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

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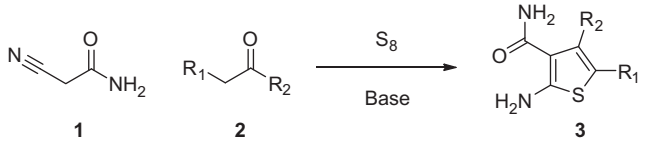
ABSTRACT

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.

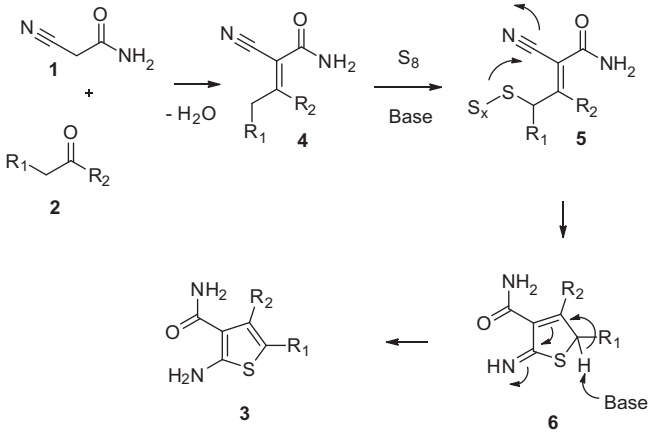
Thiophenes and thiazoles are frequently found in biologically active compounds and are used by medicinal chemists to explore structure–activity relationships (SAR) in drug discovery. During the course of a recent medicinal chemistry program aimed at kinase inhibitors, substituted 2-amino-3-carboxamidthiophenes 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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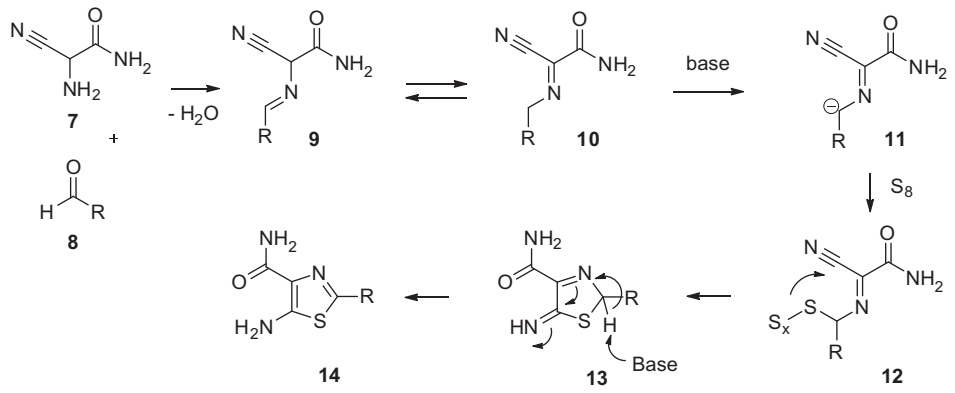
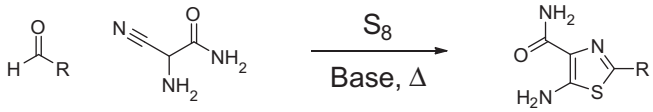


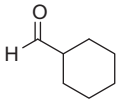
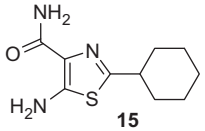
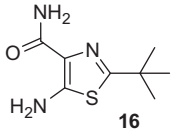
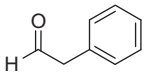
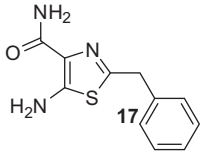
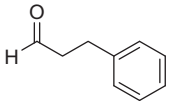
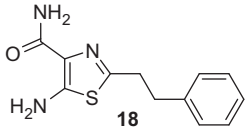
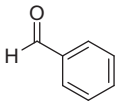
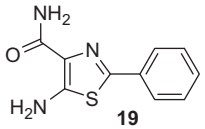
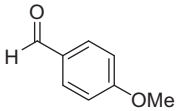
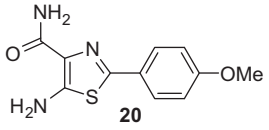
Scheme 3. Proposed mechanism for thiazole formation.

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*)