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A one-step, multi-component reaction for the synthesis of fully substituted 5-amino-4-carboxamidthiazoles

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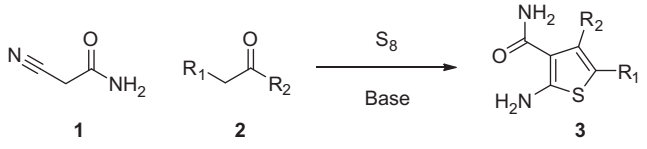
ABSTRACT

A novel multi-component reaction has been developed for the synthesis of fully substituted 5-amino-4-carboxamidthiazoles. Condensation of an aldehyde with commercially available 2-amino-2-cyanoacetamide in the presence of elemental sulfur and base affords these heterocycles in a one-pot reaction sequence. A variety of aryl, heteroaryl, and aliphatic aldehydes were successfully utilized, thus providing rapid access to functionalized thiazoles that are valuable intermediates in the synthesis of pharmacologically active compounds.

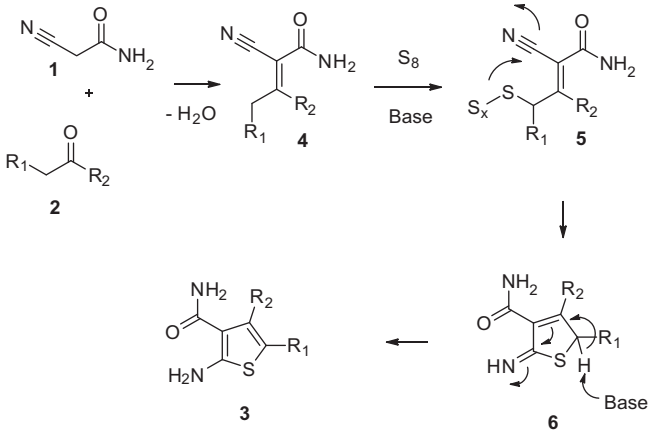
Thiophenes and thiazoles are frequently found in biologically active compounds and are used by medicinal chemists to explore structure–activity relationships (SAR) in drug discovery. During the course of a recent medicinal chemistry program aimed at kinase inhibitors, substituted 2-amino-3-carboxamidthiophenes were extensively explored.[1] These were readily accessed through the Gewald reaction,[2–4] which allowed for facile determination of SAR (Scheme 1).

The Gewald reaction cascade begins by condensation of an α-methylene ketone or aldehyde (**2**) with α-cyanoacetamide (**1**) (Scheme 2).[5] Following the deprotonation of **4** and nucleophilic attack on elemental sulfur, the proposed mechanism proceeds through cyclization and tautomerization steps to produce a substituted 2-amino-3-carboxamidthiophene (**3**) (note: C-3 esters can also be formed by using an α-cyanoacetate instead of **1**).[6]

To expand the scope of SAR exploration beyond thiophenes, access to the corresponding thiazole core was desired. It was envisioned that a sequence of mechanistic steps very similar to those found in the Gewald reaction could be used to provide these compounds (Scheme 3). A literature search revealed no analogous methods for the synthesis of 5-amino-4-carboxamidthiazoles; instead reported syntheses require additional steps where the sulfur needs to be incorporated into a reactant such as a thioester[7] or a dithioic acid.[8] Alternatively, an ethyl 2-acylamido-2-cyanoacetate can be reacted with elemental sulfur followed by ester ammonolysis to afford compounds of structure **3**.[9] This approach requires the substituent at the 2-position be brought in during the initial step of a two-step procedure through amide formation with ethyl 2-amino-2-cyanoacetate, which means one of the diversification steps has to occur at the start of the synthesis rather than at the end.



Scheme 1. The Gewald reaction.



Scheme 2. Reported Gewald mechanism.

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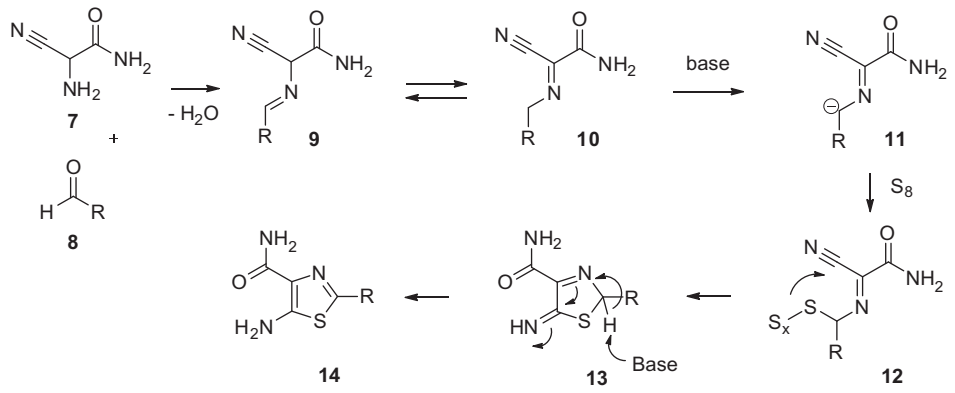
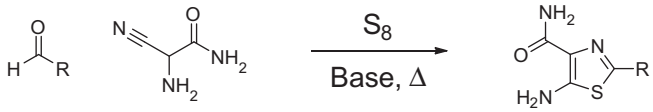


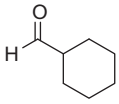
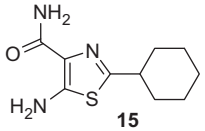
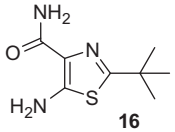
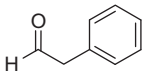
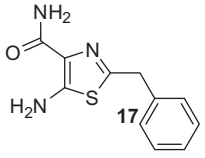
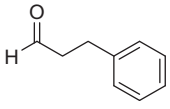
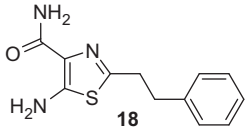
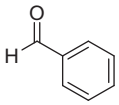
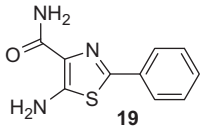
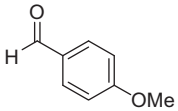
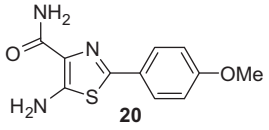
Scheme 3. Proposed mechanism for thiazole formation.

The proposed one-pot reaction begins by condensation of commercially available 2-amino-2-cyanoacetamide (**7**) with an aldehyde (**8**), which would initially provide aldimine (**9**) that could tautomerize to ketimine (**10**). Either intermediate **9** or **10** could behave similarly to unsaturated α-cyanoacetamide (**4**) when treated with a base and elemental sulfur, undergoing cyclization and tautomerization steps to produce a fully substituted 5-aminothiazole (**14**).

To examine the viability of the proposed reaction, both 4-chlorobenzaldehyde and *p*-tolualdehyde were used as model

Table 1
Synthesis of 5-amino-4-carobxamidothiazoles



Entry	Aldehyde	Product	Isolated yield (%)
1		 **15**	32[b]
2		 **16**	15[b]
3		 **17**	20[b]
4		 **18**	44[b]
5		 **19**	30[a]
6		 **20**	11[b]

(*continued on next page*)

Table 1 (*continued*)

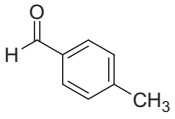
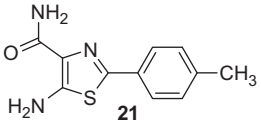
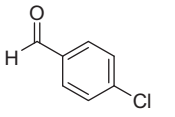
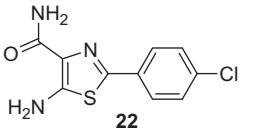
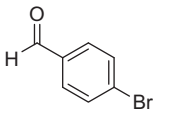
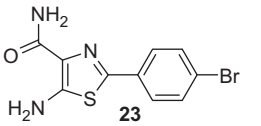
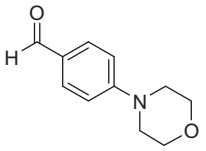
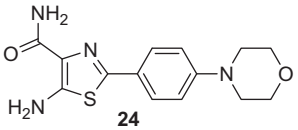
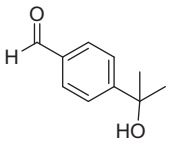
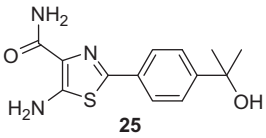
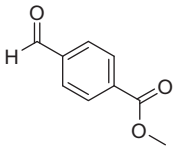
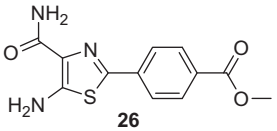
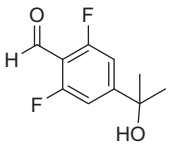
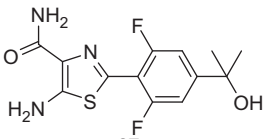
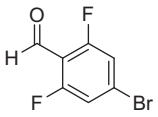
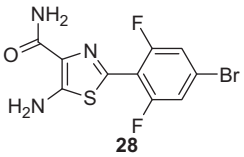
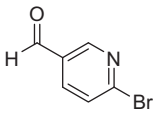
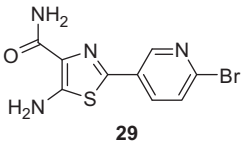
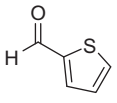
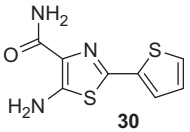
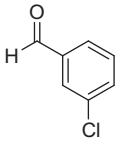
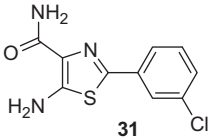
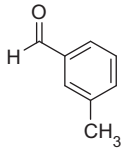
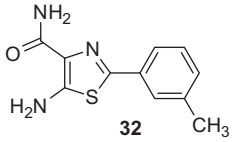
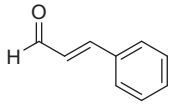
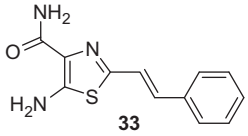
Entry	Aldehyde	Product	Isolated yield (%)
7		 **21**	40[b]
8		 **22**	28[b]
9		 **23**	23[b]
10		 **24**	18[b]
11		 **25**	8[c]
12		 **26**	11[c]
13		 **27**	24[b]
14		 **28**	17[b]
15		 **29**	21[b]
16		 **30**	14[b]
17		 **31**	17[b]

Table 1 (*continued*)

Entry	Aldehyde	Product	Isolated yield (%)
18		 **32**	14[b]
19		 **33**	0[b]

[a] 1 equiv aldehyde, 1 equiv 2-amino-2-cyanoacetamide, 1 equiv S_8, 1 equiv 1-methyl morpholine, 0.5 M DMF, 72 h at 100 °C.
[b] 1 equiv aldehyde, 1 equiv 2-amino-2-cyanoacetamide, 1–1.2 equiv S_8, 1 equiv 1-methyl imidazole, 0.5 M 1:1 toluene/NMP, overnight at 80–130 °C.
[c] 1 equiv aldehyde, 1 equiv 2-amino-2-cyanoacetamide, 1 equiv S_8, 1 equiv 1-methyl imidazole, 0.5 M DMF, 24 h at 100 °C.

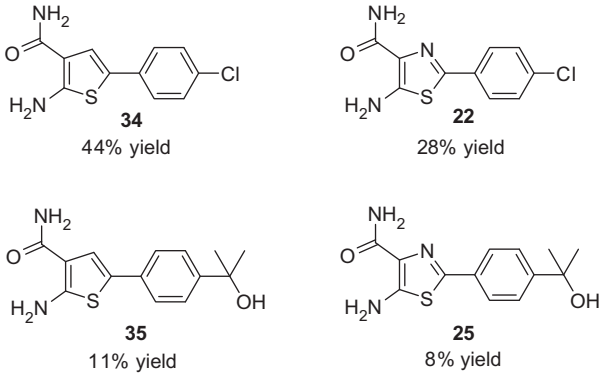


Figure 1. Comparison of Gewald and thiazole-forming reaction.

aldehydes. The aldehyde was combined with an equimolar amount of 2-amino-2-cyanoacetamide and sulfur, and a variety of bases were screened for their efficacy in promoting the desired transformation.[10] 1-Methylimidazole provided the cleanest conversion to product while stronger bases (pK_a >8) were noticeably worse. A variety of solvents were also investigated[11] with a 1:1 mixture of toluene/NMP affording the best yields, presumably due to the reasonable solubility of elemental sulfur under these conditions.

A number of other factors were examined to further enhance starting material conversion and reaction yields, although to limited effect. For example, since the first step in the reaction sequence is a condensation, sodium sulfate was introduced into the reaction mixture as a dehydrating agent; this modification did not change the yield. Varying the concentration of each reactant individually as well as in combination with other reactants similarly did not lead to any improvements. Due to the fast paced nature of a medicinal chemistry program, limited studies were completed to understand the low yields and any possible byproduct pathways. Further studies could be warranted. In the end, the best conditions were identified as equimolar concentrations of aldehyde, 2-amino-2-cyanoacetamide, S_8, and 1-methylimidazole in 1:1 toluene/NMP overnight at a concentration of 0.5 M and a temperature of 80–130 °C.

With these conditions in hand,[12] the scope of the methodology was explored. As seen in Table 1, aryl (entries 5–14, 17–18) and heteroaryl aldehydes (entries 15–16) provided the best yields. Alkyl aldehydes (entries 1 and 2) gave similar yields while a reaction with an α,β-unsaturated aldehyde (entry 19) afforded no desired product. In direct comparisons to the Gewald reaction, we found the thiazole synthesis of **34** and **35** afforded comparable yields to **22** and **25** (Fig. 1).[13]

In summary, we have developed a novel and convenient multicomponent reaction for the synthesis of fully substituted thiazoles. A key difference between this reaction and the Gewald reaction in terms of practical application is the commercial availability of the starting materials: the Gewald aldehyde needs to have a methylene group adjacent to the carbonyl, thus limiting the number of building blocks readily available for the synthesis of thiophenes, while any aldehyde can in theory be used for the synthesis of thiazoles. Commercially available starting materials and a one-pot procedure allow for rapid incorporation of alkyl, aryl, and heteroaryl functionality into a scaffold of both synthetic and medicinal chemistry interest.

Typical experimental procedure: A solution of *p*-tolualdehyde (0.24 mL, 2.0 mmol), 2-amido-2-cyanoacetamide (200 mg, 2.0 mmol), sulfur (65 mg, 2.0 mmol), 1-methylimidazole (0.16 mL, 2.0 mmol) and a 1:1 mixture of toluene:*N*-methyl-2-pyrrolidinone (4 mL, 0.5 M) were stirred at 130 °C for 25 h and then cooled to room temperature. The reaction mixture was diluted with ethyl acetate (30 mL), washed with water (2 × 10 mL) and brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica (20–70% ethyl acetate/hexanes) to afford 5-amino-2-(*p*-tolyl)thiazole-4-carboxamide (190 mg, 0.81 mmol, 40% yield) as a dark yellow solid.

Acknowledgments

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Supplementary data

Supplementary data (NMR data for compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.03.014.

References and notes

1. Wilson, K.; De Almeida, G.; Haidle, A.; Konrad, K.; Machacek, M.; Zabierek, A. Preparation of thiophenecarboxamides as inhibitors of Janus kinases (JAK) javascript, WO 2010005841A1, January 14, 2010.
2. Gewald, K.; Schinke, E.; Böttcher, H. *Chem. Ber.* **1966**, *99*, 94–100.
3. Feroci, M.; Chiarotto, I.; Rossi, L.; Insei, A. *Adv. Synth. Catal.* **2008**, *350*, 2740–2746.
4. Huang, Y.; Doemling, A. *Mol. Divers.* **2011**, *15*, 3–33.
5. Tinsely, J. M. In *Name Reactions in Heterocyclic Chemistry*; Li, J. J., Corey, E. J., Eds.; Wiley: New York, 2005; pp 193–198.

6. Peet, N. P.; Sunder, S.; Barbuch, R. J.; Vinogradoff, A. P. *J. Heterocycl. Chem.* **1986**, *23*, 129–134.
7. Hennen, W. J.; Hinshaw, B. C.; Riley, T. A.; Wood, S. G.; Robins, R. K. *J. Org. Chem.* **1985**, *50*, 1741–1746.
8. Cook, A. H.; Heilbron, I.; Smith, E. *J. Chem. Soc.* **1949**, 1440–1442.
9. Inami, H.; Mizutani, T.; Maeda, J.; Usuda, H.; Nagashima, S.; Ito, T.; Aoyama, N.; Kontani, T.; Hayashida, H.; Terasawa, T.; Seo, R.; Akamatsu, M.; Ishikawa, T.; Hayashi, K. Preparation of oxazole-carboxamide compounds as IRAK-4 inhibitors, WO 2011043371A1, April 14, 2011.
10. *The following bases were screened*: 1,8-Diazabicyclo[5.4.0]undec-7-ene, *i*-Pr_2NEt, 4-dimethylaminopyridine, 1,4-diazabicyclo[2.2.2]octane, *N*-methyl morpholine, 1-methylimidazole, diethylaniline and pyridine.
11. Toluene, xylenes, dimethylformamide, dimethylacetamide, *N*-methyl-2-pyrrolidone, dimethyl sulfoxide, 2-ethoxyethanol and an array of mixtures were investigated as reaction solvents.
12. A handful of substrates were prepared with modified conditions and were not repeated with our preferred conditions due to the nature of an industrial medicinal chemistry program.
13. *Gewald conditions*: Equimolar amounts of substrates and morpholine in 0.5 M EtOH, 75 °C, overnight.