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Synthesis of 2-aminoethyl-5-carbethoxythiazoles utilizing a Michael-like addition strategy

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Abstract—Ethyl 4-(trifluoromethyl)-2-vinylthiazole-5-carboxylate was utilized as a precursor to ethyl 4-(trifluoromethyl)-2-(aminoethyl)thiazole-5-carboxylate analogs via Michael-like addition of various secondary amines. Reactions employed 1.2 equiv of amine, and the products were isolated by solvent removal and acid/base extraction. Use of primary amines was also investigated.

Thiazole heterocycles are present in numerous molecules of interest to the natural products, synthetic organic, agricultural, and medicinal chemistry communities. Examples include the Bistratamide natural products,[1] the herbicide CMPT,[2] and the antibiotic Thiostrepton.[3] Our own research needs led to the investigation of thiazole 5-carboxylic acid derivatives as potential targets for lead exploration. One requirement of our effort was to generate analogs with acceptable levels of aqueous solubility. We decided to generate 2-aminoethyl 5-carbethoxy thiazoles as intermediates for various subsequent chemistry off the 5-position. Although Dondoni has made extensive use of the thiazole group as a surrogate for the aldehyde group[4] (accessible by a three-step one-pot reductive procedure), we decided to explore the reactivity of the ester oxidation state of the thiazole 2-carbon. By synthesizing 2-vinyl thiazole **1**, we hoped to explore the potential for Michael-like reactivity of this derivatized thiazole to obtain the desired 2-aminoethyl thiazole compounds (Fig. 1). To our knowledge, this reaction is not reported in the literature.[5]

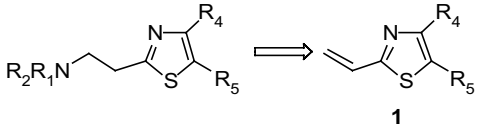
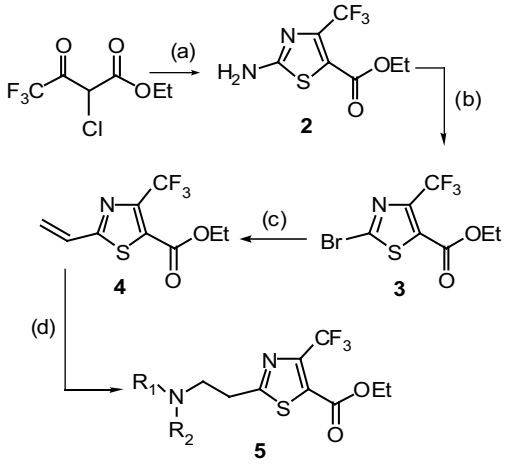


Figure 1. Retrosynthesis.

Starting from the commercially available ethyl 2-chlorotrifluoro acetoacetate (Scheme 1), condensation with thiourea provided 2-aminothiazole **2** in 75% yield. Conversion to the corresponding bromide **3** was achieved via diazatization and decomposition with CuBr and HBr, as



Scheme 1. Preparation of vinyl thiazole **4** and conversion to aminoethyl derivatives **5**. Reagents and conditions: (a) thiourea, ethanol, reflux, 75%; (b) (1) 48% HBr, $NaNO_2$, H_2O, 0 °C; (2) CuBr, 48% HBr, 0 °C to rt, 93%; (c) tributyl(vinyl)tin, $Pd(PPh_3)_4$, cat 2,6-di-*t*-butyl-4-methylphenol, toluene, 120 °C, sealed tube, 42%; (d) HNR_1R_2, EtOH, rt, 2 h.

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Table 1. Yields of the Michael reaction of **4** to compounds **5a–i**

Compound number	HNR_1R_2	Yield (%)
5a	Morpholine	63
5b	*N*-Methyl ethanolamine	79
5c	*N*,*N*′,*N*′-Trimethylethylenediamine	71
5d	*N*-Methyl *iso*-propylamine	47
5e	*N*-Methylhomopiperazine	73
5f	*N*-Methylpiperazine	55
5g	4-Methoxyethyl piperazine	69
5h	Thiomorpholine	24
5i	*n*-Butylamine	11

modified from a literature procedure[6] (93% yield). A $Pd(PPh_3)_4$ catalyzed Stille cross coupling with tributyl-(vinyl)tin provided the key compound **4** in modest yield (42%).

Investigation of the Michael reaction with morpholine in ethanol at room temperature provided the desired amino adduct **5a** (Table 1). Initial experiments conducted in methanol were complicated by formation of methyl ester products and amide side products. Presumably, the amides arise from the trans-esterified methyl esters, since the amide side-products are absent from reactions conducted in ethanol.[7] Products were conveniently isolated by removal of solvent, followed by an acid/base extraction protocol. In most cases, the compounds so obtained were analytically pure, although recourse to silica gel chromatography was occasionally required.

Reaction scope was investigated with a variety of secondary amines. Acyclic amines and diamines (**5b**, **5c**) performed best, followed closely by unhindered cyclic amines. Reaction efficiency was influenced by steric factors. Reaction of **4** with *N*-methyl isopropylamine provided product **5d** in only modest yield (47%), whereas diisopropylamine did not react at all. Likewise, the cyclic amine *cis*-dimethylmorpholine reacted in low yield (<8%). Less basic amines, exemplified by *N*-methylaniline, did not react. Cyclic secondary amines with no branching (**5e–i**) performed well, although thiomorpholine gave the desired product (**5h**) in unexpectedly low yield. Reaction conditions were unoptimized for time, temperature, and amount (1.2 equiv) of amine; further study of these parameters could possibly improve yields especially in the cases of more hindered amines. Reaction with a primary amine (*n*-butylamine) with **4** gave a mixture of secondary and tertiary amine products, as was expected. A single attempt to modify the reaction conditions by adding an ethanol solution of **4** dropwise to an excess (10 equiv) of *n*-butylamine in ethanol provided, after the usual workup, exclusively the desired secondary amine, although in surprisingly low yield (11%).

The 2-vinylthiazole moiety has been shown to be a viable Michael acceptor for a variety of amines. Future studies will examine different classes (non-amine) of nucleophiles. Additionally, saponification and further derivatization of compounds **5**, as well as results from their biological evaluation will be reported in due course.

Supplementary data

Supplementary data associated with this article can be found, in the online version at doi:10.1016/j.tetlet.2005.02.022.

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