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Recent Advances in Synthesis of Derivatives of Imidazolidine-2-thione Derivatives

Ruchi Bharti* and Renu Sharma*

[1]*Department of chemistry, University Institute of Sciences, Chandigarh University, Gharuan-140413*

[2] *Department of chemistry, University Institute of Sciences, Chandigarh University, Gharuan-140413*

[1]*ruchi.uis@cumail.in,* [2] *hod.chemistry.uis@cumail.in*

Abstract

Imidazolidine-2-thiones are an important class of five member heterocyclic compounds having considerable pharmaceutical interest. They are having various remarkable biological activities such as antimicrobial, anti HIV, antifungal and so forth. The many synthetic strategies have been developed in the past few decades for the synthesis of imidazolidine-2-thione. The main purpose of this review is to update on the progress made on the development of new methodologies for the synthesis of imidazolidine-2-thione derivatives in the period between mid-2012 to the end of 2018.

Keywords: *Imidazolidine-2-thiones, Thiourea derivatives, spiro[imidazolidine-2-thioneoxindoles], Metal complexes of Imidazolidine-2-thiones.*

1. Introduction

In the recent years much attention was given to the synthesis of fused N-, S- and O-containing heterocycles which constitute pharmacophoric fragments of known medical agents or natural biologically active organic compounds. Imidazolidine-2-thiones[1-2] **1** are special classes of biologically relevant thiourea derivatives endowed with antithyroid,[3] antitumor,[4] antimicrobial,[5] and dopamine inhibition activities.[6] Some of the pharmaceutically active imidazolidine-2-thione derivatives **1a-f** are shown in **Figure 1**.

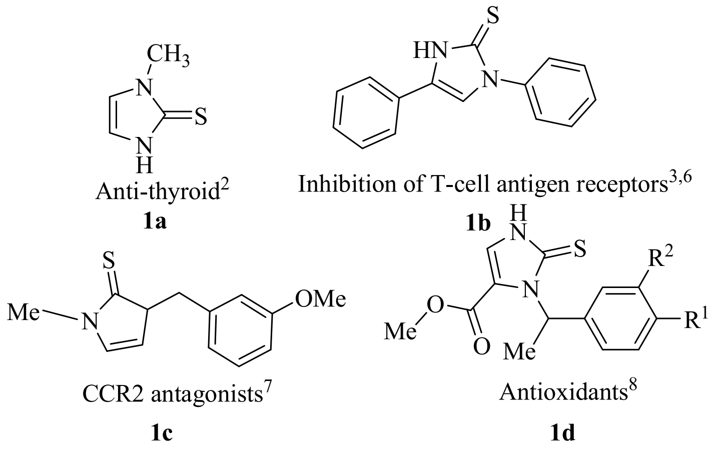


Figure 1: Examples of pharmaceutically important imidazolidine-2-thione derivatives

Imidazolidine-2-thione **1** with its functional moiety –N(H)-C(=S)-N(H)- is one of the simplest prototypes of heterocyclic thiomides have shown interesting coordination variability in their reaction with metal ions which has resulted in the formation of a diverse range of coordination compounds.[9] Recently, imidazolidine-2-thione was found to induce DNA damage to the liver, lungs, spleen and kidneys in mice.[10] Our interests are mainly on neutral imdt for two reasons, as

(i) the exocyclic sulfur is capable of coordinating metals via η_1-S, μ_2-S, μ_3-S and μ_4-S bonding modes[11-14] (**Figure 2**). This versatility of imdt is attributed to the large size of the S atom and (ii) the C=S bond can attach to a metal center at a variety of angles to form helix or nonplanar structures for different configurations.[15] Furthermore, the endocyclicc N-H moieties are capable of forming hydrogen-bonded aggregations.[16-17]

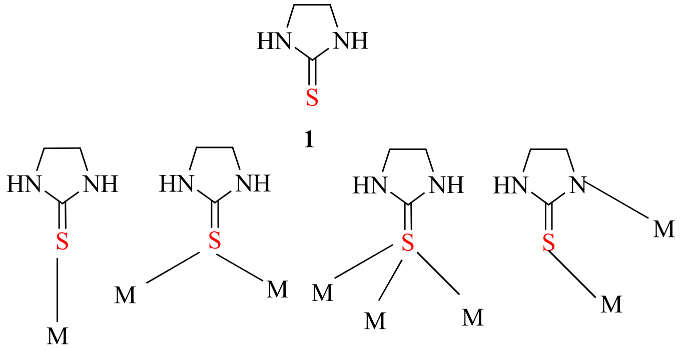


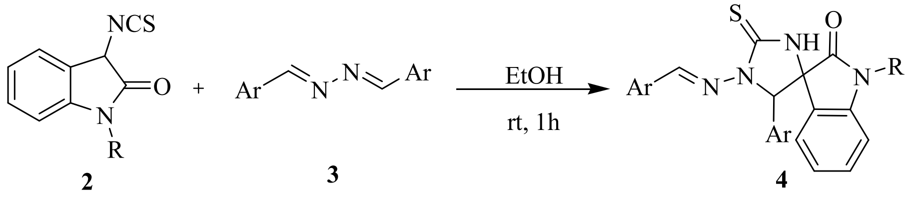
Figure 2: Four different coordination modes for S of imdt.

In spite of their relevance, the preparation of imidazolidine-2-thiones is so far troublesome. Indeed, harsh reaction conditions are often required, and access to starting materials may be somewhat difficult. In recent years, considerable efforts have been devoted to the development of novel and more efficient methods for the preparation of imidazolidine-2-thione (imdt) derivatives. Besides conventional multi-step methods, one-pot, solid-phase and microwave-assisted approaches have been published recently.[18-22]

Herein, we report a systematic study of recent advances in the synthesis of imidazolidine-2-thione (imdt) derivatives.

1.1 Synthesis of functionalized spiro[imidazolidine-2-thioneoxindoles]

An efficient protocol has been developed by Xie et al.,[23] for the synthesis of spiro[imidazolidine-2-thioneoxindoles] derivatives **4** with multi-functionalized groups via catalyst-free domino reaction by domino Mannich/cyclization of 3-isothiocyanato oxindole **2** with bis(arylmethylidene)hydrazines **3** (**Scheme 1**). The domino reaction can proceed smoothly in an environmentally benign conditions and provides pure functionalized spiro[imidazolidine-2-thioneoxindoles] derivatives **4** with excellent diastereoselectivity in moderate to excellent yield (60-94%) A variety of 3-isothiocyanato oxindole derivatives as well as bis(arylmethylidene)hydrazines were tested to synthesize highly distereoselective (> 99:1) spiro[imidazolidine-2-thioneoxindoles] derivatives **4**.



Yield = 60-94%

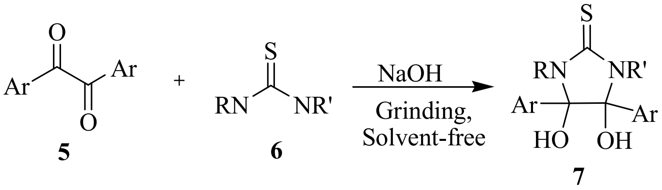
R = n-C_3H_7, Me

Ar = C_6H_5, p -ClC_6H_4, m -ClC_6H_4, p -BrC_6H_4, p -$CF_3C_6H_4$, p -$MeOC_6H_4$, m -$MeOC_6H_4$, 2-Furyl, o -ClC_6H_4, p -$NO_2C_6H_4$, m -$NO_2C_6H_4$, o -MeC_6H_4, m -MeC_6H_4,

Scheme 1: Synthesis of spiro[imidazolidine-2-thioneoxindoles] by the reaction between 3-isothiocyanato oxindoles and bis(arylmethylidene)hydrazines

1.2 One-Pot Synthesis of Imidazolidine-2-Thiones

Another novel and efficient method for the solid-phase synthesis of imidazolidine-2-thiones **7** was developed by Mohammad M . Ghanbari and his coworkers,[24] in which grinding has been applied to the reaction mixtures containing benzils **5** and thiourea derivatives **6** to achieve imidazolidine-2-thiones derivatives **7** as shown in **Scheme 2** in a good yield (88-90%), low cost, simple workup, easy purification and short reaction time. The reaction proceeded spontaneously under Solvent-Free and Grinding Conditions, and was completed within a few minutes (5 minutes only).



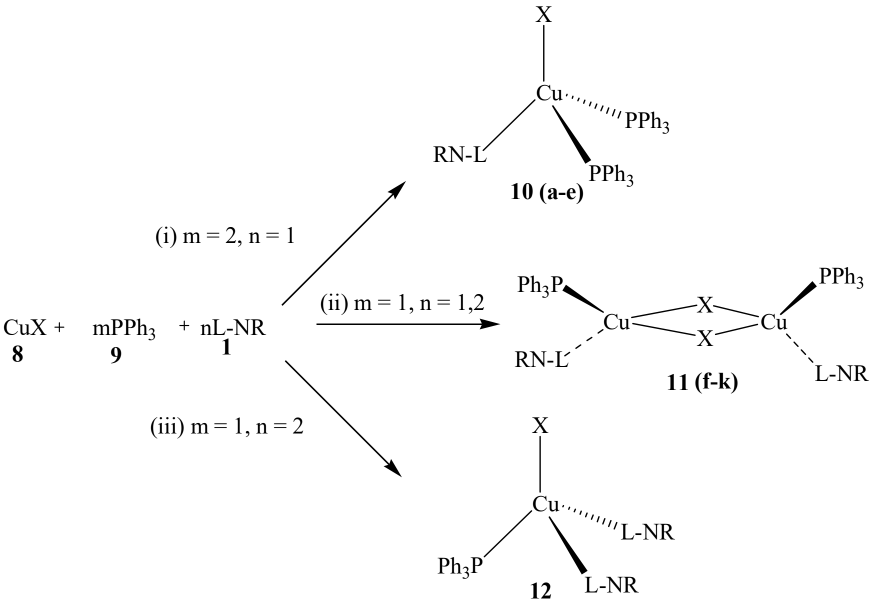
$Ar = C_6H_5, 4\text{-}MeC_6H_4$

R, R' = Me

Scheme 2: One-Pot Synthesis of Imidazolidine-2-Thiones

1.3 Synthesis of Metal complexes of imidazolidine-2-thione (Imt)

1.3.1 Copper (I) complexes of N-substituted imidazolidine-2-thiones



a: X, R = Cl, Pr^n, b: X, R = Br, Pr^n, c: X, R = Cl, Bu^n, d; X, R = I, Bu^n, e; X, R = I, Ph,

f: X, R = Br, Et, g: X, R = Cl, Pr^n, h: X, R = Br, Pr^n, i; X, R = I, Pr^n, j; X, R = Br, Ph, k; X, R = I, Ph

Scheme 3: **Synthesis of copper complexes of N-substituted imidazolidine-2-thiones**

Very recently, Lobana[25] *et al.*, have synthesized various copper (I) metal based imidazolidine-2-thione complexes (trigonal planar, dinuclear, tetranuclear and hexanuclear) and investigated their antimicrobial activity against S. aureus and a yeast C. albicans. These new copper complexes has been prepared from copper (I) halides **8** and imidazolidine-2-thiones **1** with triphenylphosphine **9** as a co-ligand (**Scheme 3**). The complexes formed are mononuclear, $[CuX(L\text{-}NR)(PPh_3)_2]$ **10 (a-e)**, $[CuBr(L\text{-}NPh)_2(PPh_3)]$ **11** and halogen-bridged dinuclear, $[Cu_2(\mu\text{-}X)_2(L\text{-}NR)_2(PPh_3)_2]$ **12**. All of the complexes are found to be bactericidal against *Staphylococcus aureus*.

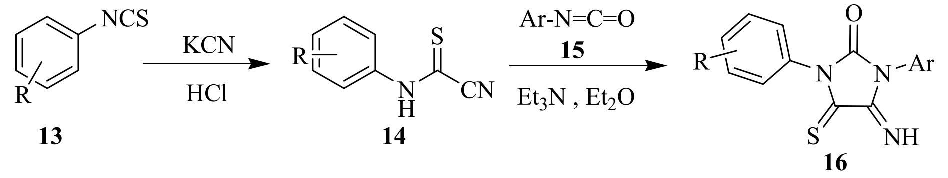
A most significant outcome of this investigation is that several complexes have shown significant activity against *Staphylococcus epidermidis* and *Enterococcus faecalis*, which is higher than that of the standard drug Gentamicin. Finally, these complexes were nearly inactive against *Shigella flexneri*, *Escherichia coli* and yeast *Candida tropicalis*.

1.3.2 Cadmium (II) complexes of imidazolidine-2-thione

R. Mahmood and his group[26] describes the synthesis and structural characterization of two polymeric cadmium(II) complexes of imidazolidine-2-thione (Imt) based on sulfate or azide ions, i.e., $[Cd(Imt)(H_2O)_2(SO_4)]_n$ and $[Cd(Imt)_2(N_3)_2]_n$. They have also reported the spectroscopic data and X-ray structures of two new 2D polymeric cadmium (II) complexes of imidazolidine-2-thiones as $[Cd(Imt)(H_2O)_2(SO_4)]_n$ and $[Cd(Imt)_2(N_3)_2]_n$.

1.4 Synthesis of imidazolidineiminothione derivatives

Ammar and group have been reported a very interesting methodologies for the synthesis of imidazolidineiminothione derivatives **16** by the reaction of N-arylcyanothioformamide derivatives **14** with aryl isocyanates **15** **(Scheme 4)**.[27] Initially, they were prepared the N-arylcyanothioformamide derivatives **14** from the reaction of N-aryl isothiocyanates **13** with potassium cyanide in the presence of hydrochloric acid (HCl). Further these compounds i.e., imidazolidineiminothione derivatives **16** were used as key synthons for the preparation of wide variety of new substituted imidazole compounds.

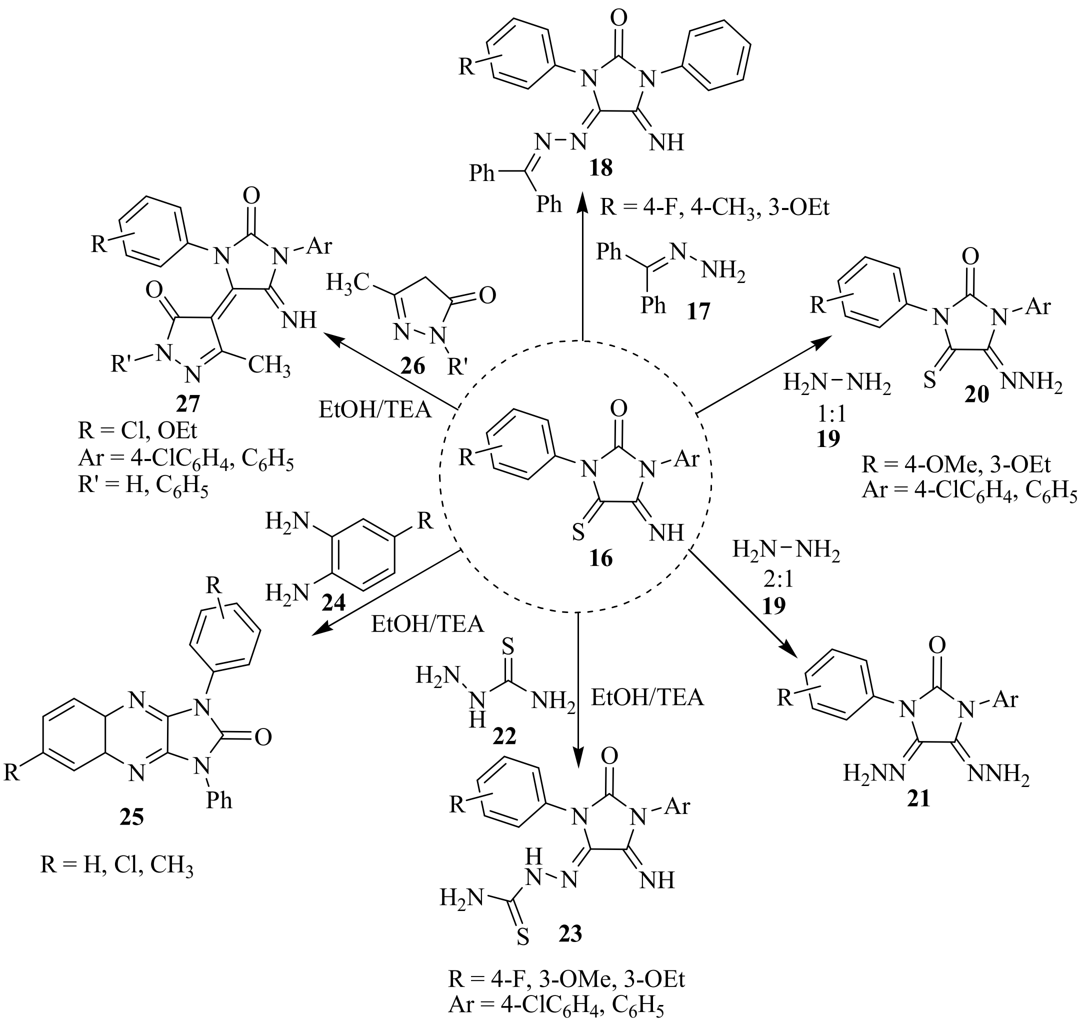


R = 4-F, 3-Cl, 4-Me, $3\text{-}OCH_3$, $3\text{-}OC_2H_5$

Ar = Ph, $3,5\text{-}(CF_3)_2\text{-}C_6H_5$, $4\text{-}ClC_6H_4$, $2\text{-}F\text{-}C_6H_4$

Scheme 4: **Synthesis of imidazolidineiminothione derivatives**

The imidazolidine derivatives contain adjacent imino and thione functional groups in the 5- and 4-positions appear promising for further chemical transformations. Therefore, it was interesting to study the reaction of imidazolidineiminothiones **16** with some amino compounds as nitrogen nucleophiles. Condensation of **16** with benzophenonehydrazone **17** in boiling ethanol using triethylamine as a basic catalyst furnished the corresponding 4-azine derivatives **18**. In addition, the reactivity of iminothione derivatives **16** towards binucliophiles was also investigated. Thus equimolecular amounts of **16** and hydrazine hydrate **19** furnished the monohydrazono derivatives **20**.

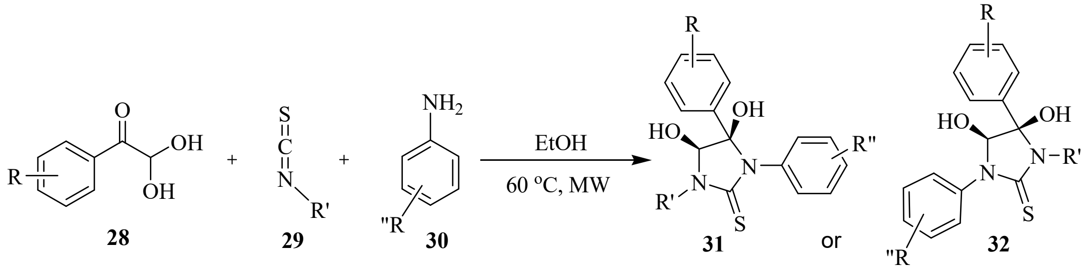


Scheme 5: Reactions of imidazolidineiminothione derivatives with different reagents

While when 2 mole of **16** is treated with 1 mole of hydrazine hydrate **19**, it furnished dihydrazono derivatives **21** were achieved as a sole product. Furthermore, upon reaction of the iminothiones **16** with thiosemicarbazide **22**, the nucleophilic addition occurred at the thio group and the corresponding 4-thiosemicarbazone derivatives **23** were obtained in good yield. In their next attempt, they condensed imidazolidineiminothione **16** with o-phenylenediamine derivatives **24** as 1,4-binucleophile in ethanol under reflux afforded yellow products which were identified as imidazo[4,5-*b*]quinoxalines **25**. While the condensation of the imidazolidineiminothiones **16** with 3-methyl-1*H*-pyrazol-5(4*H*)-one derivatives **26** in boiling ethanol using triethylamine as a basic catalyst afforded imidazolidin-4-ylidenpyrazolones **27** (**Scheme 5**).

1.5 Synthesis of polysubstituted syn-imidazolidine-2-thiones

An efficient and simple three-component reaction of aryl glyoxals **28**, isothiocyanates **29** and aryl amines **30** has been developed by Guigen Li and his coworkers where they synthesized poly-substituted syn-imidazolidine-2-thione derivatives **31** or **32** with high diastereoselective and regioselectivity (upto > 99:1) and good yields (upto 82%) via microwave-assisted three-component [2+2+1] heterocyclization with a wide diversity of substituents (**Scheme 6**).[28] The flexible structural modifications, broad functional group compatibility and mild reaction conditions make this strategy highly viable for further applications.

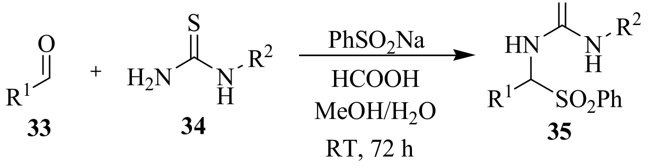


R = H, Me, OMe, NO_2, Br, F; R' = H, Me, MeO; R" =H, Br

Scheme 6: Diastereoselective synthesis of polysubstituted syn-imidazolidine-2-thiones

1.6 Synthesis of functionalized imidazolidine-2-thiones

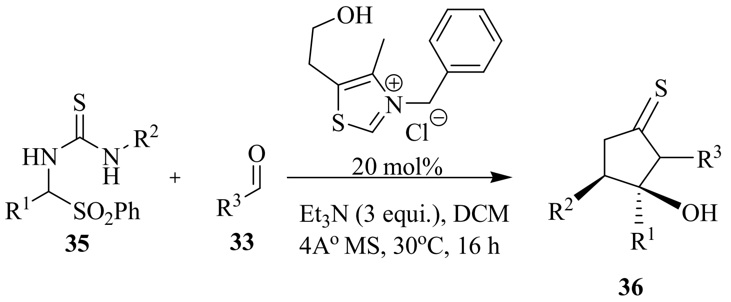
Very recently, Massi *et al.*, [29] has presented a strategy for the synthesis of biologically relevant 5-hydroxy-imidazolidine-2-thione derivatives **33**. Here, they have described an efficient methodology for the rapid assembly of the biologically relevant 5-hydroxy-imidazolidine-2-thione scaffold, which is based on a domino reaction consisting of an aza-benzoin condensation and a subsequent aza-acetalization reaction promoted by a suitable thiazolium salt as pre-catalyst under basic conditions. For aza-benzoin condensation, they have done the reaction of substituted aldehydes **33** and N-phenylthiourea **34** for the synthesis of α-sulfonylamines **35** with higher yields (66–73%) (**Scheme 7**). Finally, aza-acetalization domino reaction was performed by the reaction of various substitutes aldehydes 33 and α-sulfonylamines **35** gave the final product i.e., 5-hydroxy-imidazolidine-2-thione derivatives **36** with very high distereoselectivity (**Scheme 8**).



R^1 = Ph, 4-ClPh, 2-FPh, 3-BrPh, 3-MePh, $C(CH_3)_2$

R^2 = Ph, 4-ClPh, 2-FPh, CH_2Ph, 2-MePh, C_6H_{11}

Scheme 7: Aza-benzoin condensation for the synthesis of α-sulfonylamines



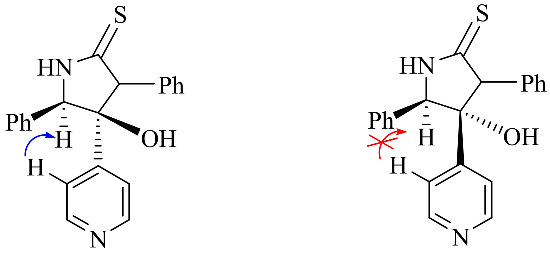
R^1 = Ph, 4-ClPh, 2-FPh, 2-ClPh, 4-OMePh, 4-CNPh, $-C(CH_3)_2$, NC_5H_4

R^2 = Ph, 4-ClPh, 2-FPh, 3-BrPh, 3-MePh, $C(CH_3)_2$

R^3 = Ph, 4-ClPh, 2-FPh, 3-BrPh, 3-MePh, $C(CH_3)_2$

Scheme 8: NHC-catalyzed/base promoted aza-benzoin/aza-acetalization domino synthesis of 5-hydroxy-imidazolidine-2-thione derivatives

The relative configuration of diastereomeric imidazolidine-2-thiones **36** was determined by HMQC and ROESY experiments using one of the pyridyl-substituted imidazolidine-2-thione derivatives **36** as the model substrate. As shown in **Figure 2**, a correlation between δ 5.68 (H-4 imidazoline ring) and δ 7.80 (H-3′ pyridyl ring) was detected for the major diastereoisomer, thereby supporting a relative syn configuration of the phenyl and hydroxyl substituents at C4 and C5 of the imidazolidine-2-thione ring.



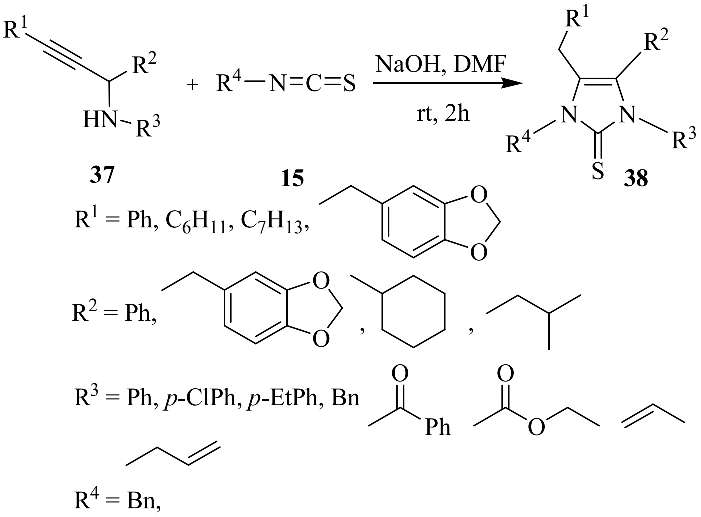
(±)-36 - major isomer (*Syn*)

(±)-36 - minor isomer (*Anti*)

Scheme 8: Relative configuration of diastereomeric imidazolidine-2-thiones

1.7 Synthesis of spiro-cyclic imidazolidine-2-thione

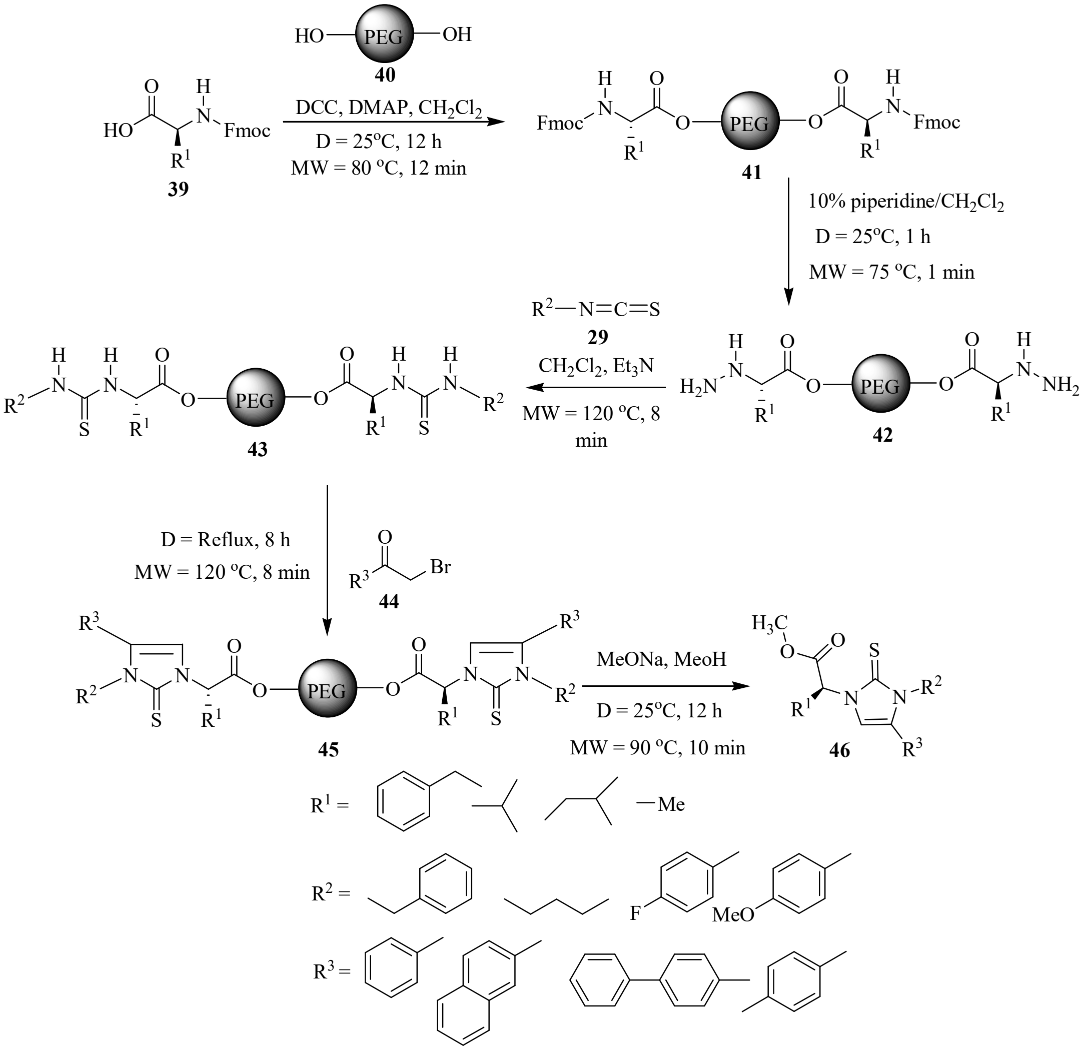
Dattatraya H. Dethe and his group has been described an intramolecular transition-metal free base mediated hydroamination of propargylamine **37** with isothiocyanates **15** for the development of one-pot synthesis of diversely substituted imidazole-2-(thi)ones **38** at ambient temperature (**Scheme 9**).[30] Wide varieties of iso(thio)cyanate **15** and propargyl amines **37** have participated in this reaction and these could be used as precursors for the formation of novel N-heterocyclic carbenes. (NHCs). The reaction goes to completion at room temperature via propargylthiourea and 65 −97% isolated yields were obtained.



Scheme 9. One-Pot Synthesis of Imidazolidine-2-thiones

1.8 Microwave-assisted efficient regioselective synthesis of 1,3,4-Trisubstituted imidazolidine-2-thiones

Chun Ming Sun and his group[31] have been investigated a novel efficient synthetic method for regioselective synthesis of optically active 1,3,4-Trisubstituted imidazolidine-2-thiones **46** on a polyethylene glycol (PEG) support. The key synthetic steps involved the synthesis of thiourea derivatives of polymer-supported amino acids with isothiocyanates **29** and one pot regioselective condensation of PEG-linked thiourea with α-bromo ketones to furnish the trisubstituted imidazolidine-2-thiones under microwave conditions (**Scheme 10**).



Scheme 10: PEG polymer supported synthesis of tri-substituted imidazolidine derivatives.

The N-Fmoc-*L*-amino acids **39** were treated with dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) in dichloromethane at room temperature for 12 h to obtain the polymer-linked N-Fmoc-*L*-amino esters **41**. The separated polymer-linked amino esters **41** were used for next step without further purification. The removal of the Fmoc group from polymer conjugates **41** was carried out with 10% piperidine in dichloromethane at room temperature for 1 h to obtain polymer-bound amino esters **42**. Afterwards, polymer-bound amino ester **42** reacts with isothiocyanate **29** under focused microwave irradiation furnishing the desired polymer-immobilized thiourea **43** in 8 min at 120°C. Then, to accomplish the targeted tri-substituted imidazolidine-2-thione derivatives **46**, the cyclization of the *L*-amino acid-derived thiourea derivatives **43** with α-bromo ketones **44** in refluxing dichloromethane. The desired polymer-bound 2-mercaptoimidazoles **45** were obtained after 8 h in refluxing dichloromethane. Finally, the removal of polymer support from **45** by cleaving the polymer ester linkage was achieved using sodium methoxide solution in methanol at ambient temperature for 12 h to furnish tri-substituted imidazolidine-2-thiones **46**. The desired cleavage of the polymer support was achieved in 10 min at 90^{o}C with the utilization of microwave irradiation. This synthetic strategy represents a well-defined tool for the rapid generation of a library of biologically important tri-substituted imidazolidine-2-thiones **46** from readily available building blocks (**Scheme 10**).

Conclusion

In summary we have given an overview of the different methodologies developed for the synthesis of Imidazolidine-2-thiones known in the literature. Imidazolidine-2-thiones exhibit various bioactivities which have intrigued scientists for decades to conduct research involving theses ring system. Imidazolidine-2-thiones are well known effective anti-microbial and anti-HIV activities. This review has outlined different innovative synthetic techniques by means of conventional as well as by microwave irradiation techniques for the synthesis of imidazolidine-2-thiones. Finally, we hope that this review will serve as a stimulus for ongoing research in the field of development of novel synthetic mode of sunbstituted imidazolidine-2-thione derivatives.

Acknowledgments

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