Tetrahedron Letters 51 (2010) 2797–2799

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

# Novel methods to functionalize thiazolo[4,5-*c*]pyridines

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ARTICLE INFO

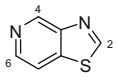
*Article history:*
Received 16 February 2010
Revised 3 March 2010
Accepted 16 March 2010
Available online 21 March 2010

ABSTRACT

Novel substituted thiazolo[4,5-*c*]pyridines have been synthesized in good yields from unsubstituted thiazolo[4,5-*c*]pyridine using direct C–H coupling reactions and N-oxide rearrangement chemistry.



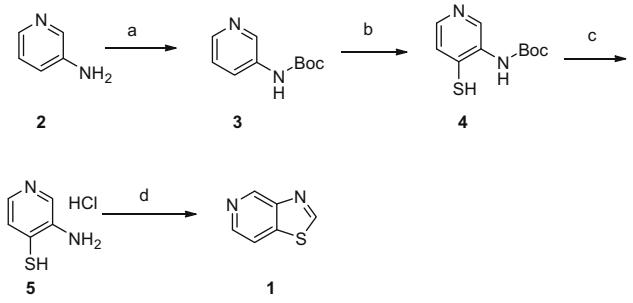
The use of heterocycles in medicinal chemistry has grown significantly in the past 20 years. Therefore, novel heterocycles that can be readily functionalized are highly sought after by medicinal chemists. This Letter will describe the synthesis of a series of functionalized thiazole[4,5-*c*]pyridine analogs that to the best of our knowledge have not been previously reported in the literature. These cores hold significant interest since similar core structures have been found to be present in kinase inhibitors as well as numerous other biological relevant compounds.[1]



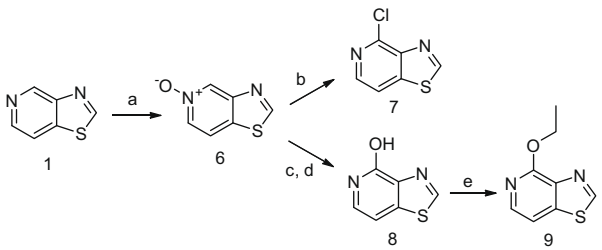
**1**

The synthesis of thiazolo[4,5-*c*]pyridine (**1**) has been previously reported in the literature.[2] Since our interests lay in the functionalizations of this ring system at the 2-, 4-, and 6-positions, it was desirable to modify the literature procedure in order to have access to multigram quantities of compound **5**, a versatile intermediate for further transformations (Scheme 1). The synthesis began with the protection of 3-aminopyridine (**2**) with a Boc group using sodium hexamethyldisilazide as a base (Scheme 1). The use of triethylamine, Hunig's base or DMAP in this reaction provided lower yields of the desired product due to competing reactions between the pyridine nitrogen and the 3-amino group. Compound **3** was treated with two equivalents of *n*-BuLi and then quenched with elemental sulfur to provide compound **4**. The removal of the Boc group was achieved by treatment of a solution of **4** in acetic acid with 4 M HCl dioxane. The product could be easily filtered at this stage to provide the hydrochloride salt of **5** or cyclized to the corresponding pyridylthiazole **1** by treatment with refluxing formic acid. Using this chemistry, multigram quantities of compounds **1** and **5** could be synthesized and used for further transformation.

It is known that the treatment of N-oxides of pyridine with either phosphorus oxychloride or acetic anhydride at high temperatures can provide rearrangement products.[3] We envisioned that this chemistry could be used on compound **1** to provide substitution at the 4- or 6-position. Treatment of compound **1** with *m*-CPBA provided the N-oxide **6** which was treated with refluxing phosphorus oxychloride to provide a good yield of the corresponding chloride **7** (Scheme 2).[4] Treatment of the N-oxide **6** with refluxing



**Scheme 1.** Synthesis of thiazole[4,5-*c*]pyridine. Reagents: (a) NaHMDS, $Boc_2O$, 79%; (b) 2.5 M *n*-BuLi, sulfur, 50%; (c) 4 M HCl dioxane, AcOH, 95%; (d) formic acid, 90%.



**Scheme 2.** Functionalization of the 4-position. Reagents: (a) *m*-CPBA, $CH_2Cl_2$, 95%; (b) $POCl_3$, 80%; (c) $Ac_2O$; (d) 7 M $NH_3$ in MeOH (50% over two steps); (e) $Ag_2CO_3$, Etl, chloroform, 55% (4:1 O vs N-alkylation).

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doi:10.1016/j.tetlet.2010.03.069

acetic anhydride, followed by 7 N ammonia in methanol provided product **8**. It is important to note that both these reactions provided exclusively the 4-substituted derivatives **7** and **8**. Compound **8** could be further transformed to the *O*-alkyl pyridines such as compound **9** by treatment with the corresponding alkyl halide and silver carbonate in refluxing chloroform. This reaction provided a 4:1 O versus N ratio that was easily separable by column chromatography.

The 4-chloro intermediate **7** is a very versatile intermediate that could be used in various coupling reactions or nucleophilic displacement reactions, but our research focused on the incorporation of small alkyl functionality at this position. The use of Grignard reagents to incorporate small alkyl groups provided decomposition of the starting material, but it was found that the commercially available trialkylaluminums could be used in the presence of palladium (0) sources to provide good yields of the corresponding 4-alkyl compounds **10–14** (Table 1).[5] The cyclopropyl substituted analog **14** was synthesized using the corresponding cyclopropylzincbromide in the presence of palladium (0) in good yield.[6]

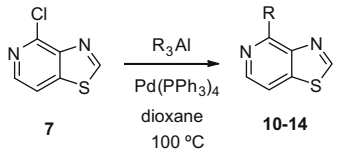
Next, we turned our attention to the 6-position of the pyridylthiazole. Since the N-oxide rearrangement chemistry worked well to provide access to the 4-position of the heterocyclic core, this chemistry was revisited using compound **10** with the hope that the 4-methyl group would induce substitution at the 6-position. Treatment of **10** with *m*-CPBA in methylene chloride provided a good yield of the N-oxide **15** (Scheme 3). The N-oxide **15** was subjected to refluxing phosphorus oxychloride, but the only product isolated was the rearrangement product **16**. This problem was solved when the acetic anhydride rearrangement provided a mixture of compounds **17** and **18** that could be easily separated by column chromatography. The synthesis of compound **18** allowed for further transformation to compounds of type **19**.

The functionalization of the 2-position could be carried out in multiple ways. One of our thoughts was to treat compound **5** with various acids in order to access novel substitution patterns. Thus, the treatment of compound **5** with acetic acid or benzoic acid provided modest yields of products **20**–**21** (Table 2). The use of acid chlorides or activated acids for the cyclization failed due to the instability of compound **5** under basic conditions reaction conditions. Treatment of compound **5** with ethylcyanoacetate provided a good yield of compound **22**, but when similar reactions were performed with various benzonitriles very low yields of compounds such as **23** were obtained.

Since our research required the ability to introduce a variety of aryl groups at the 2-position, we required a more robust method to incorporate these functionalities. We envisioned that compound **1** could be a good substrate for a direct C–H coupling reaction since it is known that benzothiazole undergoes this reaction readily.[7] When compound **1** was treated with a palladium (0) source, CuI, cesium carbonate and a corresponding aryl/heteroaryl iodide/bromide, good yields of the biaryl compounds **23**–**31** were achieved (Scheme 4).[8] Compounds **23**–**26** suggest that the position of ring substitution does not greatly affect the yield of the direct coupling. The vastly different yields obtained for compounds **27** and **28** suggest that electronics may play a role in the direct coupling reaction, but more detailed studies would be needed to confirm this hypothesis. The good yield of compound **29** demonstrates that the direct coupling is selective for the iodide versus the chloride. Compounds **30** and **31** confirm that the direct coupling reaction does not suffer when using heteroaryl halides. The reasonable yield of **31** also suggests that aryl bromides can be coupled efficiently using this method.

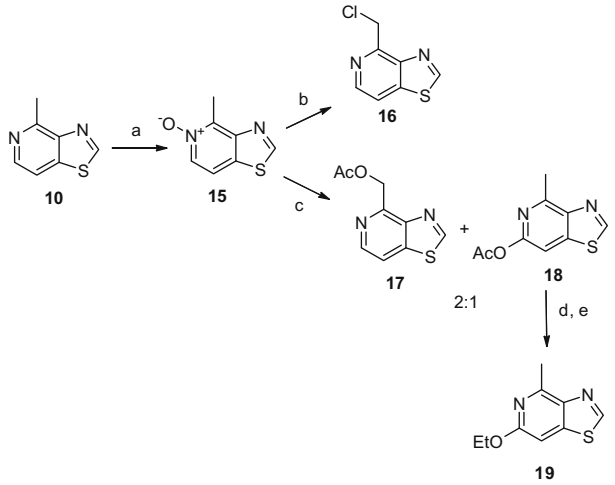
In summary, we have developed methods to provide substituted novel pyridylthiazole ring systems. The chemistry developed allowed for the multigram scale synthesis of these interesting heterocycles with a variety of functional groups. Further efforts are ongoing to expand the scope of functionalization around this novel thiazole[4,5-*c*]pyridine core.

**Table 1**
Pd-catalyzed alkylations



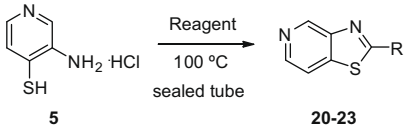

| R | Compound | Yield (%) |
|---|---|---|
| Me | **10** | 84 |
| Et | **11** | 80 |
| *n*-Propyl | **12** | 72 |
| *i*-Pr | **13** | 70 |
| Cyclopropyl | **14** | 75[a] |

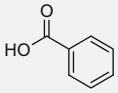
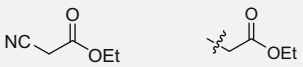
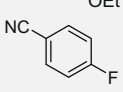
[a] Reaction was performed using 0.5 M cyclopropylzincbromide in THF in the presence of $Pd(PPh_3)_4$.

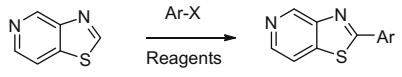



**Scheme 3.** Functionalization of the 6-position. Reagents: (a) 77% *m*-CPBA, $CH_2Cl_2$, 95%; (b) $POCl_3$, 85%, (c) $Ac_2O$ (30% of **18**); (d) 7 M $NH_3$ in MeOH; (e) EtI, $Ag_2CO_3$, $CHCl_3$ (51% d + e).

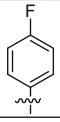
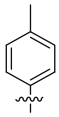
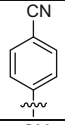
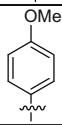
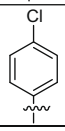
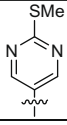
**Table 2**
Functionalization of the 2-position using compound **5**




| Compound | Reagent | R | Yield (%) |
|---|---|---|---|
| **20** |  | Me | 62 |
| **21** |  | Ph | 43 |
| **22** |  |  | 80 |
| **23** |  | 4-F-Ph | <10 |




1

| Compound | Ar | X | Yield % |
|---|---|---|---|
| **23** |  | **I** | 70 |
| **24** |  | **I** | 91 |
| **25** |  | **I** | 71 |
| **26** |  | **I** | 92 |
| **27** |  | **I** | 89 |
| **28** |  | **I** | 32 |
| **29** |  | **I** | 83 |
| **30** |  | **I** | 75 |
| **31** |  | **Br** | 64 |

**Scheme 4.** Direct coupling via C–H activation. Reagents: (a) $Pd(PPh_3)_4$, CuI, $Cs_2CO_3$, Ar-I, DMF, 110 °C.

## References and notes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3. (a) Anderson, W.; Dean, D.; Endo, T. *J. Med. Chem.* **1990**, *33*, 1667–1675; (b) Walters, M.; Shay, J. *Tetrahedron Lett.* **1995**, *36*, 7575–7578.
4. Representative experimental for compound **7**. Compound **1** (4.0 g, 29.4 mmol) was dissolved in methylene chloride (150 mL) and 77% *m*-CPBA (11.4 g, 52 mmol) was added. The reaction was stirred for 2 h and then quenched with a solution of 1 M potassium carbonate. The aqueous layer was saturated with brine and extracted with methylene chloride several times. The organic layers were dried over sodium sulfate and concentrated to provide the crude N-oxide **6** (4.25 g). Crude compound **6** (4.25 g, 27.9 mmol) was dissolved in phosphorus oxychloride (70 mL) and refluxed for 2 h. The reaction was concentrated under reduced pressure and then slowly quenched with ice chips. The reaction mixture was treated with saturated sodium bicarbonate solution and extracted with ethyl acetate several times. The combined organic layers were dried over sodium sulfate and concentrated. Column chromatography (1:1 ethyl acetate/hexanes) provided provide compound **7** (3.79 g).
   $^1$H NMR spectrum (400 MHz, $CDCl_3$ $\delta$: 9.15 (s, 1H), 8.4 (d, 1H), 7.9 (d, 1H). Spectrum $^{13}$C NMR (DMSO-$d_6$ $\delta$: 118, 143.4, 144.5, 144.8, 146.7, 159.8. LRMS: [M+H] = 171.03.
5. Joubert, N.; Pohl, R.; Klepetarova, B.; Hocek, M. *J. Org. Chem.* **2007**, *72*, 6797–6805.
6. Representative experimental for compound **10**. Compound **7** (1.6 g, 9.35 mmol), and $Pd(PPh_3)_4$ (400 mg, 0.346 mmol) were dissolved in dioxane (30 mL) under a nitrogen atmosphere and 2 M $AlMe_3$ in hexanes (14 mL, 28 mmol) was added. The reaction was refluxed for 3 h and then was cooled in an ice bath and slowly quenched with water and then extracted with ethyl acetate several times. The combined organic layers were dried over sodium sulfate and concentrated. Column chromatography (2:1 ethyl acetate/hexanes) provided compound **10** (1.2 g).
   $^1$H NMR spectrum (400 MHz, $CDCl_3$ $\delta$: 9.05 (s, 1H), 8.45 (d, 1H), 7.76 (d, 1H), 3.05 (s, 3H). Spectrum $^{13}$C NMR (DMSO-$d_6$ $\delta$: 21.5, 115.9, 141.8, 143.4, 148.6, 154.1, 156.8. LRMS: [M+H] = 151.25.
7. Sommai, P.; Tetsuya, S.; Yoshiki, K.; Masahiro, M.; Masakatsu, N. B. *Chem. Soc. Jpn.* **1998**, *71*, 467–473.
8. Experimental for compound **23**. Compound **1** (200 mg, 1.45 mmol), 4-fluoroiodophenol (383 mg, 1.74 mmol), $Pd(PPh_3)_4$, (83 mg, 0.072 mmol), CuI (14 mg, 0.072 mmol), and cesium carbonate (1.41 g, 4.35 mmol) were combined in DMF (10 mL) and stirred at 120 °C for 2 h. The reaction mixture was filtered over Celite and diluted with water and ethyl acetate. The organic layer was washed with water and brine, dried over sodium sulfate, and concentrated. Column chromatography (1:1 ethyl acetate/hexanes) provided compound **23** (233 mg).
   $^1$H NMR spectrum (400 MHz, $CDCl_3$ $\delta$: 9.4 (s, 1H), 8.55 (d, 1H), 8.1–8.2 (m, 2H), 7.95 (d, 1H), 7.2–7.3 (m, 2H). Spectrum $^{13}$C NMR (DMSO-$d_6$ $\delta$: 116.9, 117.1, 117.9, 130.4, 130.5, 142.9, 144.3, 144.9, 150.6, 163.4, 165.9, 168.1. LRMS: [M+H] = 231.23.