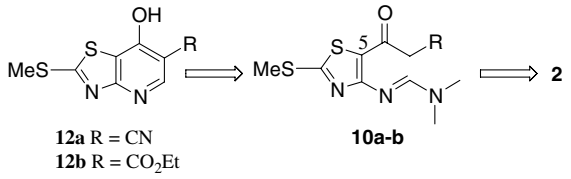
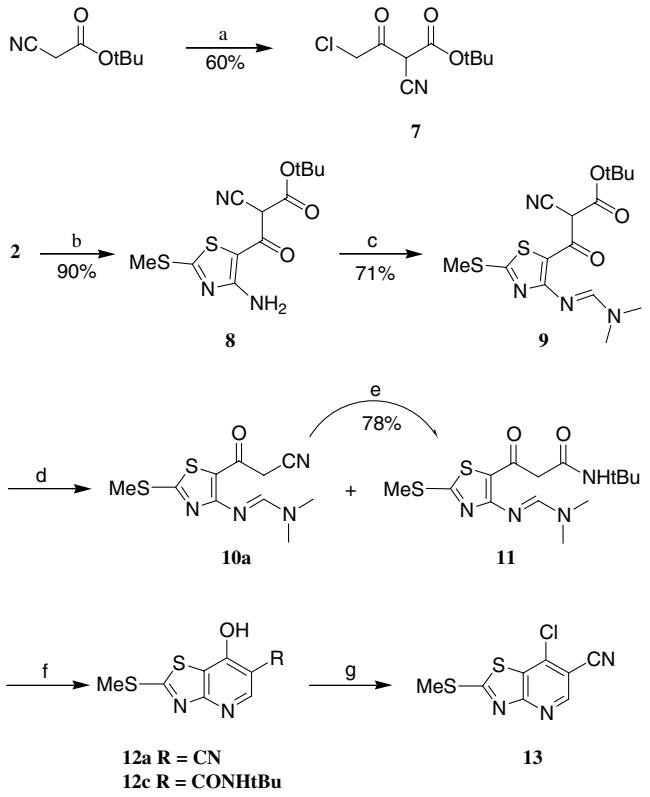


Scheme 1. Reagents and conditions: (a) $ClCH_2CO_2Me$, acetone, Et_3N; (b) DMF–DMA, DMF; (c) (1) LiHMDS, CH_3CN, THF; (2) **4**; (d) AcOH or Et_3N, DMF or MeONa, MeOH.



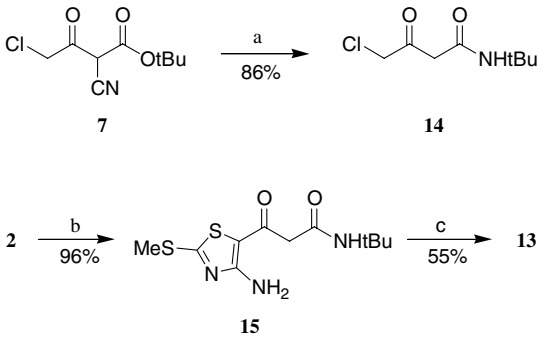
Scheme 2. Retrosynthetic analysis.



Scheme 3. Reagents and conditions: (a) NaH, THF, chloroacetyl chloride; (b) **7**, acetone; (c) DMF-DMA, DMF, 100 °C; (d) 1:1 TFA, DCM; (e) 1:1 TFA, DCM, *t*-BuOH; (f) IPA reflux; (g) $SOCl_2$, DMF, 21% overall yield for steps d–g.

8. Treatment with DMF dimethylacetal led to the amidine **9**. TFA mediated decarboxylation gave the expected product **10a** along with varying amounts of the β-ketoamide **11**, the product of a Ritter type reaction. Consistent with this mechanism, the addition of excess *t*-butanol to the original reaction conditions completely converted isolated **10a** to **11**. Attempts to cyclize **10a** by treatment with the NaH conditions successfully employed to cyclize the beta-ketoester, **10b**, to the ester derivative **12b**, led to decomposition. Instead, **10a** was thermally cyclized in IPA to provide **12a**. It was subsequently found that isolated intermediates **10a** and **11** or a crude mixture thereof could be taken forward to product, **12a** and/or **12c**. Finally, the C-7 alcohol was converted over to the chloride **13** by Vilsmeier–Haack protocol. Fortuitously, these conditions also convert the *t*-butylamide group in **12c** to the nitrile, eliminating the need for harsher reaction conditions. Intermediate **8** was routinely carried through to compound **13** with only extractive isolation of the intermediates along the way and without noticeably diminishing the yield. The overall yield, however, was only 8% and thus presented a challenge for large-scale production.

The overall yield was improved by moving the decarboxylation step up in the synthetic sequence (Scheme 4). In the presence of excess *t*-butanol, the acid mediated decarboxylation and formal *t*-butyl group transfer converted **7** to the *t*-butylamide **14**. Our initial concern regarding the stability of 1-chloro-3-cyanoacetone was

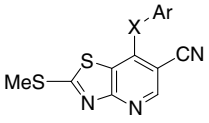


Scheme 4. Reagents and conditions: (a) 95%TFA(aq):DCM (1:1), excess *t*-BuOH; (b) **14**, acetone; (c) (1) DMF-DMA, DMF, 80 °C; (2) $SOCl_2$, 0 °C to rt, 2 h.

not an issue with the synthon **14**. Alkylation and cyclization of **2** with **14** proceeded uneventfully to give **15** in excellent yield. Treatment of **15** with DMF dimethylacetal at elevated temperatures led directly to intermediate **12c**. In lieu of isolation, the reaction was cooled and treated with thionyl chloride to directly give intermediate **13**.[9] This shortened route was more conducive to scale-up, improved the overall yield to 27%, and was carried through without chromatography.

The differentially activated intermediate **13** was sequentially derivatized on C-7 and C-2 to give the compounds in Tables 1 and 2, respectively. The synthesis of these compounds was performed as outlined in Scheme 5 without optimization for any given analog. First, the C-7 chloride of **13** was displaced by nucleophiles such as anilines, phenols, and thiophenols to provide **16** (Table 1).[10] The sterically more congested nucleophiles required the addition of base and correspondingly gave lower yields; for instance **16a–b** versus **16c–d**. The

Table 1. Substitution on C-7 of thiazolo[4,5-*b*]pyridine-6-carbonitrile



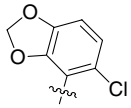
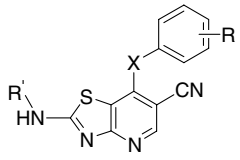
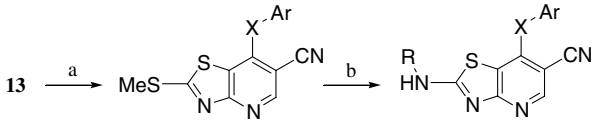
Compound	Ar	X	Yield (%)
16a	3-Cl, 4-FPh	NH	70
16b	3-HCCPh	NH	67
16c	2,4-DiCl, 5-MeOPh	NH	53
16d		NH	45
16e	3-CF_3OPh	O	76
16f	2,4-DiClPh	O	52
16g	3-BrPh	S	73
16h	2-Cl, 4-FPh	S	40

Table 2. Substitution on C-2 of thiazolo[4,5-*b*]pyridine-6-carbonitrile



Compound	R	X	R′	Yield (%)[a]
17a	3-Cl, 4-F	NH	$(CH_2)_3$-morpholin-4-yl	4
17b	3-Cl, 4-F	NH	6-Cl-pyridin-3-yl	16
17c	3-Cl, 4-F	NH	4-(CH_2-morpholin-4-yl)Ph	27
17d	3-Cl, 4-F	NH	6-MeO-pyridin-3-yl	50
17e	3-CCH	NH	$(CH_2)_2$-morpholin-4-yl	10
17f	2,4-DiCl, 5-OMe	NH	4-(CH_2-morpholin-4-yl)Ph	19
17g	2,4-DiCl	O	4-OCH_2-(1-CH_3)-piperidin-3-yl-Ph	29
17h	2-Cl, 4-F	S	4-OCH_2-(1-CH_3)-piperidin-3-yl-Ph	38

[a] Overall isolated yield from methylsulfanyl intermediate, **16**; 2 steps.



Scheme 5. Reagents and conditions: (a) ArXH, IPA, 120–160 °C (sealed reactor) or ArXH, LHMDS, DMF; (b) (1) MCPBA, $CHCl_3$, $NaHCO_3$(aq); (2) RNH_2, DCM.

methyl mercapto group of **16** was then oxidized with MCPBA to activate it for subsequent displacement with amines, giving the products **17** (Table 2). Oxidation with MCPBA generally gave a mixture of sulfoxide and sulfone intermediates, with the sulfoxide as the major product. When adding anilines in the subsequent step the sulfoxides proved to be kinetically more reactive than the sulfones. Complete reaction of the sulfoxides, based on LCMS monitoring, was routinely seen prior to consumption of the sulfones. Displacements with aliphatic amines were always low yielding (**17a,e**) with hydrolysis the major product of the reaction.

In summary, we have developed a concise route for synthesis of the versatile intermediate **13**. Masking the cyano group as a *t*-butylamide provided a convenient means of improving the yield and shortening the synthetic route. The orthogonal activity of the C-2 and C-7 positions on **13** allowed for selective substitution at these two sites on the bicyclic ring.

Acknowledgements

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References and notes

1. Artyomov, V. A.; Ivanov, V. L.; Shestopalov, A. M.; Litvinov, V. P. *Tetrahedron* **1997**, *53*, 13351–13360.
2. Ismail, N. A.; Khalifa, F. A.; Fekry, R. M.; Abdel Azim, Y. N. *Phosphorus, Sulfur Silicon Relat. Elem.* **1992**, *66*, 29–35.
3. Leysen, D. C.; Haemers, A.; Bollaert, W. *J. Heterocycl. Chem.* **1984**, *21*, 1361–1366.
4. Wissner, A.; Berger, D. M.; Boschelli, D. H.; Floyd, M. B., Jr.; Greenberger, L. M.; Gruber, B. C.; Johnson, B. D.; Mamuya, N.; Nilakantan, R.; Reich, M. F.; Shen, R.; Tsou, H.; Upeslacis, E.; Wang, Y. F.; Wu, F.; Zhang, N. *J. Med. Chem.* **2000**, *43*, 3244–3256.
5. Hayakawa, I.; Tanaka, Y. *Heterocycles* **1984**, *22*, 1697–1700.
6. Dahn, H.; Hauth, H. *Helv. Chim. Acta* **1964**, *47*, 1424–1428.
7. (a) Claisen, L. *Chem. Ber.* **1909**, *42*, 59–68; (b) Sauers, R. R.; Van Arnum, S. D. *J. Heterocycl. Chem.* **2003**, *40*, 655–658.
8. (a) Benary, E. *Chem. Ber.* **1908**, *41*, 2399–2411; (b) Boosen, K. J. *Helv. Chim. Acta* **1977**, *60*, 1256–1261.
9. *Representative synthesis*: Example **13**: Commercially available **2** (21.3 g, 125 mmol) was added to a solution of **14** (23.9 g, 125 mmol) at 0 °C in acetone (300 mL). The reaction was stirred for 1 h at 0 °C and then at rt for 18 h.

The solvent was removed under vacuum and the product extracted into EtOAc from water. The combined organic extracts were dried over $MgSO_4$, then filtered and evaporated to give **15** (34.6 g) as a tan solid. The material was used in the next step without further purification. ^{1}H NMR (DMSO) δ 7.73 (br s, 3H), 3.35 (s, 2H), 2.68 (s, 3H), 1.27 (s, 9H). MS (*m*/*z*) 288 (M+H).

A mixture of **15** (34.6 g, 120 mmol), DMF-dimethyl acetal (34.0 mL, 240 mmol, 94% purity) and DMF (200 mL) were combined and heated to 80 °C for 90 min. The conversion to the cyclized intermediate, **12c**, was confirmed by LCMS (MS (*m*/*z*) 298 (M+H). The mixture was then cooled to 0 °C and $SOCl_2$ added dropwise (44 mL, 600 mmol). The reaction mixture was stirred for 2 h at ambient temperature, then cooled back down to 0 °C prior to dropwise quenching with H_2O. The resulting brown solid was collected by filtration and subsequently washed with water and MeOH to provide a tan solid (16.1 g, 55%). ^{1}H NMR (300 MHz; DMSO-d_6) δ 9.09 (s, 1H), 2.91 (s, 3H). ^{13}C NMR (300 MHz; DMSO-d_6) δ 179.3, 165.1, 151.9, 138.4, 128.9, 114.5, 104.5, 16.2. MS (*m*/*z*) 242, 244 (M+H), 264, 266 (M+Na).

10. All compounds in Tables 1 and 2 were in agreement with their MS, LCMS and NMR spectra.