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An efficient protocol for the formation of aminothiatriazoles from thiocarbamoylimidazolium salts

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Abstract—A new protocol for the formation of substituted aminothiatriazoles from thiocarbamoylimidazolium salts is outlined. Thiocarbamoylimidazolium salts are synthesized from the corresponding amines by treatment with thiocarbonyldiimidazole (TCDI) followed by methylation with iodomethane. Thiocarbamoylimidazolium salts are shown to act as thiocarbamoyl cation equivalents. Substitution of the salts by azide anion followed by electrocyclization affords substituted aminothiatriazoles in good to excellent yields. © 2002 Published by Elsevier Science Ltd.

Heterocyclic compounds occupy a prominent position amongst modern pharmaceuticals and crop protection agents.[1] Whether they are generated by traditional, structure-based or combinatorial approaches, new methods for their synthesis are required.[2] This is particularly true in the case of lead generation, where efficient and operationally straightforward synthetic methods are required to meet the growing demands of creating diverse compound libraries. One important family of heterocycles are the azoles,[3] which are important both as biologically active compounds as well as synthetic intermediates. As part of our research into these compounds,[4–6] we have become interested in the synthesis of substituted thiatriazoles,[7] and aminothiatriazoles in particular. Monosubstituted aminothiatriazoles **1** (Fig. 1) have been reported to possess a range of interesting biological properties, including antihypertensive,[8] antibacterial,[9] antitubercular,[10] antiviral,[11] fungicidal,[12] anticancer,[13] central nervous system stimulant and muscle relaxant activities.[14] Of the currently available procedures for the synthesis of monosubstituted aminothiatriazoles **1**, the most widely used is based upon the method originally outlined by Freund and co-workers,[15] which involves treatment of thiosemicarbazides with nitrous acid.[10,13,14,16] A related aza transfer procedure with diazonium salts has also been reported.[17] Monosubstituted aminothiatriazoles **1** have also been synthesized through the reaction of hydrazoic acid,[16b,c,18] trimethylsilyl azide[18b,19] or sodium azide[20] with isothiocyanates. These latter reactions are presumed to occur by both 1,3-dipolar cycloaddition and electrocyclization mechanisms. Limitations of these methods include low product yields and the use of hazardous reagents and intermediates.

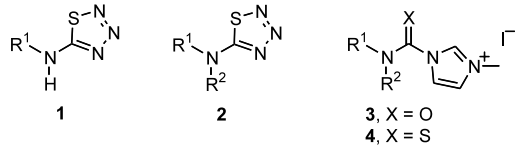

Figure 1.

The synthesis of disubstituted aminothiatriazoles is much less common, despite the fact that such compounds are more stable and less prone to decomposition than their monosubstituted analogs. Lieber and co-workers have reported a two-step protocol for the synthesis of disubstituted aminothiatriazoles from amines, thiophosgene and sodium azide in poor to moderate yields.[21] Thiocarbonyldiimidazole (TCDI) also reacts with hydrazoic acid and trimethylsilyl azide to form 5-(1-imidazolyl)-1,2,3,4-thiatriazole in moderate yields.[22] A lack of a safe and practical synthesis for disubstituted aminothiatriazoles **2** has greatly hindered biological evaluation of these compounds. Consequently, there is a need for an efficient and general method for the synthesis of mono- and disubstituted aminothiatriazoles.

We have recently shown that carbamoylimidazolium salts **3** act as stable and efficient carbamoylation reagents, effectively replacing the use of their unstable and unpleasant carbamoyl chloride equivalents. Nucle-

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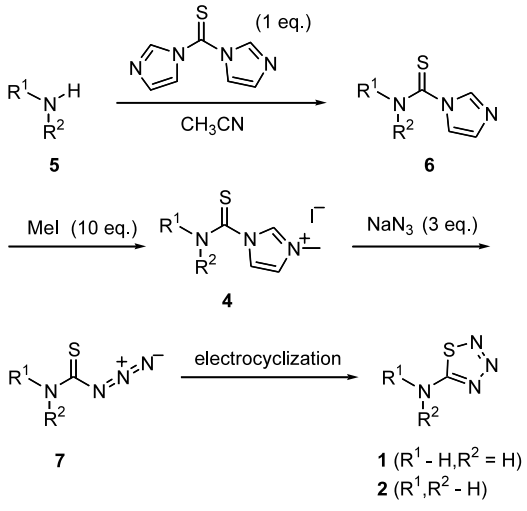
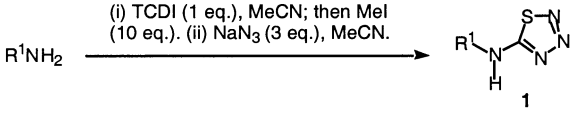
ophilic displacement of the salts **3** results in their ready conversion to ureas,[4a,c] carbamates and thiocarbamates.[4b] By analogy, thiocarbamoylimidazolium salts **4** should act as thiocarbamoylating reagents, and potentially provide a means to synthesize aminothiatriazoles. The requisite thiocarbamoylimidazolium salts **4** are readily prepared by a two step route involving treatment of primary or secondary amines **5** with TCDI to generate thiocarbamoylimidazole intermediates **6** (Scheme 1). Although these intermediates can act as thiocarbamoylating reagents, application of the imidazolium effect, via alkylation of the imidazole ring of **6**, provides the more activated salts **4**. Nucleophilic attack of azide anion would then result in displacement of the *N*-methylimidazole, forming intermediate thiocarbamoyl azides **7**, which can then undergo rapid electrocyclization[23] at room temperature to give the corresponding aminothiatriazoles **1** or **2**.

Our initial studies focussed upon the synthesis of monosubstituted aminothiatriazoles **1**. Reaction of primary amines (1.0 equiv.) with TCDI (1.0 equiv.) in MeCN furnished the thiocarbamoyl imidazoles **6** after 30 minutes of stirring at room temperature. Reaction of **6** with MeI (10 equiv.) over 18–24 hours at room temperature produced the imidazolium salts **4**. The imidazolium salts **4** were then azeotroped with MeCN (2×) to remove excess MeI before reaction with sodium azide (3.0 equiv.) in MeCN for 3–18 hours to afford the monosubstituted aminothiatriazoles **1** (Table 1). In the majority of cases, the only detectable by-product produced was *N*-methyl imidazole, which was easily removed by washing the organic layer (EtOAc) with dilute ammonium chloride. All reactions gave monosubstituted aminothiatriazoles within 2 days at room temperature in good to excellent yields (reaction yields are unoptimized). The protocol for this synthesis does not involve chromatographic purification of the intermediates. Compared to existing protocols for the formation of monosubstituted aminothiatriazoles **1**, this procedure avoids the use of harsh reaction conditions, unpleasant reagents or extremes of pH.



Scheme 1.

Table 1. Formation of monosubstituted aminothiatriazoles **1** via thiocarbamoylimidazolium salts



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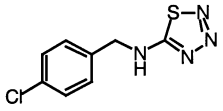
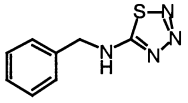
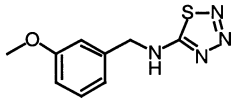
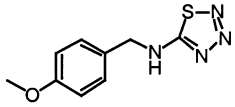
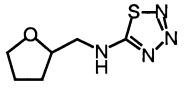
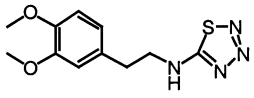
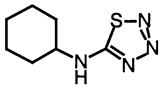
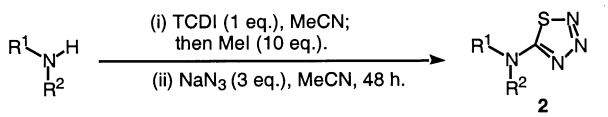
1		quant.
2		77%
3		88%
4		quant.
5		70%
6		80%
7		84%

Interestingly, treatment of the thiocarbamoyl imidazoles **6** with sodium azide at room temperature gave products in half the reaction time but in lower yields than when the activated salts **4** were employed. Heating the thiocarbamoyl imidazoles **6** with sodium azide at 60°C was also attempted, but not pursued, since this method was found to result in by-product formation.

The existing method for the synthesis of disubstituted aminothiatriazoles utilizes highly toxic thiophosgene. The application of this protocol for the preparation of disubstituted aminothiatriazoles **2** is hence of greater significance (Scheme 1 and Table 2). For example, reaction of morpholine with TCDI (1.0 equiv.) at room temperature generated the corresponding thiocarbamoyl imidazole intermediate **6** in 1 hour, which was then activated to the salt **4** by treatment with MeI (10 equiv.) for 1 day. Optimal reaction times for the methylation were 1 or 2 days, depending upon the substrate used. Thus, the starting materials 1,2,3,4-tetrahydroquinoline and *N*-isopropylbenzylamine required 2 days for methylation, while all others required 1 day. A 10-fold excess of iodomethane was used in these exploratory studies, but less alkylating agent can also be used. Azeotropic removal of the excess MeI with

Table 2. Formation of disubstituted aminothiatriazoles **2** via thiocarbamoylimidazolium salts[24]



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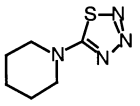
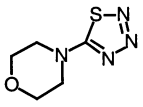
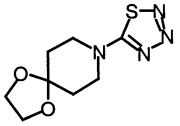
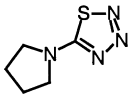
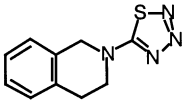
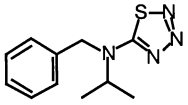
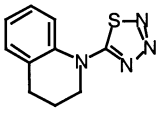
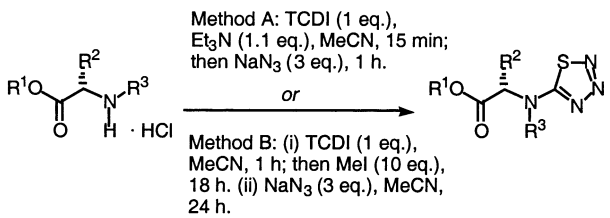
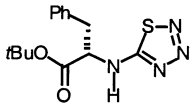
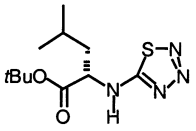
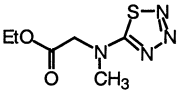
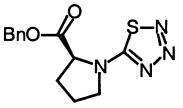
1		74%
2		96%
3		80%
4		62%
5		91%
6		62%
7		73%

MeCN, followed by reaction with azide ion (3.0 equiv.) for 18–24 hours afforded the disubstituted aminothiatriazoles in good to excellent yields (Table 2). The products require column chromatography to remove minor impurities after the final step. Although the protocol for this synthesis does not involve purification of the intermediates, the disubstituted intermediates **6** and **4** can be purified and stored if necessary. For comparison, the monosubstituted intermediates **6** and **4** ($R^1 \neq H$, $R^2 = H$) are less stable, and were always used directly for the next reaction.

We are also interested in the use of heterocycle-peptide conjugates as peptidomimetics. As a preliminary test of this chemistry N-terminal aminothiatriazole modified amino acids have been synthesized using two methods (Table 3). In the case of monosubstituted aminothiatriazoles, the amino acid derivatives are converted into the thiocarbamoyl imidazoles **6**, but here activation to the salts **4** is not required, with attack by azide anion

Table 3. Formation of mono- and disubstituted amino acid derived aminothiatriazoles



Entry	Product	Method	Isolated Yield (%)
1		A	quant.
2		A	78%
3		B[25]	94%
4		B	77%

on **6** occurring in good yields. Thus, the primary amines, Phe-O^{t}Bu·HCl and Leu-O^{t}Bu·HCl, react with TCDI (1.0 equiv.) and triethylamine (1.1 equiv.) at room temperature for 15 minutes to afford intermediates **6** which required no additional purification. Direct treatment with sodium azide (3.0 equiv.) and stirring at room temperature for 1 hour gave monosubstituted amino acid derived thiatriazoles in good yield (method A) (Table 3, entries 1 and 2). For the synthesis of disubstituted amino acid thiatriazoles, activation as the salts **4** was required (method B) (Table 3, entries 3 and 4).[24,25]

In conclusion, mild methods for the preparation of mono- and disubstituted aminothiatriazoles from commercially available starting materials have been developed. The products are easily isolated by simple extraction or column chromatography techniques and are obtained in high yields. The method is particularly useful for the preparation of disubstituted aminothiatriazoles, which despite their greater stability have not been thoroughly biologically evaluated, due to difficulties in their synthesis using highly toxic thiophosgene. We are now integrating this method into our combinatorial chemistry program, and will report further applications of thiocarbamoylimidazolium salts to solution phase and polymer-supported chemistry in due course.

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23. Recent calculations (6-31G basis set) indicate that electrocyclization of thioformyl azide to thiatriazole is exothermic by 5 kcal mol^{-1}, occurring with an activation barrier of 18 kcal mol^{-1}. See: Abu-Eittah, R. H.; Moustafa, H.; Al-Omar, A. M. *Chem. Phys. Lett.* **2000**, *318*, 276–288.
24. General synthetic procedure. *CAUTION: although we encountered no problems, azides and nitrogen rich compounds can be potentially explosive and should be handled with due caution.*[26] To a solution of TCDI (258 mg, 1.3 mmol) in MeCN (5 mL) was added the amine (1.3 mmol) and this was stirred at room temperature for 1 h. Iodomethane (0.81 mL, 13.0 mmol) was then added and the reaction stirred at room temperature for 18–48 h. The excess iodomethane was fully removed by azeotropic distillation with MeCN (2×20 mL). The resulting residue was taken up in MeCN (5 mL). NaN_3 (254 mg, 3.9 mmol) was added and the mixture was stirred at room temperature for 18–24 h. The solvent was removed in vacuo, and the crude product purified using silica gel column chromatography.
25. **(Methyl-[1,2,3,4]thiatriazol-5-yl-amino)-acetic acid ethyl ester** (Table 3, entry 3): The crude reaction mixture was purified by silica gel chromatography (7:3 hexanes/EtOAc to 1:1 hexanes/EtOAc as a gradient). The product was obtained as a yellow oil in 94% yield (223 mg). $R_f = 0.15$ (7:3 hexanes/EtOAc); IR (nujol) ν 2927, 2853, 1747, 1557, 1448, 1375, 1210, 1026 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.39 (2H, s), 4.22 (2H, q, $J = 7.0$ Hz), 3.29 (3H, s), 1.28 (3H, t, $J = 7.0$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.48, 167.74, 62.20, 55.37, 44.17, 14.50; HRMS (EI) calculated for (M^+) $C_6H_{10}N_4O_2S$: 202.0519; observed: 202.0525.
26. For discussion on the hazards associated within azides, see: *Prudent Practices in the Laboratory: Handling and Disposal of Chemicals*; National Academy Press: Washington, DC, 1995.