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Original Article

Synthesis of antimicrobial active benzimidazole-2-thioate derivatives of 2-mercaptobenzimidazole

Pratapsinha Gorepatil[1], Mahadev Gaikwad[2], Amarsinha Gorepatil[3], Vilas Ingle[4]*

[1]Department of Chemistry, Sangameshwar college, Solapur, Dist- Solapur (MH), India 413 001
[2] Department of Chemistry, B. P. C. A. S. Angar, Dist-Solapur (MH), India 413 214
[3]Department of Chemistry, S. G. R. G. S. College, Paranda, Dist-Osmanabad (MH), India 413 502
[4]Department of Chemistry, S. C. S. College, Omerga, Dist- Osmanabad (MH), India 413 606

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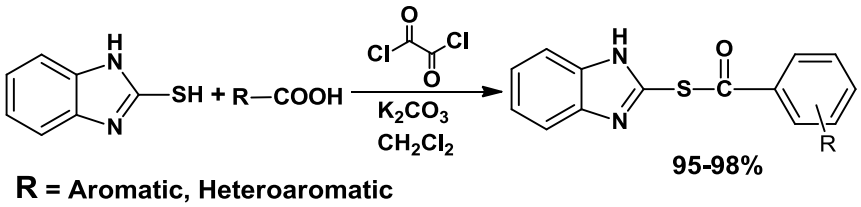
ABSTRACT



A facile, green, efficient and one pot synthetic method for biological active benzimidazole-2-thioate derivatives comprising the reaction of corresponding 2-Mercaptobenzimidazole with various substituted aromatic carboxylic acids using oxalyl chloride has been described.

Keywords: 2-Mercaptobenzimidazole, Carboxylic acids, Thioesters, Oxalyl chloride, One pot synthesis

INTRODUCTION

Nitrogen- and sulfur-containing heterocycles are ubiquitous substructures in a huge number of biologically active natural products and small-molecule in pharmaceuticals [1], one of them is 2-mercaptobenzimidazole (MBI) and it is important derivative of benzimidazole.

Substituted 2-mercaptobenzimidazole molecules have drawn much attention of synthetic chemists because of their broad range of biological activities such as antimicrobial [2], antitubercular [3], antifungal [4], antagonist and antihistamine [5].

The compound, 2-mercapto-5-difluoromethoxy-1H-benzimidazole, an important intermediate required for the synthesis of pantoprazole, is a new medicinal intermediate. Pantoprazole is a substituted benzimidazole which markedly inhibits basal and stimulated gastric acid secretion [6-7] and some of 2-mercaptobenzimidazole derivatives show antiepileptic activity and anti-diabetic activity [8]. Thioesters, an important class of sulfur-containing compounds, are widely present in a great number of biologically active compounds and natural products [9]. In recent years; there are a many of reports on the synthesis of bioactive proteins thioesters by native chemical ligation [10].

The ubiquity of thioesters in biology implicates them as prospective compounds of importance to the origin of life. Similar to phosphoanhydrides e.g. ATP, the hydrolysis of thioesters is relatively slow despite the large thermodynamic feasibility of the reaction. Wachtershauser and de Duve found that thioesters may have played a critical role in early metabolism, primarily as chemical reservoirs of energy [11]. Some thioesters are very important for pheochromocytoma cell (PC) 12 inhibitors, it is most widely used of all neuronal cell line and some are used for fatty acid synthase inhibitor.

Although a great deal of effort has been directed toward the use of nucleophilic thiols [12] for the formation of C-S bond, thioacids [13] have not been explored in organic synthesis as they are less nucleophilic and hence less reactive. But, the thioesters obtained from thioacids as nucleophiles are synthetically more valuable because of their

***Corresponding Author Address:** Dr. **Vilas Ingle,** Department of Chemistry, S. C. S. College, Omerga, Dist- Osmanabad (MH), India 413 606; E-mail: dr.pratapgorepatil@gmail.com, inglevilas71@yahoo.in*

widespread application in pharmaceutical chemistry [14] and also they serve as key intermediates in the synthesis of various bioactive molecules [15]. Moreover, thioesters are used as coupling partners in organometallic reactions [16], building blocks for the synthesis of heterocyclic compounds [17], and acyl transfer reactions [18].

From last some decade several synthetic methodologies have been developed for the synthesis of thioesters from carboxylic acid using various catalysts or reagents such as, Na_2S mediated by Ethyl-3-(3-dimethylaminopropyl) carbodiimidode (EDC) [19], azopyridine and triphenyl phosphine is a suitable electron-deficient reagent for Mitsunobu thioesterification reactions [20], isobutyl carbonochloridate and triethyl amine [21], Tetramethyl fluoroformamidium hexafluorophosphate (TFFH) as the coupling reagent [22], hafnium(IV) or zirconium(IV) salts [23]. Various thiols can be acetylated using acetic anhydride in the presence of catalyst like silver triflate [24], acetonyltriphenylphosphonium bromide [25], and Copper (II) triflate [26] and some other methods are also reported for synthesis of thioesters [27, 28]. Most of these methods suffer from one or more drawbacks such as long reaction times, expensive reagents, drastic reaction conditions, low yields, tedious work-up procedures and generation of acidic/metallic wastes.

Considering the biological applications and disadvantages in synthetic methods of thioesters and in continuation of seeking newer synthetic routes for 1,3-azole derivatives [29], here we tried to develop a new simple and convenient method for synthesis of biologically active thioesters from available carboxylic acids and 2-mercaptobenzimidazoles using green chemistry protocols and we found oxalyl chloride as a versatile reagent giving rise to carboxylic acid derivatives and a building block for the formation of heterocyclic products, and it is known as acyl halide reagent [30].

MATERIAL AND METHODS

General procedure for the conversion of carboxylic acid to benzimidazole-2-thioates: A mixture of carboxylic acid (1.0 mmol) and oxalyl chloride (0.126g, 1.0 mmol) in dichloromethane (4 mL) was stirred at room conditions. After completion of chlorination, MBI (0.150g, 1.0 mmol) was added in same pot with further addition of dichloromethane (4mL) and potassium carbonate (0.25gm) and mixture was refluxed with stirring. Progress of the reaction is monitored by TLC and CH_2Cl_2 (10 mL) was added. The organic layer was washed with saturated aqueous potassium carbonate (3×5 mL) and aqueous sodium thiosulfate (2×5 mL) respectively and dried. The pure product was obtained by Colum chromatography using silica gel and n-hexane/ethyl acetate (4:1) as eluent.

Characterization of selected compounds:

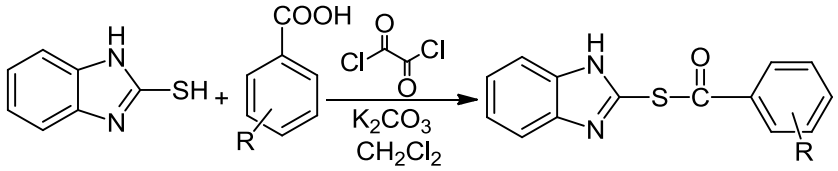
S-1H-benzimidazol-2-yl benzothioate (Table 5.5, entry a): **^{1}H NMR Spectrum** (400 MHz, DMSO-*d6*), δ, ppm (*J*, Hz): 12.50 (1H, s, N-H); 8.30-8.00 (3H, m, H Ar); 7.80 (2H, d, 2H, *J* = 8.0, H Ar); 7.51 (2H, d, *J* = 8.2, H Ar); 7.40 (2H, t, *J* = 8.2, H Ar). **^{13}C NMR Spectrum** (100 MHz, DMSO- *d6*), δ, ppm: 179.8 (C=O); 169.1 (-N=C-N- Ar); 134.9 (C Ar); 131.8 (C Ar); 130.8 (C Ar); 129.0 (C Ar); 128.6 (C Ar); 125.1 (C Ar); 115.6 (C Ar).
Mass spectrum (EI, 80 eV) *m/z* (%): 254 [M^+] (17)

S-1H-benzimidazol-2-yl 4-methylbenzothioate (Table 1, entry b): **^{1}H NMR Spectrum** (400 MHz, DMSO- *d6*), δ, ppm (*J*, Hz): 11.70 (1H, s, N-H); 7.80 (2H, d, *J*= 8.3, H Ar); 7.53 (2H, d, *J* = 8.0, H Ar); 7.42 (2H, d, *J* = 8.3, H Ar); 7.31 (2H, d, *J* = 8.0, H Ar); 2.4 (3H, s, -CH_3).
^{13}C NMR Spectrum (100 MHz, DMSO- *d6*): δ 176.2 (C=O); 168.2 (-N=C-N- Ar); 135.1 (C Ar); 134.2 (C Ar); 130.2 (C Ar); 129.0 (C Ar); 127.8 (C Ar); 125.0 (C Ar); 115.4 (C Ar); 22.1 (-CH_3).
Mass spectrum (EI, 80 eV) *m/z* (%): 269 [M^+] (25).

S-1H-benzimidazol-2-yl 4-nitrobenzothioate (Table 1, entry d): **^{1}H NMR Spectrum** (400 MHz, DMSO- *d6*), δ, ppm (*J*, Hz): 12.40 (1H, s, N-H); 7.90 (2H, d, *J*= 8.2, H Ar); 7.50 (2H, d, *J* = 8.2, H Ar); 7.42 (2H, d, *J* = 8.0, H Ar); 7.30 (2H, t, *J* = 8.0, H Ar). **^{13}C NMR Spectrum** (100 MHz, DMSO- *d6*): δ 181.1(C=O); 165.3 (C-NO_2 Ar); 153.4 (-N=C-N- Ar); 134.6 (C Ar); 132.0 (C Ar); 126.8 (C Ar); 122.2 (C Ar); 121.0 (C Ar); 114.2 (C Ar). **Mass spectrum** (EI, 80 eV) *m/z* (%): 299.06 [M^+] (21)

RESULTS AND DISCUSSION

In order to find the best experimental conditions, we describes a simple method for synthesis of a new class of benzimidazole-2- thioate derivatives from one-pot reaction between substituted 2-mercaptobenzimidazole derivatives and aromatic carboxylic acids. Here we report oxalyl chloride first time as chlorinating agent for synthesis of thioesters (**Scheme 1**).



Scheme 1

As mentioned above, due to the problems encountered with isolation process of the byproducts and great attention in using commercially available reagents, we report, use of oxalyl chloride to perform a very clean and efficient reaction for chlorination of carboxylic acids. In this system, the resulting byproducts are gaseous like CO_2, CO, HCl and can be removed by simple heating.

To find the optimized condition, we did chlorination of benzoic acid (1 mmol) using oxalyl chloride (1.0 mmol) at room temperature (30-40℃) and desired benzoyl chloride, was obtained in excellent yield (100%) in dichloromethane (5 mL) as compare to other organic solvents, such as acetonitrile, toluene and ethyl acetate at different temperatures to find the most suitable condition for the reaction (Results of optimization are summarized in **Table 1**) then addition of MBI (1 mmol) in same pot under reflux condition resulted in conversion of benzoyl chloride to *S*-1H-benzimidazol-2-ylbenzothioate (98%) in short reaction time (30 minute) in excellent yield. After optimization extended of our study towards carboxylic acids containing electron donating and withdrawing groups and we found this reaction condition is very useful for transformation of carboxylic acids to corresponding thioesters. Results are summarized in **Table 2.**

Biological screening: The new synthesized benzimidazole-2-thioate derivatives were screened for their biological activity. The biological activity was tested by disc plate method of assay in nutrient agar media. Compounds were tested at 50, 100, 125 mg/mL concentration and minimum zone inhibition was determined. Streptomycin was taken as standard for antimicrobial screening. Five compounds (Table 1, Entry a–e), showed good biological activity against *Salmonella Typhi* and *Escherichia Coli*. The details are given in **Table 3 and Table 4.**

CONCLUSION

We have found simple, efficient, economical and one pot methodology for synthesis of biologically active new *S*-1H-benzimidazol-2-yl thioates from 2-mercaptobenzimidazole and carboxylic acids by using oxalyl chloride as a chlorinating agent first time for synthesis of thioesters. This protocol offers several advantages such as good yield of product in very short reaction time, very easy to handle, environmentally safe and less costly.

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TABLES

Table 1: Synthesis of benzoyl chloride from benzoic acids[a]:

Entry	Solvent	Time[b] (min)	Yield[c] (%)
a	Dichloromethane	8	100
b	Acetonitrile	12	85
c	Toluene	22	72
d	Ethyl acetate	18	80

a- **Reaction condition-** Benzoic acid (1 mmol), oxalyl chloride (1.0 mmol), solvent (5 mL)
b- Time required for the completion of reaction
c- Isolated yield.

Table 2: One pot synthesis of benzimidazole-2-arylthioates from carboxylic acids[a]:

Entry	Products	Time[b] (min)	Yield[c] mg (%)	M. P. (℃)
a	*S*-1H-benzimidazol-2-yl benzothioate	30	249 (98)	315-317
b	*S*-1H-benzimidazol-2-yl 4-methylbenzothioate	35	257 (96)	195-197
c	*S*-1H-benzimidazol-2-yl-2-methyl-4-nitrobenzothioate	25	306 (98)	280-282
d	*S*-1H-benzimidazol-2-yl 4-nitrobenzothioate	25	293 (98)	287-289
e	*S*-1H-benzimidazol-2-yl 4-chlorobenzothioate	25	289 (95)	230-232
f	*S*-1H-benzimidazol-2-yl 4-methoxybenzothioate	40	278 (98)	185-187
g	*S*-1H-benzimidazol-2-yl 2-phenylethanethioate	25	254 (95)	222-224
h	*S*-1H-benzimidazol-2-yl pyridine-2-carbothioate	20	245 (96)	190-192
i	*S*-1H-benzimidazol-2-yl 2-methylbenzothioate	32	247 (95)	196-198

a- **Reaction condition-** carboxylic acids (1 mmol), oxalyl chloride (1.0 mmol), MBI (1 mmol), DCM (8 mL).
b- Time required for the completion of reaction
c- Isolated yield.

Table 3: Antimicrobial activity on *Salmonella Typhi*

Entry	Zone of inhibition (*cm*) in different concentrations (mg/ ml)		
	50	**100**	**125**
a	0.35	0.57	0.79
b	0.38	0.45	0.65
c	0.34	0.55	0.76
d	0.40	0.65	0.85
e	0.37	0.49	0.58
Streptomycin	**0.50**	**0.85**	**1.00**

Table 4: Antimicrobial activity on *Escherichia Coli*

Entry	Zone of inhibition (*cm*) in different concentrations (mg/ ml)		
	50	**100**	**125**
a	0.44	0.57	0.83
b	0.40	0.65	0.79
c	0.42	0.50	0.80
d	0.32	0.42	0.76
e	0.39	0.61	0.73
Streptomycin	**0.60**	**0.95**	**1.10**

REFERENCES

1. a) Mavrova AT et al. Synthesis, antitrichinnellosis and antiprotozoal activity of some novel thieno[2,3-d]pyrimidin-4(3H)-ones containing benzimidazole ring. Eur J Med Chem 2010; 45: 5856-5861. (b) Pietrancosta N et al. Imino-tetrahydro-benzothiazole derivatives as p53 inhibitors: discovery of a highly potent in vivo inhibitor and its action mechanism. J Med Chem 2006; 49: 3645-3652.
2. (a) Gurrala S et al. Symmetrical coupling of 2mercapto benzimidazole derivatives and their antimicrobial activity. Int J Phar Pharm Sci 2011; 3: 217-220. (b) Mauro VA et al. Synthesis of 2-mercaptobenzothiazole and 2-mercaptobenzimidazole derivatives condensed with carbohydrates as a potential antimicrobial agents. J Sulfur Chem 2007; 28: 17-22.
3. Gupta SK, Pancholi SS. Synthesis and evaluation of antitubercular activity of some thiobenzimidazolyl derivatives. Der Pharma Chemica 2011; 3: 274-279.
4. Huang W et al. Design, Synthesis, and Fungicidal Activities of New Strobilurin Derivatives. J Agric Food Chem 2007; 55: 3004-3010.
5. Okamoto O et al. Identification of novel benzimidazole series of potent and selective ORL1 antagonists. Bioorg Med Chem Lett 2008; 17: 3278-3281.
6. Garcia CV et al. Structural elucidation of rabeprazole sodium photodegradation products. J Pharm Biomed Anal 2008; 46: 88-93.
7. Bruton LL. The Pharmacological Basis of Therapeutics, McGraw Hill, New York, 1966; 901.
8. Shingalapur RV et al. Derivatives of benzimidazole pharmacophore: synthesis, anticonvulsant, antidiabetic and DNA cleavage studies. Eur J Med Chem 2010; 45: 1753-1759.
9. (a) Neumann CS, Walsh CT. Biosynthesis of (-)-(1S,2R)-allocoronamic acyl thioester by an Fe^{II}-dependent halogenase and a cyclopropane-forming flavoprotein. J Am Chem Soc 2008; 130: 14022-14023. (b) Schwarzer D et al. Probing intein-catalyzed thioester formation by unnatural amino acid substitutions in the active site. Biochemistry 2012; 51: 233-242.
10. (a) Dheur J et al. Synthesis of thiazolidine thioester peptides and acceleration of native chemical ligation. Org Lett 2011; 13: 1560-1563. (b) Hou W et al. Peptidyl N,N-bis(2-mercaptoethyl)-amides as thioester precursors for native chemical ligation. Org Lett 2011; 13: 386-389.
11. (a) Huber C, Wachtershauser G. Peptides by activation of amino acids with CO on (Ni, Fe)S surfaces: implications for the origin of life. Science 1998; 281: 670-672. (b) Huber C, Wachtershauser G. Activated acetic acid by carbon fixation on (Fe, Ni)S under primordial conditions. Science 1997; 276: 245-247. (c) de Duve C. Blueprint for a cell, Neil Patterson Publishers, Burlington, 1991.
12. Mariola ZB et al. Ring-closure reactions through intramolecular substitution of thiophenoxide by oxygen and nitrogen nucleophiles: simple stereospecific synthesis of 4,5-dihydroisoxazoles and 4,5-dihydropyrazoles. Tetrahedron 2005; 61: 5235-5240.
13. (a) Li H et al. Organocatalytic asymmetric conjugate addition of thioacetic acid to enones. Tetrahedron Lett 2006; 47: 3145-48. (b) Fanjul S et al. Achieving high selectivity and facile displacement with a new thiol auxiliary for boron-mediated aldol reactions. Org Lett 2006; 8: 4219-4222. (c) Hu L et al. Efficient synthesis of taurine and structurally diverse substituted taurines from aziridines. J Org Chem 2007; 72: 4543-4546.
14. Yang ZN et al. Synthesis and neurotrophic activities of N-p-Tolyl/phenylsulfonyl L-amino acid thiolester derivatives. Chin J Chem 2008; 26: 547-552.
15. (a) Chakor N et al. First total synthesis of the antifungal antibiotic thiobutacin. Tetrahedron Lett 2008; 49: 5056-5058. (b) Lueond RM et al. Assessment of the active-site requirements of 5-aminolevulinic acid dehydratase: evaluation of substrate and product analogs as competitive inhibitors. J Org Chem 1992; 57: 5005-5013.
16. (a) Villalobos JM et al. A new paradigm for carbon−carbon bond formation: aerobic, copper-templated cross-coupling. J Am Chem Soc 2007; 129: 15734-15735. (b) Prokopcova H et al. Synthesis of 5-aroyldihydropyrimidinones via Liebeskind-Srogl thiol ester-boronic acid cross-couplings. Synlett 2007; 43-45.
17. Ibarra AC et al. A Novel Method of Synthesis of 2-Methylthio-1,3-oxazoles. Synthesis 1989; 7: 560-562.
18. Sviridov AF et al. Selenoesters in organic synthesis. A novel synthesis of ketones. Tetrahedron Lett 1983; 24: 4355-4358.
19. Vishwanatha TM et al. Facile N-Urethane-Protected α-Amino/Peptide Thioacid Preparation Using EDC and Na_2S. Synlett, 2012; 23: 89-92.
20. Iranpoor N et al. Easily prepared azopyridines as potent and recyclable reagents for facile esterification reactions. An efficient modified mitsunobu reaction. J Org Chem, 2008; 73: 4882-4887.
21. Tokuyama H et al. Reduction of ethanethiol esters to aldehydes. Synthesis 2002; 1121-1123.
22. Pittelkow M et al. TFFH as an excellent reagent for acylation of alcohol, thiols and dithiocarbamates. Synthesis 2004; 2485-2492.
23. Ishihara K et al. Direct ester condensation from a 1: 1mixture of carboxylic acids and alcohols catalyzed by hafnium (IV) or zirconium (IV) salts. Tetrahedron 2002; 58: 8179-8188.
24. Das R, Chakraborty D. Silver triflate catalysed acetylation of alcohols, thiols, phenols and amines. Synthesis 2011; 1621-1625.
25. Khan AT et al. Acetonyltriphenylphosphonium bromide (ATPB): A versatile reagent for the acylation of alcohols, phenols, thiols and amines and for 1,1-diacylation of aldehydes under solvent-free conditions. Eur J Org Chem 2005; 2782-2787.
26. Chandra KL et al. Lewis acid catalyzed acylation reactions: scope and limitations. Tetrahedron 2002; 58: 1369-1374.
27. Katritzky AR et al. A New Convenient Preparation of Thiol Esters Utilizing N-Acylbenzotriazoles. Synthesis 2004; 1806-1813.
28. Blaszczyk A et al. Bromine catalyzed conversion of S-tert-butyl groups into versatile and, for self-assembly processes accessible, acetyl-protected thiols. Org Biomol Chem 2004; 2: 2722-2724.
29. (a) Gorepatil PB et al. Samarium (III) Triflate as an efficient and reusable catalyst for facile synthesis of Benzoxazoles and Benzothiazoles in aqueous medium. Synlett 2013; 24: 2241-2244. (b) Gorepatil PB et al. Samarium (III) triflate: a new catalyst for facile synthesis of benzothiazoles and benzoxazoles from carboxylic acids in aqueous media. Res Chem Intermed 2015; 41: 8355-8362.
30. (a) Zhang A, Nie JJ. Enantioselective synthesis of the female sex pheromone of the pink hibiscus mealybug, maconellicoccus hirsutus. Agric Food Chem 2005; 53: 2451-2455. (b) Paquette LA. In Encyclopedia of Reagents for Organic Synthesis, Ed., John Wiley & Sons: Chichester 1995; vol. 6, pp. 3814.