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Cyclization of Activated Methylene Isocyanides with Methyl *N*(*N*),*N*′-Di(tri)substituted Carbamimidothioate: A Novel Entry for the Synthesis of *N*,1-Aryl-4-tosyl/ethoxycarbonyl-1*H*-imidazol-5-amines

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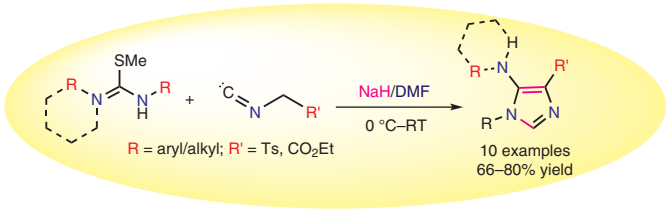

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Abstract Base-induced cyclization of active methylene isocyanides with carbamimidothioates for the synthesis of *N*,1-aryl-4-tosyl/ethylcarboxy-1*H*-imidazol-5-amines is reported. The diversity of the reactions is exemplified by using various carbamimidothioates obtained from symmetrical *N*,*N*-disubstituted, unsymmetrical *N*,*N*,*N*-trisubstituted, and unsymmetrical *N*,*N*-disubstituted thioureas. This diversity is further enriched by different isocyanides. A mechanism for the formation of the title compounds is proposed.

Key words imidazoles, isocyanides, cyclization, carbamimidothioate, oxazole

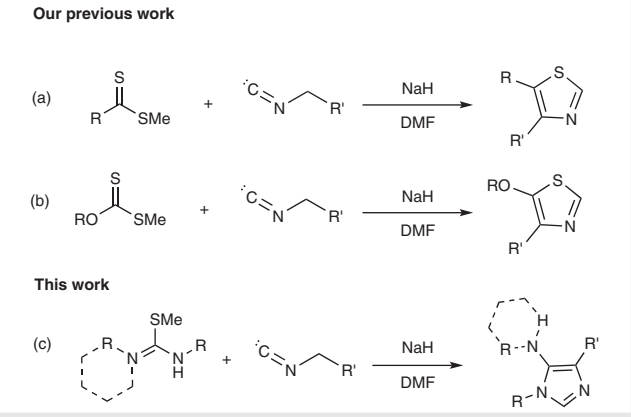
Imidazoles are an important group of heterocyclic compounds with respect to their applications in medicinal chemistry. For instance, they exhibit antimicrobial,[1] antitubercular,[2] antidepressant,[3] anticancer,[4] antiviral,[5] antileishmanial,[6] anti-inflammatory, and analgesic activity.[7] Besides, they demonstrate p38 MAP kinase,[8] CYP26A1,[9] EGFR,[10] haem oxygenase,[11] aldosterone synthase,[12] histone deacetylase,[13] 17α-hydroxylase-17,20-lyase[14] and HIV-1 reverse transcriptase inhibition activities.[15] Furthermore, other examples are agonists of opioid,[16] α2-adrenergic,[17] TAAR1,[18] and γ-aminobutyric acid receptors,[19] while other examples are nonpeptide ACE,[20] orthopoxvirus IL-18,[21] histamine H_3,[22] and leukotriene B4 receptor antagonists.[23] Given this large range of biological activities, the development of new synthetic methods for the synthesis of imidazoles is of continuing interest.

Classical methods for the synthesis of imidazoles are the Radiszewski synthesis, the Wallach synthesis and the Markwald synthesis.[24] Recently reported methods include Cu-catalyzed cyclization of *N*-arylbenzamidines, nitroalkanes and aryl acetic acids,[25] *N*-arylbenzamidines and nitroalkenes,[26] Rh-catalyzed reaction between 1-sulfonyl triazoles and nitriles,[27] Cu-catalyzed cyclization of alkynes with amidines,[28] $FeCl_3/I_2$-catalyzed aerobic oxidative coupling of amidines and chalcones,[29] and cyclization of α-azido chalcones, aryl aldehydes and anilines.[30] However, methods available for the synthesis of aminoimidazoles are scant. The reported methods include the reaction of α-nitroepoxides, cyanamide and amines,[31] reaction of propargylamines with carbodiimides,[32] Staudinger/aza-Wittig/Ag(I)-catalyzed cyclization/isomerization reaction of propargylazides, isocyanates and amines,[33] [3+2] annelation of 1,2,4-oxadiazoles/4,5-dihydro-1,2,4-oxadiazoles with ynamides[34] and cyclization of 2-bromo-2-alkenones with guanidine.[35]

Since the area of imidazole synthesis is so broad, we focused our attention on their synthesis from isocyanides. Such approaches include cyclization of isocyanides with carbodiimides,[36] reaction of imidoyl chlorides with active methylene isocyanides,[37] homocyclization of active methylene isonitriles,[38] reaction of unsaturated isonitriles from amines[39] and cyclization of active methylene isocyanides with azo compounds,[40] triazine,[41] formimidates,[42] imines,[43]

N-tosylimines,[44] nitriles,[45] and isonitriles.[46] Other methods involve cyclization of isocyanoacetates with isothiocyanates,[47] isocyanoacetamides with sulfenyl chlorides[48] and enaminoisonitriles with amines.[49] The Ugi and Passerni reactions may also afford imidazoles.[50] Unfortunately, these methods suffer from one or more limitations such as use of moisture-sensitive substrates,[36,37,44,47] lack of structural diversity,[38] difficult to obtain substrates[39,49] or long reaction times. To our knowledge, the synthesis of imidazoles from carbamimidothioates has not been reported.

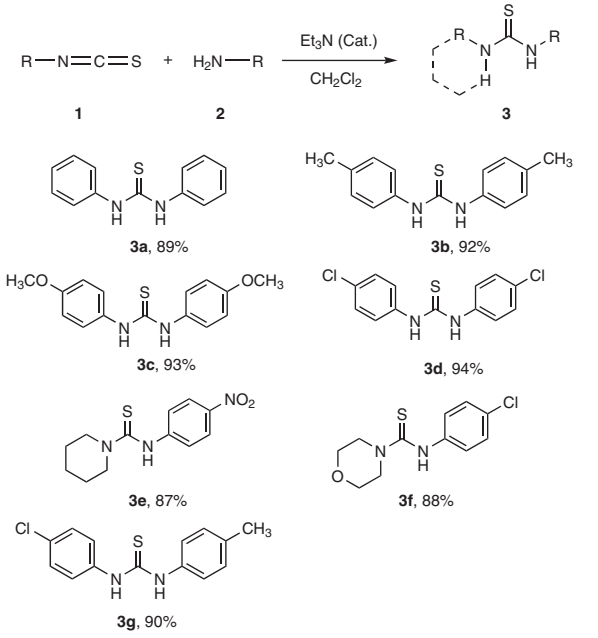
We are actively involved in developing new sulfur building blocks and exploring their synthetic applications.[51] In parallel, we have also reported isocyanide cyclization reactions such as base-induced cyclization of active methylene isocyanides with dithioesters (Scheme 1a),[51a] xanthate esters (Scheme 1b),[51f] tandem sequential-tandem cyclization of carboxylic acids, tosyl chloride and TosMIC[52] and benzyl alcohols/benzyl bromides with TosMIC via oxidation with T3P® in DMSO.[53] In a continuation of these studies, we have developed a new protocol for the synthesis of *N*,*N*′(*N*)-di(tri)substituted carbamimidothioates and extended their application for the synthesis of *N*,1-aryl-4-tosyl/ethylcarboxy-1*H*-imidazol-5-amines by cyclization with active methylene isocyanides in the presence of sodium hydride (Scheme 1c).



Scheme 1 Our previous work and present work

We started our study by synthesizing the required substrates according to Table 1 and Table 2. Thus, *N*,*N*-disubstituted thioureas **3** were synthesized by reacting arylisothiocyanates **1** with amines **2** in dichloromethane catalyzed by triethylamine[54] to furnish symmetrical disubstituted thioureas **3a–d** in 89–94% yield and unsymmetrical thioureas in **3e–g** in 87–90% yield (Table 1). These were regioselectively *S*-methylated with methyl iodide to form carbamimidothioates **4** in a heterogeneous medium of benzene and 20% sodium hydroxide in the presence of tetrabutylammonium bromide as phase-transfer catalyst (Table 2).[55] Thus, the symmetrical disubstituted thioureas **3a–d** furnished the corresponding carbamimidothioates **4a–d** in 94–97% yield. Similarly, unsymmetrical trisubstituted thioureas **3e** and **3f** furnished **4e** and **4f** in 89 and 90% yield, respectively. Finally, the unsymmetrical disubstituted thiourea **3g** gave an inseparable regioisomeric mixture of carbamimidothioates **4g** and **4h** in 85% yield.

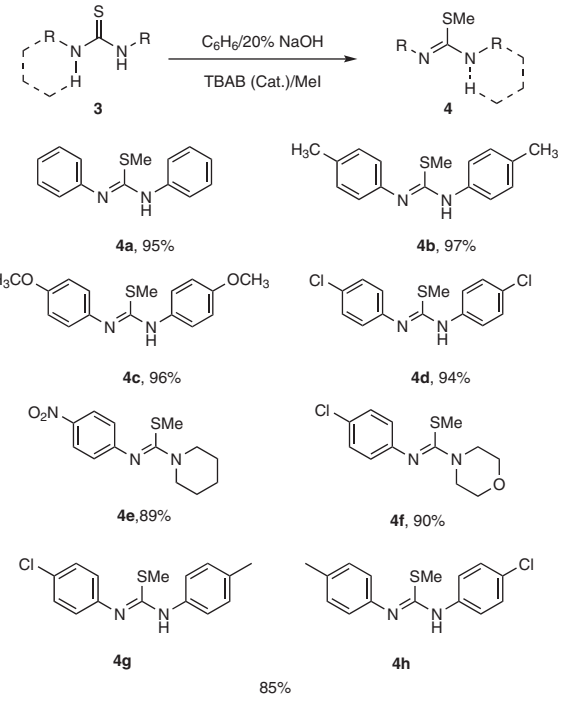
Table 1 Synthesis of Thioureas **3** from Isothiocyanates **1** and Amines **2**[a]



[a] Reaction conditions: **1** (10 mmol), **2** (10 mmol), Et_3N (0.1 mmol), CH_2Cl_2 (10 mL), 1–2 h.

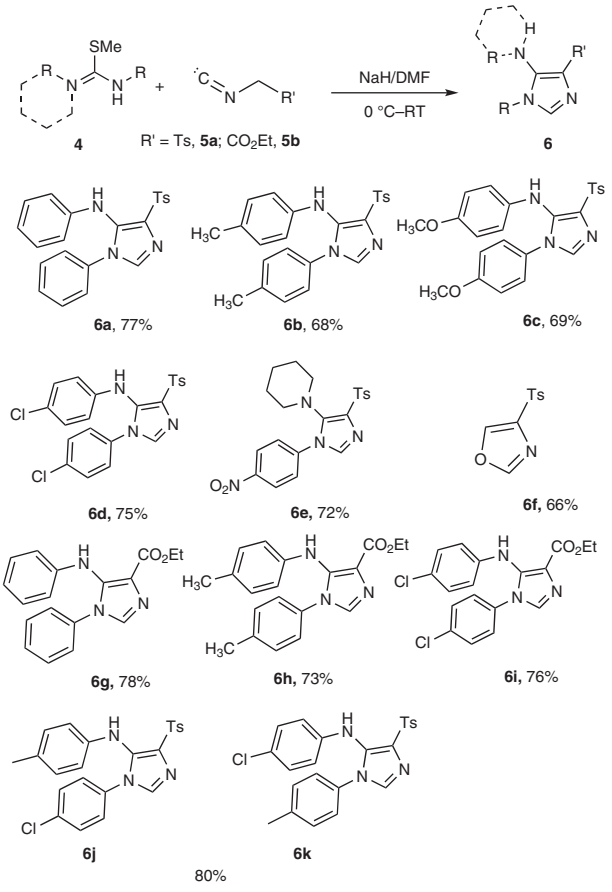
Subsequent to the synthesis of the required substrates, we examined a model reaction of methyl *N*,*N*′-diphenylcarbamimidothioate **4a** with TosMIC **5a** in the presence of various bases such as sodium hydride, potassium *tert*-butoxide, DBU, triethylamine and K_2CO_3 in DMF as a solvent of choice. Among these, sodium hydride was found to be the best base, giving *N*,1-diphenyl-4-tosyl-1*H*-imidazol-5-amine (**6a**) in 77% yield (Table 3).[56] The generality of the method was demonstrated for the synthesis of *N*,1-diaryl-4-tosyl-1*H*-imidazol-5-amines **6b–d**, which were obtained in 68–75% yield from the corresponding carbamimidothioates **4b–d**. Furthermore, methyl *N*-(4-nitrophenyl)piperidine-1-carbimidothioate (**4e**) gave 1-(1-(4-nitrophenyl)-4-tosyl-1*H*-imidazol-5-yl)piperidine (**6e**) in 72% yield. Interestingly, the structural analogue of **4e**, methyl *N*-(4-chlorophenyl)morpholine-4-carbimidothioate (**4f**) did not furnish the anticipated product 1-(1-(4-chlorophenyl)-4-tosyl-1*H*-imidazol-5-yl)morpholine; instead 4-tosyloxazole **6f** was obtained in 66% yield. The unexpected product **6f** was obtained *via* 1,3-dipolar cycloaddition of TosMIC with DMF followed by elimination. At this stage, reason for the low reactivity of **4f** with ToSMIC is not clear.

Table 2 Synthesis of Methyl Carbamimidothioates **4** from Thioureas **3**[a]



[a] Reaction conditions: **3** (8 mmol), tetra-*n*-butylammonium bromide (TBAB; 0.8 mmol), MeI (8 mmol), C_6H_6 (20 mL), 20% NaOH (20 mL), 30–60 min.

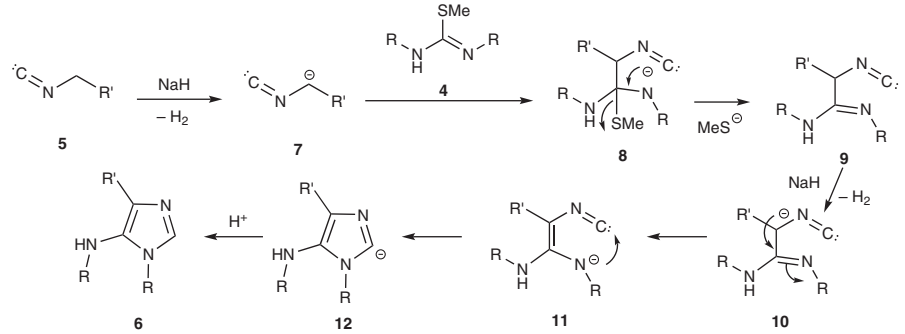
Table 3 Synthesis of *N*,1-(Aryl)-4-tosyl/ethylcarboxy/aryl-1*H*-imidazol-5-amine **6**[a]



[a] Reaction conditions: **4** (3 mmol), **5** (3 mmol), NaH (6 mmol), DMF (3 mL), 0.5–2 h.

The structural diversity of the methodology was tested by reacting ethyl isocyanoacetate with carbamimidothioates **4a**, **4b** and **4d**, which furnished the corresponding ethyl 1-aryl-5-(arylamino)-1*H*-imidazole-4-carboxylates **6g–i** in 73–78% yield. Finally, the regioisomeric mixture of methyl *N*′-(4-chlorophenyl)-*N*-(*p*-tolyl)carbamimidothioate (**4g**) and methyl *N*-(4-chlorophenyl)-*N*′-(*p*-tolyl)carbamimidothioate (**4h**) also underwent smooth reaction with TosMIC to give 1-(4-chlorophenyl)-*N*-(*p*-tolyl)-4-tosyl-1*H*-imidazol-5-amine (**6j**) and *N*-(4-chlorophenyl)-1-(*p*-tolyl)-4-tosyl-1*H*-imidazol-5-amine (**6k**) in 80% yield, although these proved to be inseparable by column chromatography.

A plausible mechanism for the formation of imidazoles **6** is depicted in Scheme 2. The first step involves abstraction of a proton from activated methylene isocyanide **5** by sodium hydride. Condensation of carbanion **7** with carbamimidothioate **4** gives an intermediate **9** *via* formation of **8**. Abstraction of another proton by sodium hydride from **9** gives anion **10**, cyclization of which gives imidazole carbanion **11**, which is protonated during work-up to give the final imidazole **6**.



Scheme 2 Plausible mechanism for the formation of imidazoles **6**

In conclusion, we have developed a new route for the synthesis of *N*,1-aryl-4-tosyl/ethylcarboxy-1*H*-imidazol-5-amines by the base-induced cyclization of activated methylene isocyanides with carbamimidothioates. The generality of the protocol has been demonstrated with carbamimidothioates obtained from symmetrical *N*,*N*-disubstituted, unsymmetrical *N*,*N*,*N*-trisubstituted, and unsymmetrical *N*,*N*-disubstituted thioureas. Both TosMIC and ethyl isocyanoacetate successfully formed the corresponding products. Unexpectedly, methyl *N*-(4-chlorophenyl)morpholine-4-carbimidothioate gave 4-tosyloxazole.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690328.

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(54) **Synthesis of Substituted Thioureas 3; General Procedure:** A mixture of arylisothiocyanate **1** (10 mmol), amine **2** (10 mmol) and triethylamine (0.1 mmol) in dichloromethane (10 mL) was stirred for 1–2 h. The progress of the reaction was monitored by TLC and, after completion, the dichloromethane was removed under reduced pressure. The residue was treated with conc. HCl (1 mL) in water (50 mL) and filtered. The precipitate was washed with water, drained, and dried at room temperature.
1,3-Diphenylthiourea (3a): Yield: 89%; white solid; mp 150–153 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 8.19 (s, 2 H, NH), 7.35–7.41 (m, 8 H, Ar-H), 7.24–7.28 (m, 2 H, Ar-H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 179.6, 137.1, 129.6, 127.1, 125.3. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{13}N_2S$: 229.0799; found: 229.0790.
(55) **Synthesis of Carbamimidothioates 4; General Procedure:** To a solution of substituted thiourea **3** (8 mmol) in benzene (20 mL) and 20% NaOH (20 mL), *tetra-n*-butylammonium bromide (0.8 mmol) and MeI (8 mmol) were added. The progress of the reaction was monitored by TLC and, after the completion of the reaction, the organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 20 mL). The combined organic layers were washed with water (25 mL), brine (25 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to obtain the crude product, which was purified by column chromatography over silica gel, eluting with hexane/ethyl acetate (8:2).
Methyl *N,N′*-Diphenylcarbamimidothioate (4a): Yield: 95%; white solid; mp 95–100 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.08–7.33 (m, 10 H, Ar-H), 6.34 (s, 1 H, NH), 2.30 (s, 3 H, SCH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 150.0, 131.6, 129.0, 123.1, 134.0, 131.4, 123.5, 121.6, 121.1, 14.5. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{15}N_2S$: 243.0955; found: 243.0950.
(56) **Synthesis of Imidazole 6; General Procedure:** To a solution of sodium hydride (6 mmol) in DMF (3 mL), substituted carbamimidothioate **4** (3 mmol) and tosylmethyl isocyanide/ethyl isocyanoacetate **5** (3 mmol) were added at 0 °C. The reaction mixture was stirred at room temperature and the progress of the reaction was monitored by TLC. After completion of the reaction, water (25 mL) was added and the mixture was

extracted with ethyl acetate (3 × 25 mL), the combined organic phases were washed with brine (25 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give the crude product, which was purified by column chromatography over silica gel, eluting with hexane/ethyl acetate (8:2).

***N*,1-Diphenyl-4-tosyl-1*H*-imidazol-5-amine (6a):** Yield: 77%; brown solid; mp 204–209 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.79 (d, *J* = 8.0 Hz, 2 H, Ar-H), 7.49 (s, 1 H, Ar-H), 7.25–7.28 (m, 2 H, Ar-H), 7.20–7.25 (m, 4 H, Ar-H), 6.97–7.00 (m, 2 H, Ar-H), 6.89 (s, 1 H, Ar-H), 6.78–6.80 (m, 2 H, Ar-H), 6.60 (d, *J* = 8.0 Hz, 2 H, Ar-H), 2.36 (s, 3 H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 143.9, 142.1, 138.6, 136.2, 134.7, 129.6, 129.4, 128.9, 128.7, 128.1, 127.5, 126.1, 124.2, 122.1, 117.7, 29.6. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{20}N_3O_2S$: 390.1276; found: 390.1274.