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A simple, three-component synthesis of 2-aminothiazoles using trimethylsilyl isothiocyanate

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ABSTRACT

The first multicomponent, solution-phase protocol to prepare privileged 2-aminothiazoles from α-bromocarbonyl compounds and amines (aromatic and aliphatic) using commercially available trimethylsilyl isothiocyanate is described.

Despite the fact that 2-aminothiazoles have been recently flagged as undesired structural elements for screening library design (arguably, due to their thiourea-like character and tendency to modulate promiscuously multiple biological targets),[1,2] this heterocyclic core was key in the design of kinase inhibitors (e.g., the marketed cancer drug, dasatinib[3]) and continues to prove its worth in medicinal chemistry practice. Its privileged character is evidenced by 2-aminothiazoles being reported as antiviral,[4] antiprion,[5] anti-inflammatory,[6] antimicrobial,[7] antitubercular,[8] and anticancer[9] agents.

Numerous methods to access 4-substituted 2-aminothiazoles **1** have been reported in the literature, with most based on the Hantzsch-type[10] condensation of α-halocarbonyl compounds **2** with various thioureas **3**. The latter can, in turn, be generated from primary and secondary amines using isothiocyanate sources such as (a) benzoyl isothiocyanate (**4**) (with subsequent alkaline hydrolysis),[4] (b) Fmoc-isothiocyanate (**5**) (followed by the Fmoc group removal with piperidine),[11] or (c) *tert*-butyl isothiocyanate (**6**), requiring subsequent *tert*-butyl group cleavage under strongly acidic conditions (Scheme 1).[12] However, despite recent developments in the Hantzsch thiazole synthesis (including syntheses under microwave irradiation,[13] in aqueous medium,[14] on solid support,[11] as well as in a flow reactor[15]), there appears to be no convenient protocol that allows conversion of a wide range of α-halocarbonyl compounds and amines (aliphatic and aromatic) into 2-aminothiazoles, in a truly multicomponent format. In this Letter, we report on the development of the first multicomponent solution-phase protocol[16] for the synthesis of 2-aminothioazoles using commercially available trimethylsilyl isothiocyanate (TMSNCS) along with readily available amine and β-halocarbonyl components.

A few isolated examples of the preparation of 2-aminothiazoles using TMSNCS are available in the patent literature.[17] These typically include stepwise transformation of a secondary aliphatic amine into its *N*-thiocarbamoyl derivative, which in turn is exposed to an α-haloketone to give, upon several hours of reflux in EtOH, the desired 2-aminothiazoles (Scheme 2). This literature precedent prompted us to use TMSNCS to prepare the same heterocycles in a multicomponent format.

Initially, we investigated the possibility of transforming a set of substituted anilines into the respective 2-aminothiazoles. To our delight, simple mixing of the anilines with the respective α-bromocarbonyl compounds **2**, followed by addition of TMSNCS and heating the reaction mixture at 70 °C afforded the target 2-aminothiazoles **1a–n** (Scheme 3, equation 1) in good to excellent yields (Table 1). The latter were isolated as hydrobromide salts by simple filtration.

When we attempted to extend the same approach to primary aliphatic amines, we realized that in order for the desired product to be formed, an equivalent of triethylamine[18] had to be added. This observation appeared to be consistent with the following mechanistic considerations (Scheme 4). When exposed to ethanol, TMSNCS rapidly releases isothiocyanic acid,[19] which could react with the α-bromocarbonyl compound **2** to form the respective thiocyanate **7**.[20] While anilines are certainly capable of scavenging

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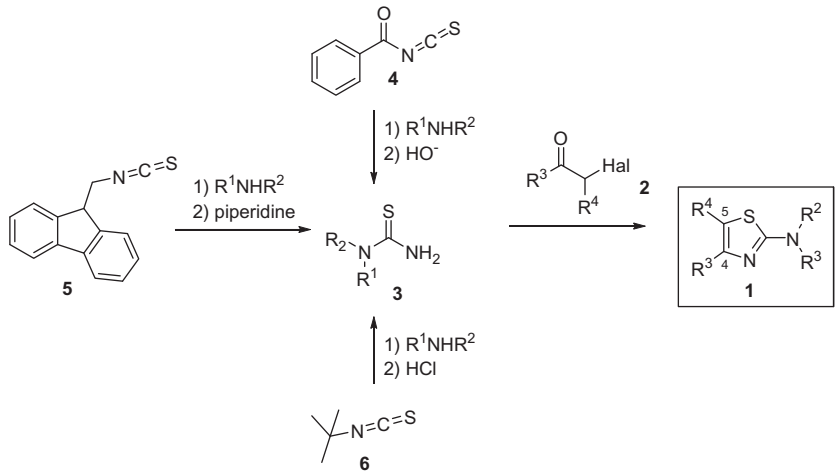
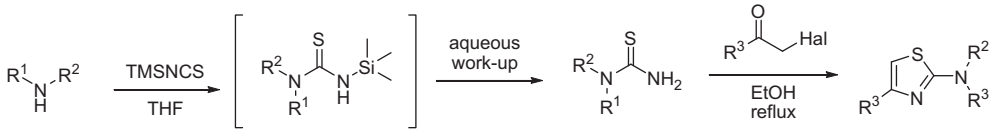
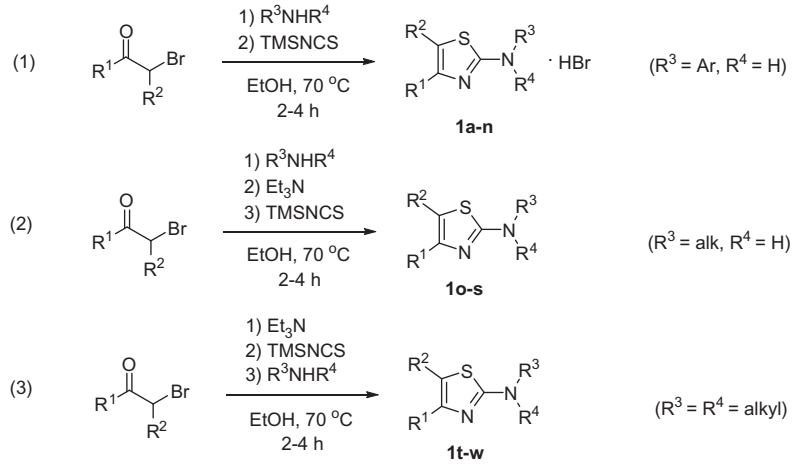


Scheme 1. Various isothiocyanate sources for 4-substituted 2-aminothiazole synthesis reported in the literature.

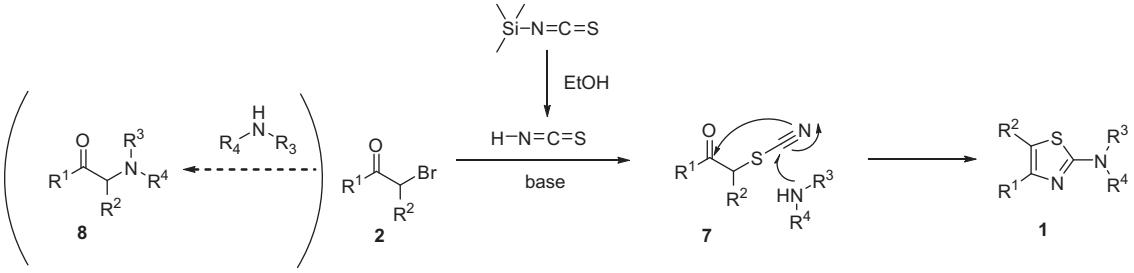


Scheme 2. Examples of the use of TMSNCS to prepare 2-aminothiazoles.[17]



Scheme 3. Multicomponent approach to 2-aminothiazoles developed in this work (see the general procedure for the order of addition of the reagents).

the HBr released when **7** is formed, they are not as basic as aliphatic amines and the amount of unprotonated aniline in the reaction mixture is sufficient to drive the reaction forward, while the 2-aminothiazole product formed becomes a competent scavenger of HBr, thus leading to complete conversions (vide supra). With aliphatic amines, due to their higher basicity, all of the amine present in the reaction mixture is likely to be protonated (as the result of the formation of **7**), and the use of an added organic base is necessary for the reaction to proceed. Apart from this aspect, the general protocol applied to primary aliphatic amines was identical to



Scheme 4. A plausible mechanism for the multicomponent synthesis of 2-aminothiazoles.