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## Graphical Abstract

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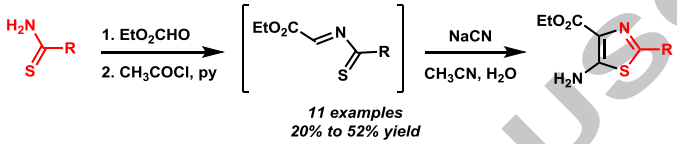

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# A Strecker approach to 2-substituted ethyl 5-aminothiazole-4-carboxylates

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ABSTRACT

A general approach to 2-substituted ethyl 5-aminothiazole-4-carboxylates is reported herein. Both aliphatic and aromatic thioamides undergo 1,2-addition to ethyl glyoxylate to give hemiaminals which, when treated with acetyl chloride, undergo elimination to the corresponding imines. Upon exposure to aqueous sodium cyanide the imines undergo a Strecker addition-cyclization reaction to provide the target heterocycles in modest to good yields over the 3-step process.



The thiazole ring is present in a large number of natural products and pharmaceutically active molecules. Certain thiazole-containing compounds have been found to display a range of important biological activities (Figure 1), including antitumor (tiazofurin, **1**), antibiotic (sulfathiazole, **2**), antifungal (abafungin, **3**), and antiviral (ritonavir, **4**).[1]

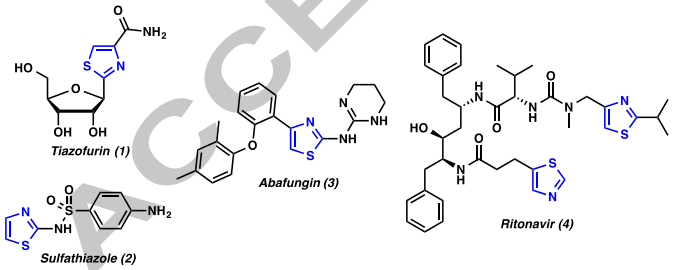



**Figure 1.** Selected biologically active thiazoles

Given this wide array of important biological activity, the efficient synthesis of substituted thiazoles remains an important endeavor for synthetic chemistry. In the context of a development program in our laboratories, we were confronted with the need to prepare 2-substituted 5-aminothiazole-4-carboxylic acids **5** (Figure 2), a starting material that has been used to prepare inhibitors of MAP kinase,[2] glycogen phosphorylase,[3] PIM kinase,[4] and Janus kinase.[5]

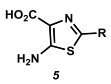
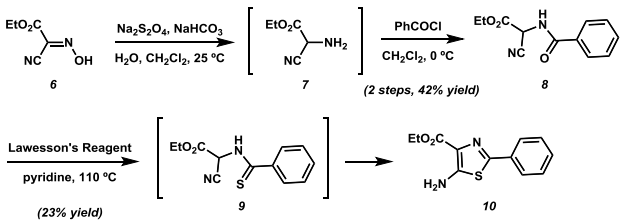



**Figure 2.** 2-Substituted 5-aminothiazole-4-carboxylic acids

The literature preparation of ethyl 5-amino-4-carboxylates involves a three-step sequence (Scheme 1).[4g,6] Commercially available oxime **6** is reduced to amine **7**, which is then acetylated with an acid chloride (e.g. benzoyl chloride) to give the corresponding amide **8**. Thioamide formation then yields **9**, which undergoes *in situ* ring-closure and tautomerization to produce the thiazole product **10** in 10% yield over 3 steps (average 47% yield per step).




**Scheme 1.** Literature approach to ethyl 5-amino-2-phenylthiazole-4-carboxylate (**10**)

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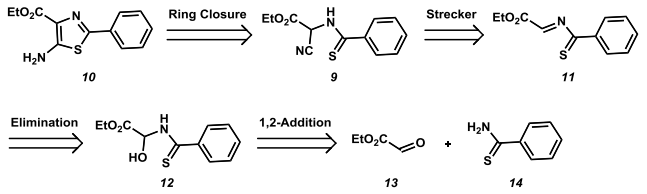
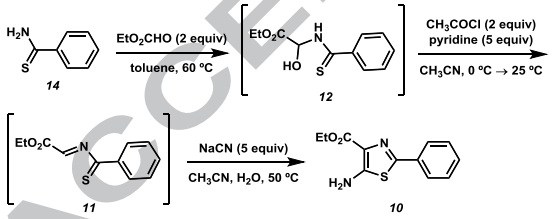
The above method was found to be difficult to scale up due to the use of Lawesson's reagent (waste generation) and pyridine, the poor conversion[7] and tedious column purification in the final step, and the low overall yield. It was reasoned that producing thioamide intermediate **9** under milder conditions should enable a more efficient ring-closing event to form **10**. Thus an alternative disconnection was envisaged in which **9** would be produced through addition of cyanide to activated imine **11** (Scheme 2). This activated imine[8] could potentially be formed by dehydration of hemiaminal **12**, which in turn could possibly be accessed through a simple carbonyl addition of thioamide **14** to ethyl glyoxylate (**13**).




**Scheme 2.** Retrosynthetic analysis of ethyl 5-amino-2-phenylthiazole-4-carboxylate (**10**)

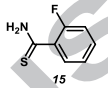
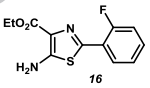
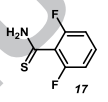
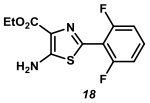
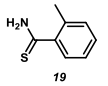
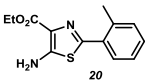
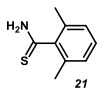
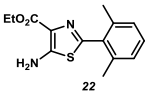
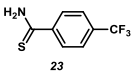
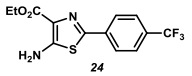
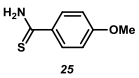
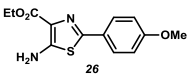
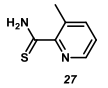
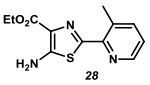
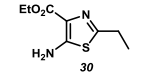
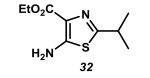
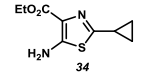
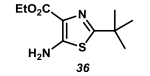
Following initial small-scale optimization experiments, it was found that heating thioamide **13** with 200 mol% ethyl glyoxylate[9] in toluene furnished the corresponding 1,2-addition product **12** (Scheme 3). Exposure of the crude hemiaminal to pyridine and acetyl chloride[10] enabled elimination to the corresponding imine intermediate **11**. Addition of the crude imine solution to warm aqueous sodium cyanide,[11] followed by extractive workup, column chromatography, and crystallization[12] furnished thiazole **10** in 40% yield over 3 steps on 20 g scale (average 74% yield per step).[13] Both the conversion and crude HPLC purity for the first 2 steps were >90%, while the final step gave complete conversion but afforded a mixture containing several unidentified side products in addition to the major product **10**.




**Scheme 3**. Strecker synthesis of ethyl 5-amino-2-phenylthiazole-4-carboxylate (**10**)

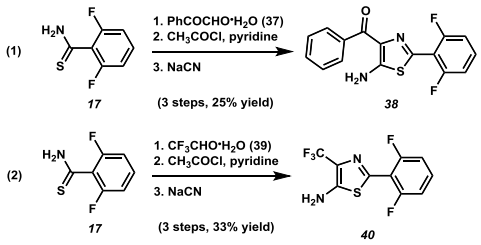
With this encouraging result in hand the scope of the thioamide substrate was examined on gram-scale (Table 1). In terms of aromatic groups it was found that electron-withdrawing (*o*-fluoro and *o*,*o*-difluoro, entries 1 and 2, 45% yield and 49% yield) and weakly electron-donating (*o*-methyl and *o*,*o*-dimethyl, entries 3 and 4, 35% yield and 46% yield) substituents led to similar isolated yields when compared to the parent phenyl system (Scheme 3, 40% yield). However, both a strongly electron-withdrawing (*p*-$CF_3$, entry 5, 28% yield) and electron-donating (*p*-OMe, entry 6, 22% yield) substituent led to diminished isolated yields. A heterocyclic group (3-methylpyridine-2-carbothioamide, **27**) functioned well in the thioamide addition step, but ultimately afforded multiple unidentifiable side products in the final reaction mixture, presumably due to the competing nucleophilic nature of the pyridine nitrogen in the acetylation step (entry 7). Alkyl-substituted thioamides were examined next, and were found to also participate in the 3-step thiazole-forming process. Linear alkyl (entry 8), branched alkyl (entry 9), and cyclopropyl groups (entry 10) performed similarly, producing the thiazole products in modest yields (20-26%). The higher yield obtained for the *t*-butyl group (entry 11, 52% yield) may be reflective of steric crowding near the thiocarbonyl functionality which could block access to this reactive center, thus favoring productive nucleophilic attack at the imine center.

**Table 1.** Scope of thioamides in 5-aminothiazole formation

| entry[a] | Thioamide Substrate | Thiazole Product | Yield (%)[c] |
|---|---|---|---|
| 1 |  15 |  16 | 45 |
| 2[b] |  17 |  18 | 49 |
| 3 |  19 |  20 | 35 |
| 4 |  21 |  22 | 46 |
| 5 |  23 |  24 | 28 |
| 6 |  25 |  26 | 22 |
| 7 |  27 |  28 | 0 |
| 8 |  29 |  30 | 26 |
| 9 |  31 |  32 | 20 |
| 10 |  33 |  34 | 23 |
| 11 |  35 |  36 | 52 |

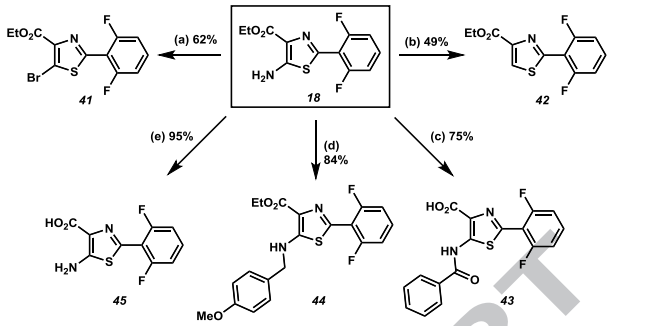
[a]Reactions carried out on 30 mmol scale utilizing conditions shown in Scheme 3. [b]Carried out on 58 mmol scale. [c]Isolated yield after column chromatography and crystallization.

It was surmised that the scope of the 3-step transformation could be further extended if ethyl glyoxylate were replaced with a different electrophilic aldehyde.[14] This was indeed found to be the case: employing phenylglyoxal monohydrate (**37**) furnished a thiazole with a ketone group in the 3-position (eq 1, 25% yield, Scheme 4), while use of trifluoroacetaldehyde monohydrate (**39**) afforded a thiazole bearing a trifluoromethyl substituent (eq 2, 33% yield).




**Scheme 4**. Alternative aldehyde partners

The product ethyl 5-aminothiazole-4-carboxylates possess a useful juxtaposition of amine and ester groups which could be exploited in further chemoselective transformations (Scheme 5). For example, the amine group of thiazole **18** could be replaced with either a bromide group or a hydride using diazotization conditions, affording derivatives **41** (62% yield) and **42** (49% yield), respectively. The amine group was nucleophilic enough to participate in both amide formation and reductive amination[15] reactions to furnish **43** (75% yield) and **44** (84% yield), respectively. Finally, the ester group could be readily saponified to the corresponding carboxylic acid, providing **45** in 95% yield.




**Scheme 5**. Selected transformations of ethyl 5-aminothiazole-4-carboxylate **18**. (a) isoamyl nitrite, $CuBr_2$, $CH_3CN$, 65 ºC; (b) isoamyl nitrite, $CH_3CN$, 65 ºC; (c) PhCOCl, *i*-$Pr_2NEt$, THF, 60 ºC; (d) *p*-anisaldehyde, TFA, $NaBH(OAc)_3$, THF, 25 ºC; (e) NaOH, $H_2O$, 70 ºC.

In summary, a 3-step sequence has been discovered to convert thioamides and ethyl glyoxylate to 5-aminothiazole-4-carboxylate products. The process is marked by: (a) improved yields relative to the existing routes; (b) the practicality of a telescoped 3-step process that obviates the use of Lawesson's reagent; (c) generation of a variety of alkyl and aryl substituents at the 2-position of the thiazole; and (d) a range of orthogonal synthetic transformations available to the products.

**Acknowledgments**

The authors thank Christine Gu (Genentech, Inc.) for obtaining the HRMS data.

**Supplementary data**

Supplementary data (full experimental details, compound characterization, and selected spectra for key compounds) associated with this article can be found, in the online version, at http://XXXXX.

[1] Reviews: (a) De Souza, M. V. N. *J. Sulfur Chem*. **2005**, *26*, 429-449. (b) Davyt, D.; Serra, G. *Mar Drugs* **2010**, *8*, 2755-2780.

[2] Michelotti, E. L. et al. PCT Int. Appl., 2010019930, 18 Feb 2010.

[3] Evans, K. et al. PCT Int. Appl., 2006052722, 18 May 2006.

[4] (a) Burger, M. et al. PCT Int. Appl., 2009109576, 11 Sep 2009. (b) Burger, M. et al. U.S. Pat. Appl. Publ., 20100216839, 26 Aug 2010. (c) Burger, M. et al. PCT Int. Appl., 2012004217, 12 Jan 2012. (d) Burger, M. et al. U.S. Pat. Appl. Publ., 20120225061, 06 Sep 2012. (e) Burger, Matthew et al. PCT Int. Appl., 2014033631, 06 Mar 2014. (f) Ge, Yu et al. PCT Int. Appl., 2013020371, 14 Feb 2013. (g) Burch, J. et al. U.S. Pat. Appl. Publ., 20140088117, 27 Mar 2014.

[5] Machacek, M. R. et al. PCT Int. Appl., 2010011375, 28 Jan 2010.

[6] (a) Ashwell, S. et al. PCT Int. Appl., 2005066163, 21 Jul 2005. (b) Wang, X. et al. U.S. Pat. Appl. Publ., 20110059961, 10 Mar 2011. (c) Wang, X. et al. PCT Int. Appl., 2011124580, 13 Oct 2011. (d) Bleicher, K. et al. PCT Int. Appl., 2011154327, 15 Dec 2011. (e) Hodges, A. J. et al. U.S. Pat. Appl. Publ., 20130079321, 28 Mar 2013.

[7] Golankiewicz, B.; Januszczyk, P. *Tetrahedron* **1985**, *41*, 5989-5994.

[8] At the outset, it was not clear that such a 1,3-thiaza-1,3-butadiene would in fact be stable enough to generate in the absence of the cyanide nucleophile. For an alternative method of forming such unstable species, and their *in situ* reactions, see: Shimada, K.; Aikawa, K.; Fujita, T.; Sato, M.; Goto, K.; Aoyagi, S.; Takikawa, Y.; Kabuto, C. *Bull. Chem. Soc. Jpn*. **2001**, *74*, 511-525.

[9] Use of 1.5 equivalents ethyl glyoxylate led to incomplete conversion.

[10] Using a stronger base (triethylamine) led to fragmentation of the hemiaminal back to the thioamide starting material.

[11] Use of less than 5 equiv of sodium cyanide resulted in a lower yield and a greater amount of unidentified side products. Potassium cyanide and sodium cyanide were found to function equally well.

[12] HPLC mass assay showed 12% loss of product to the mother liquor.

[13] Representative procedure: To a suspension of benzothioamide (**14**, 20.0 g, 146 mmol, 1.00 equiv) in toluene (146 mL) was added ethyl glyoxylate solution (50 wt% in toluene, 57.7 mL, 292 mmol, 2.00 equiv). The mixture was heated to 60 °C, held for 1 h, then cooled to 25 °C and concentrated *in vacuo*. The resulting crude hemiaminal intermediate was dissolved in $CH_3CN$ (200 mL), and pyridine (58.9 mL, 730 mmol, 5.00 equiv) was added. The solution was cooled to 0 °C and acetyl chloride (20.8 mL, 292 mmol, 2.00 equiv) was added over 20 min while maintaining the temperature below 10 °C. The mixture was warmed to 25 °C over 30 min and then held for 1 h. The resulting solution of crude imine intermediate was transferred over 15 min to a 50 °C solution of sodium cyanide (35.72 g, 730 mmol, 5.00 equiv) in $H_2O$ (200 mL). [CAUTION: use base scrubber]. The mixture was stirred for 15 min at 50 °C, then cooled to 25 °C and isopropyl acetate (250 mL) was added, followed by $H_2O$ (250 mL). The mixture was filtered through Celite and then

the phases were separated. The aqueous layer was washed with isopropyl acetate (100 mL). The combined organic extracts were washed with half-saturated aqueous $NH_4Cl$ (150 mL), brine (75 mL), dried over anhydrous $MgSO_4$, and filtered. Celite (60.0 g) was added to the filtrate, which was then concentrated *in vacuo* and purified by flash chromatography (dichloromethane/methanol 100:0 → 98:2) to provide a brown solid. The crude product was dissolved in refluxing EtOH (50 mL), cooled to 25 °C over 2 h, and then $H_2O$ (25 mL) was added over 15 min. The slurry was held for 2 h and then the resulting crystals were filtered, washed with EtOH/$H_2O$ (67:33, 20 mL), and dried *in vacuo* under $N_2$ purge at 60 °C to furnish **10** as pale yellow crystals. Yield: 14.4 g (40%). MP: 137.7–138.3 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.83 – 7.75 (m, 2H), 7.44 – 7.31 (m, 3H), 6.10 (s, 2H), 4.42 (q, *J*=7.1 Hz, 2H), 1.44 (t, *J*=7.1 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 164.82, 159.61, 149.44, 133.23, 129.43, 128.76, 126.08, 122.64, 60.68, 14.57. HRMS. Calcd. For $C_{12}H_{12}N_2O_2S$: 249.0692; Found $[M+H]^+$: 249.0694.

[14] Use of benzaldehyde led to the corresponding aminal product, which did not participate in the subsequent elimination or Strecker steps.

[15] Chen, L.; Li, Z. M.; Zhou, J.; Song, H. R.; Xu, B. L. *Chinese Chem Lett*. **2012**, *23*, 695-698.