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Syntheses of 4- and 6-substituted thiazolo[4,5-*c*]pyridines

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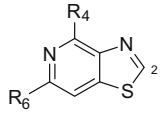
ABSTRACT

A general synthetic approach to 4,6-substituted thiazole[4,5-*c*]pyridines, involving a novel one-pot thiol deprotection-cyclization key step, is described.

Heterocycles continue to play an increasingly important role in medicinal chemistry. For example, Haginoya et al. described a synthesis of thiazole[4,5-*c*]pyridine **1a**, and its application as an intermediate in the construction of factor Xa (fXa) inhibitors.[1]



1a; R_4=R_6=H

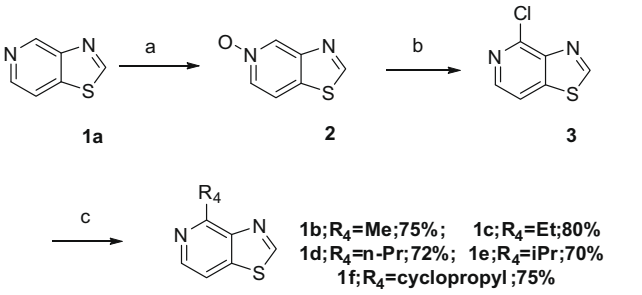
Having incorporated **1a** into a successful medicinal chemistry program we wanted to further expand the SAR of our active entities by incorporating alkyl groups at the 4- and 6-positions of the pyridylthiazole ring. In the preceding paper a general synthesis of 4-alkyl mono-substituted derivatives is described (Scheme 1).[2]

Treatment of compound **1a** with mCPBA provided the N-oxide **2** in good yield. Subsequent exposure to refluxing phosphorus oxychloride provided the corresponding 4-substituted chloride **3**, exclusively. Finally, alkyl groups were introduced using an appropriate triakylaluminum in the presence of tetrakis(triphenylphosphine)palladium(0) in acceptable yields (**1b–1f**; 70–80%). Surprisingly, we could not find any literature reference to these relatively simple compounds.

To progress the project further and expand on the range of this class of heterocycle by introducing functionality at the 6-position, we decided to devise and execute the syntheses of pyridylthiazoles **4**, **5**, and **6** (Diagram 1). Analogue **4** is the 6-methyl homologue of **1b**. Compound **5** should lead to the 6-positional analogues of **1b–1f**, whereas, the chloride **6**, provides the flexibility to obtain the corresponding 6-methyl analogues of **1c–1f**.

We based our synthetic strategy toward compounds **4–6** around the formylation-condensation final step in Haginoya's synthesis of **1a** (Scheme 2).[1] When exposed to refluxing formic acid, the amino thiol **7** proceeded smoothly to the pyridylthiazole **1a**, presumably via an intermediate, the vicinally substituted thiolformamide **8**, although it was never observed during the course of the reaction.

We reasoned if we could generate the same disposition of functional groups, in situ, from the cleavage of a suitable thiol-protecting group in an acid media, then ring closure would follow. This would avoid problems commonly associated with aryl mercaptans (e.g., oxidation to the disulfide). To this end, we were particularly attracted to the *p*-methoxybenzyl group (PMB) **9** which could release the thiol **10** in refluxing TFA.[3] Subsequent dehydration would thus generate the desired substituted pyridyl thiazole **11**.



Scheme 1. Reagents: (a) mCPBA, CH_2Cl_2, 95%; (b) $POCl_3$, 50%; (c) R_3Al, $Pd(PPh_3)_4$, AcOH.

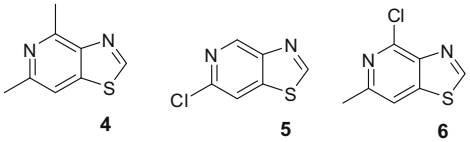


Diagram 1. 6-Substituted pyridylthiazoles **4**, **5** and **6**.

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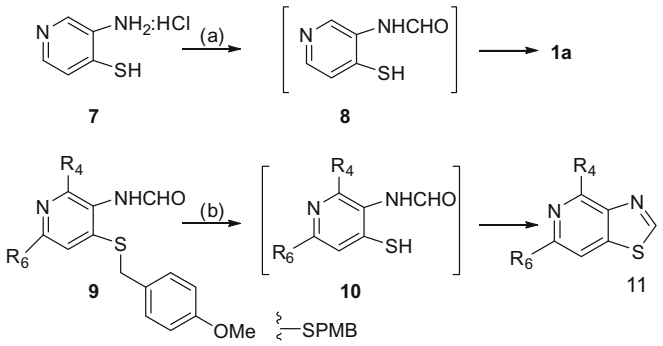
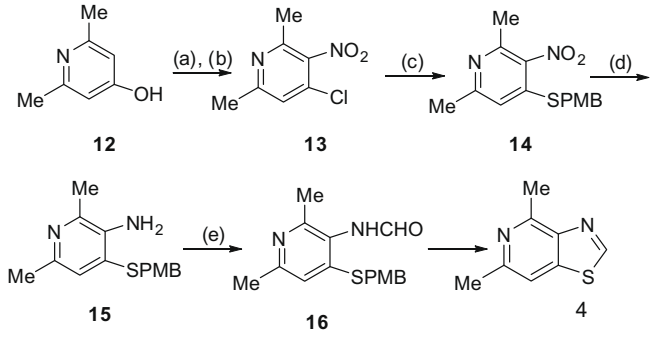


Scheme 2. Reagents: (a) HCO_2H, reflux, 90%; (b) TFA, reflux.

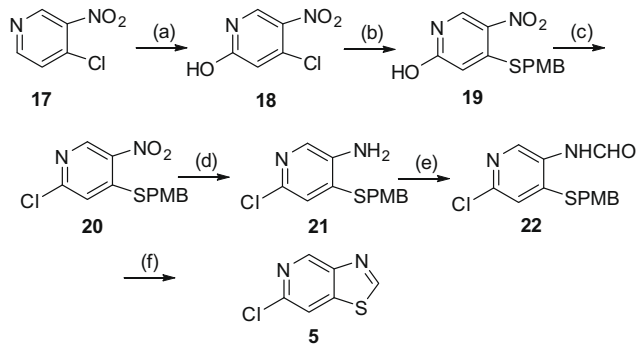


Scheme 3. Reagents: (a) HNO_3, H_2SO_4, 93%; (b) $POCl_3$, DMF, toluene, 69%; (c) 4-methoxy-α-toluenethiol, NaH, THF, 96%; (d) $SnCl_2/2H_2O$, HCl, Et_2O, H_2O, 100%; (e) HCO_2H, reflux, followed by TFA, $AgBF_4$, 100%.

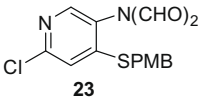
With this in mind, our synthesis of the, 4,6-dimethylpyridyl thiazole **4** is shown in Scheme 3. Thus, commercially available 2,6-dimethyl-4-hydroxypyridine **12** was converted, via a two-step process, to the nitrate **13**, using previously reported procedures.[4,5] The protected thiol functionality was introduced, in good isolated yield, by nucleophilic chloro displacement with the anion generated from 4-methoxybenzylthiol at room temperature. Reduction of the nitro **14** was achieved, efficiently, using tin(II) chloride dihydrate. Formylation of the resulting amine **15** proceeded smoothly to the formamide **16**, in refluxing, neat, formic acid. The reaction was generally complete within 3 h. Rather than isolating the amide **16**, TFA (threefold volume relative to formic acid) was added to the mixture, and heating resumed for a further 24 h. LCMS analysis revealed an approximate 50% conversion to the desired pyridylthiazole **4**, which could easily be separated from the starting material **16** using silica gel column chromatography. Similar results were achieved by refluxing in neat TFA in the absence or presence of *o*-cresol.[6] Satisfactory reaction conditions were finally achieved by adding an equal volume of TFA to **16** in the formylation media and adding silver tetrafluoroborate[7] (20 mol %) at ambient temperature. The one-pot deprotection and ring closure were complete, without warming, within 1 h, providing an excellent yield of the desired bicycle **4**.[8]

With the fundamental chemistry in place, we next turned our attention to the 6-chloro intermediate **5** (Scheme 4).

Our starting material **18** with the desired substitution pattern for the synthesis of the chloride **5** was obtained from inexpensive 4-chloro-3-nitropyridine **17** via hydroperoxide vicarious nucleophilic substitution.[9] As shown previously (Scheme 3), the chloride **18** was transformed into thioether **19**, followed by conversion of the 2-pyridone functionality to the chloropyridine **20** with phosphorous oxychloride. Reduction of the nitro group proceeded smoothly to the corresponding amine **21**. When exposed to refluxing formic acid, the amine **21** largely decomposed. However, treatment with cold acetic-formic anhydride (AFA) generated the desired formamide **22**, usually in less than 1 h. It was necessary to manipulate this reaction as soon as the reaction was determined to be complete. If allowed to warm to room temperature overnight, the formamide **22** proceeded to the diformyl imide **23**. Following work-up, the crude formamide **22** is treated with silver tetrafluoroborate in TFA to give the pyridylthiazole **5**.[10]



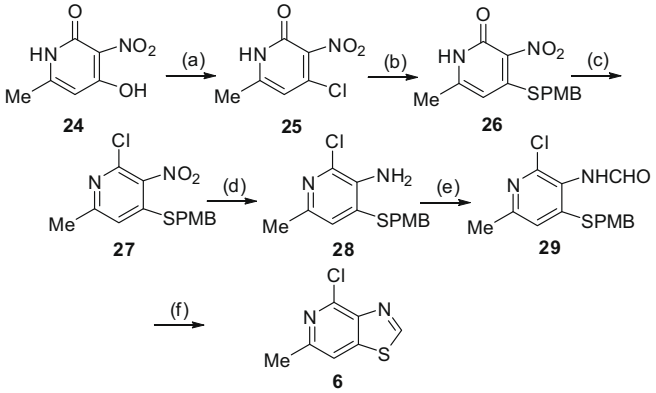
Scheme 4. Reagents and conditions: (a) KO^{t}Bu, ^{t}BuOOH, NH_3, THF 91%; (b) 4-methoxy-α-toluenethiol, NaH, THF, 91%; (c) $POCl_3$, reflux, 100%; (d) $SnCl_2/2H_2O$, HCl, Et_2O, H_2O, 97%; (e) AFA, ice bath; (f) $AgBF_4$, TFA, 61% from **21**.



The synthesis of our last example, compound **6**, is shown in Scheme 5. Beginning with commercially available 4-hydroxy-6-methyl-3-nitro-2-pyridone **24**, the 4-hydroxyl was transformed selectively into the chloride **25** by formation of the cyclohexylamine salt and subsequent treatment with phosphoryl chloride.[11]

The protected thiol functional group was installed as previously described, albeit in lower yield. The resulting sulfide **26** was exposed to additional phosphorous oxychloride to provide the 2-chloropyridine **27**. Reduction and formylation of the amine **28** provided the formamide **29**, which was treated, in crude form, with silver tetrafluoroborate in TFA to give the pure 4-chloro-6-methylpyridylthiazole **6** following silica gel column chromatography.[12]

In summary, a general synthetic approach to 4- and 6-mono and di-substituted thiazole[4,5-*c*]pyridines was successfully executed. We hope that this methodology will be helpful in the construction



Scheme 5. Reagents and conditions: (a) cyclohexylamine, MeOH, room temperature, then $POCl_3$, room temperature, 80 h, 81%; (b) 4-methoxy-α-toluenethiol, NaH (2.2 equiv), THF, 53%; (c) $POCl_3$, reflux, 75%; (d) $SnCl_2/2H_2O$, HCl, Et_2O, H_2O, 100%; (e) AFA, ice bath; (f) $AgBF_4$, TFA, 45% from **28**.

of other thiazole-containing systems. The application of pyridylthiazoles **4**, **5**, and **6** in the preparation of biologically active molecules will be presented elsewhere.

References and notes

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8. *One-pot deprotection-cyclization with TFA-formic acid*. A solution of the amine **15** (4.00 g; 14.6 mmol) in formic acid (40 ml) was heated to reflux, under an atmosphere of nitrogen, for 2 h. After cooling, TFA (40 ml) was added followed by silver tetrafluoroborate (0.56 g; 2.9 mmol) and the resulting mixture was stirred at room temperature for 1 h. The volatiles were removed under reduced pressure and the residue partitioned between CH_2Cl_2 and satd aq $NaHCO_3$. The aqueous phase was separated and further extracted with CH_2Cl_2 ($\times 3$). The combined organic phases were dried ($MgSO_4$) and the solvent was removed in vacuo. The crude reaction product was purified by silica gel column chromatography using EtOAc/hexanes (2:3) as an eluent to give the desired pyridylthiazole **4** (2.39 g; 100%), as a light-brown solid. Data for compound **4** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.88 (1H, s), 7.55 (1H, s), 2.97 (3H, s), 2.64 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.90, 152.50, 152.21, 146.72, 144.33, 113.30, 24.41, 21.48. HRMS calcd for $C_8H_9{}^{35}ClN_3S$ $[M+H]^+$: 165.0486, found 165.0481.
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10. *Data for compound* **5**. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.53 (1H, s), 9.19 (1H, d, J = 2 Hz), 8.43 (1H, d, J = 2 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.63, 149.36, 145.21, 144.69, 144.32, 117.62. HRMS calcd for $C_8H_7{}^{35}ClN_3S$ $[M+H+ACN]^+$: 212.00492, found 212.00496.
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12. *Data for compound* **6**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.48 (1H, s), 8.10 (1H, q, J = 2 Hz), 2.58 (1H, d, J = 2 Hz); HRMS calcd for $C_7H_5{}^{35}ClN_2S$ $[M+H]^+$: 184.99347, found 184.99355.