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Synthesis of 2,5-dihalothiazole-4-carboxylates

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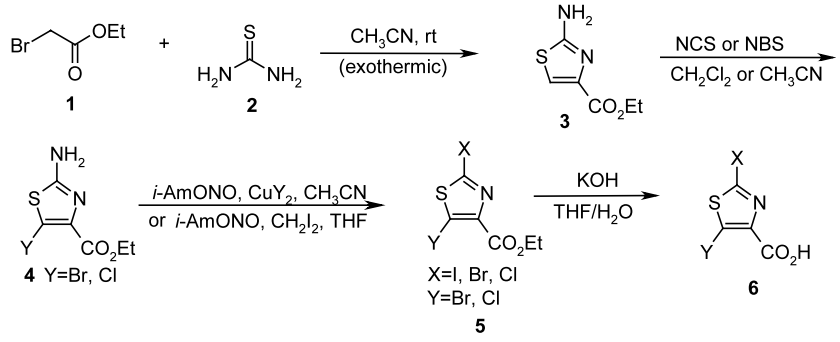
Abstract—An efficient synthesis of 2,5-dihalothiazole-4-carboxylates has been described. Halogenation of aminothiazole carboxylate with NBS or NCS and subsequent diazotization with isoamyl nitrite and halogenation with $CuBr_2$, $CuCl_2$ or CH_2I_2 provided the corresponding diahalothiazole derivatives. The four-step process described is amenable to scale-up and requires no chromatographic purification in all the steps. © 2002 Published by Elsevier Science Ltd.

Diverse biological activities have been derived from thiazoles making them one of the most extensively pursued heterocycles. For example, many compounds containing the 2-aminothiazole moiety have been found to display a wide range of biological activities including anti-inflammatory, antiviral and antibacterial properties.[1] Most recently, there has been a flurry of competitive activity on the development of aminothiazole derivatives as protein kinase inhibitors with potential for treatment of cancer and cell proliferative disorders.[2] Thiazoles have also found wide agricultural applications.[3] Examples include photosystem II inhibiting herbicides,[4] succinate dehydrogenase inhibiting thiazole carboxanilide fungicides,[5] and the recently introduced aminothiazole carboxamide fungicide (ethaboxam).[6]

Because of the importance of thiazoles and their ease of synthesis, the literature and patents are rich in the synthesis and applications of thiazoles. However, on a closer look it became apparent to us that most of the applications and synthesis of thiazoles are based on the Hantzsch synthesis and related cyclocondensation reactions.[2f,7] Only a few examples describe substantial elaboration and manipulation of functionalities around a thiazole template.[5d,8] Consequently, the structural diversity seen in thiazoles described in the literature have, for the most part, been limited to those accessible by the Hantzsch synthesis and related cyclocondensation reactions. With this in mind, we envisioned that using dihalothiazole carboxylates as synthetic intermediates would offer differential and orthogonal reactivity that would allow for elaboration to highly fucntionalized and diverse thiazole derivatives. A recent report by Hodgett and Kershaw[9] on selective reactivity of 2-bromo-5-chlorothiazole-5-carboxylates in metal mediated cross-coupling reactions has prompted us to disclose some of our efforts in this regard. Herein, we report the synthesis of a variety of 2,4-dihalothiazole-4-carboxylates shown in the Scheme 1.



Scheme 1. Preparation of 2,5-dihalothiazole-4-carboxylates.

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2,5-Dihalothiazole-4-carboxylates were readily prepared in four steps (Scheme 1). The synthesis started with the cyclocondensation of ethyl bromopyruvate (**1**) with thiourea (**2**) in CH_3CN by the standard Hantzsch reaction. The reaction initially exothermic but was left to run overnight at room temperature. The aminothiazole carboxylate was obtained as HBr salt which was freed by treatment with a solution of NH_3/MeOH in CH_2Cl_2. Aminothiazole derivatives are highly electron rich at the 5 or 4 position and, as a consequence, are readily halogenated with the common halogenating reagents like Br_2, *N*-chlorosuccinimide (NCS) and *N*-bromosuccinimide (NBS).[8a,d] Thus, treatment of 2-aminothiazole-4-carboxylate (**3**) with NBS or NCS in CH_2Cl_2 or CH_3CN readily provided the 5-halogenated derivative **4**. In the case of the reaction with NCS, it was necessary to further treat the reaction mixture with Et_3N for at least 2 h to drive the reaction to completion. The halogen at the 2-position was introduced by diazotization of the 2-amino group and subsequent halogenation. Several methods and examples of this transformation are described in the literature.[8b,c,10] We noticed during our attempts to diazotize and halogenate the 2-amino group that the intermediate 2-diazonium thiazole salt was very susceptible to reduction generating prohibitive amounts of the reduced thiazole derivative. We found that to avoid or minimize the formation of the reduced thiazole derivative, the 2-bromo or chlorothiazole derivatives were best prepared by diazotization with isoamyl nitrite (*i*-AmONO) and halogenation with $CuBr_2$ or $CuCl_2$ in CH_3CN and that it was helpful to run this reaction at low temperature (0°C). The 2-iodo derivative was prepared by diazotization with *i*-AmONO and halogenation with CH_2I_2. The resulting 2,5-dihalothiazole-4-ethyl esters (**5**) were readily hydrolyzed to the corresponding acids by treatment with KOH in a 1:1 solution of THF/H_2O. In order to make the process amenable to scale-up, we devised a method in which the halogenation in the second step (Scheme 1) was run in CH_3CN and the subsequent diazotization/halogenation was run in one pot.[11] The dihalothiazole esters were then isolated by a simple filtration through silica gel eluting with EtOAc/hexanes (1:2). All these transformations were highly efficient requiring no chromatographic purification in all the steps. The dihalothiazole carboxylic acids were obtained with an overall yield of 74% for the four steps. Attempts to prepare the 2-florothiazole derivative by diazotization and florination with tetrafloroboric acid were unsuccessful in our hands, leading instead to exclusive reduction at the 2-position.

In conclusion, we have described an efficient synthesis of dihalothiazoles carboxylates that is amenable to scale-up. Exploiting the differential and orthogonal reactivity provided by the halogen and carboxylate functionality on thiazole should provide access to a wide diversity of novel thiazole derivatives. An elegant example demonstrating the sequential metal mediated cross-coupling reactions of such a template has recently been reported.[8c,9] Our efforts in this regard are underway and will be reported in due course.

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11. Typical procedure for preparation of dihalothiazole from amino thiazole is as follows. All compounds were characterized by LC/MS, ^{1}H and ^{13}C NMR: a mixture of aminothiazole (25.0 g, 144 mmol) and NCS (23.0 g, 173 mmol) in CH_3CN (150 mL) was stirred overnight at rt. The reaction mixture was cooled to 0°C and $CuBr_2$ (38.45 g, 172 mmol) was added followed by dropwise addition of isoamyl nitrite (26.6 g, 30.5 mL, 215 mmol). The mixture was stirred for 2 h. The solvent was removed by evaporation under reduced pressure and the residue was extracted with EtOAc/hexane (1:2) and filtered through silica gel. The combined filtrates were evaporated under reduced pressure to provide a yellow solid. The product was triturated with EtOAc/hexanes to provide the desired 2-bromo-4-carboethoxy-5-chlorothiazole as a yellow solid (30 g, 77%).