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-1H-imidazol-5-amines

Dukanya a,b
Toreshetahally R. Swaroop a,*
Shobith Rangappa c
Kanchugarakoppal S. Rangappa a,b
Basappa a,*

a Department of Studies in Organic Chemistry, University of Mysore, Manasagangothri, Mysuru 570 006, Karnataka, India, swarooptr@gmail.com
salundibasappa@gmail.com
b Department of Studies in Chemistry, University of Mysore, Manasagangothri, Mysuru 570 006, Karnataka, India
rangappaks@gmail.com
c Adichunchanagiri Institute for Molecular Medicine, Nagamangala 571448, Karnataka, India

N R' C NaH/DMF 0 °C–RT

R = aryl/alkyl; R' = Ts, CO2Et 10 examples 66–80% yield

Received: 27.06.2019
Accepted after revision: 29.07.2019
Published online: 19.08.2019

License terms: CC BY

Abstract Base-induced cyclization of active methylene isocyanides with carbamimidothioates for the synthesis of N,1-aryl-4-tosyl/ethoxycarbonyl-1H-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 antianxiety,4 antiviral,5 antileishmanial,6 anti-inflammatory, and analgesic activity.7 Besides, they demonstrate p38 MAP kinase,8 CYP26A1,9 EGFR,10 haem oxygehase,11 aldosterone synthase,12 histone deacetylase,13 17β-hydroxysteroid-17,20-lyase14 and HIV-1 reverse transcriptase inhibition activities.15 Furthermore, other examples are agonists of opioid,16 a2-adrenergic,17 TAAR1,18 and γ-amino butyric acid receptors,19 while other examples are nonpeptide ACE,20 orthopoxvirus IL-18,21 histamine H3,22 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 Radiszelewski 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 FeCl3/I2-catalyzed aerobic oxidative coupling of amidines and chalcones,29 and cyclization of α-azido chalcones, aryl aldehydes and amines.30 However, methods available for the synthesis of aminomidazoles are scant. The reported methods include the reaction of α-nitroepoxides, cyamidame 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 ynamides34 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 amines39 and cyclization of active methylene isocyanides withazo compounds,40 triazine,41 formimidates,42 imines,43
N-tosylimines, nitriles, and isonitriles. Other methods involve cyclization of isocynoacetates with isothiocyanates, isocyanacetamides with sulfonyl chlorides and enaminoisothiocyanates with amines. The Ugi and Passerni reactions may also afford imidazoles. Unfortunately, these methods suffer from one or more limitations such as use of moisture-sensitive substrates, lack of structural diversity, difficult to obtain substrates 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. In parallel, we have also reported isocyanide cyclization reactions such as base-induced cyclization of active methylene isocyanides with dithioesters (Scheme 1a), xanthate esters (Scheme 1b), tandem sequential-tandem cyclization of carboxylic acids, tosyl chloride and TosMIC and benzyl alcohols/benzyl bromides with TosMIC via oxidation with T3P in DMSO. 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-1H-imidazol-5-amine by cyclization with active methylene isocyanides in the presence of sodium hydride (Scheme 1c).

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 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). 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 regiosomeric mixture of carbamimidothioates 4g and 4h in 85% yield.

| Table 1 | Synthesis of Thioureas 3 from Isothiocyanates 1 and Amines 2 |

![Scheme 1](image-url)

Subsequent to the synthesis of the required substrates, we examined a model reaction of methyl \( N,N'\)-diphenylcarbimidothioate 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-1H-imidazol-5-amine (6a) in 77% yield (Table 3). The generality of the method was demonstrated for the synthesis of \( N,1\)-diaryl-4-tosyl-1H-imidazol-5-amine 6b–d, which were obtained in 68–75% yield from the corresponding carbamimidothioates 4b–d. Furthermore, methyl \( N\)-(4-nitrophenyl)piperidine-1-carbamimidothioate (4e) gave 1-\((1\times4\text{-nitrophenyl})-4\text{-tosyl-1H-imidazol-5-yl)piperidine (6e}) in 72% yield. Interestingly, the structural analogue of 4e, methyl \( N\)-(4-chlorophenyl)morpholine-4-carbamimidothioate (4f) did not furnish the anticipated product 1-\((1\times4\text{-chlorophenyl})-4\text{-tosyl-1H-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.
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)-1H-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-1H-imidazol-5-amine (6j) and N-(4-chlorophenyl)-1-(p-tolyl)-4-tosyl-1H-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 carb-anion 11, which is protonated during work-up to give the final imidazole 6.
In conclusion, we have developed a new route for the synthesis of N₁,1-aryl-4-tosyl/ethylcarboxy-1H-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,N-disubstituted thioureas. Both TosMIC and ethyl isocyanacete successfully formed the corresponding products. Unexpectedly, methyl N-(4-chlorophenyl)morpholine-4-carbamidothioate gave 4-tosyloxazole.

Funding Information
This research was supported by University Grants Commission (UGC) and Israel Science Foundation (ISF) (ISF-UGC: FNO. 6-6/2016(IC)); Council of Scientific and Industrial Research (CSIR; No. 02/0291/17/EMR-II), Department of Biotechnology, Ministry of Science and Technology and Technology (DBT: No. BT/PR/8064/BID/7/441/2013), and the Vision Group on Science and Technology (VGST/CESEM-637/2018).

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

References and Notes
Synthesis of Imidazole 6; General Procedure:

(56)


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-1H-imidazol-5-amine (6a):** Yield: 77%; brown solid; mp 204–209 °C. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta = 7.79$ (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), 7.00 (m, 2 H, Ar-H), 6.97–7.00 (m, 2 H, Ar-H), 6.79 (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): $\delta = 143.9$, 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$_3$O$_2$S: 390.1276; found: 390.1274.