Synthesis and Reactions of 3-Oxobutyl Isothiocyanate (OB ITC)

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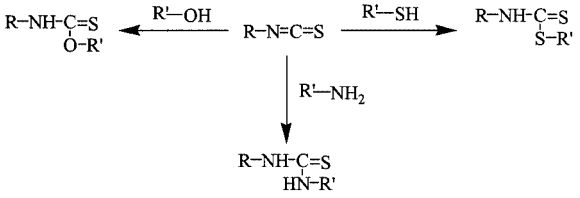
In this review an attempt has been made to compile all the existing comprehensive literature for the synthesis of 3-oxobutyl isothiocyanate (OB ITC), also known as 4-isothiocyanato-2-butanone, and its reactions with compounds possessing different functional groups, such as amines, diamines, amino alcohols, amino thiols, amino phenols, amino thiophenols, and amino acids. The peculiar behavior of OB ITC is due to its sensitivity towards acids, different products being obtained when the reaction is performed in the absence and in the presence of an acid. The pH of the reaction conditions also plays an important role. Normally, OB ITC gives thiourea derivatives when treated with amines, but reactions become interesting with compounds possessing an amino group together with another functional group (NH_2, OH, SH, COOH) in the *ortho* position, providing condensed bicyclic or tricyclic heterocycles of biological importance, with ring nitrogen and/or sulfur.

I. Introduction

A large number of available synthetic and naturally occurring isothiocyanates belonging to an important class of compounds are proving to be useful for novel synthetic transformations, especially in the construction of heterocycles.[1−4] The reactions of isothiocyanates (the sulfur analogs of isocyanates) greatly resemble those of isocyanates.[5,6] It should further be noted that isothiocyanates are less unpleasant than isocyanates and also less hazardous.[1] Isothiocyanates undergo nucleophilic addition reactions, cycloadditions to unsaturated systems, Diels−Alder reactions, and reactions with bifunctional compounds to yield heterocyclic compounds.[7,8] The highly electrophilic central carbon atom of the −N=C=S group reacts rapidly and under mild conditions with oxygen-, sulfur- or nitrogen-centered nucleophiles to give rise to carbamates, thiocarbamates, or thiourea derivatives, respectively.[9]



Isothiocyanates posses a wide range of biological activities and have been used medicinally.[10] Several isothiocyanates have been used as chemopreventive agents in experimental animal models and have been considered for use in humans.[11−21] Isothiocyanates have also been reported to exhibit other interesting biological effects such as antimicrobial,[22−24], antibiotic,[25,26] analgesic,[27,28] anti-HIV,[29,30] antibacterial,[31−33] antiseptic,[34] gastrointestinal,[35] anthelmintic,[36] antiplatelet,[37,38] and antiinflammatory properties.[11,39]

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Rajeshwar Prasad Verma was born in 1966 in Barh (India). He received his M.Sc. (1988), and Ph.D. (1992) degrees in Chemistry from Magadh University, Bodh-Gaya. He spent a year at the same university as a postdoctoral fellow with Professor K. S. Sinha and then joined Roorkee University (Now IIT Roorkee) as a research associate and worked with Professor S. M. Sondhi (1993−1997). He also worked as a Lecturer in Chemistry at Gurukula Kangri University, Hardwar (1994−1995). In December 1994 he won a Research Associateship Award from the Council of Scientific & Industrial Research, New Delhi (India). In 1997, he moved to Pomona College to join the renowned QSAR research group of Professor Corwin Hansch & Cynthia Selassie, working as a postdoctoral research associate. Dr. Verma's research interests include the isolation, characterization, and synthesis of natural products derived from medicinal plants, chemistry of isothiocyanates, synthesis of biologically important heterocycles and phenoliclactive hydrogen compounds, the application of principles of quantitative structure activity relationships (QSAR) to the study of antifolates, multidrug resistance, and free-radical-mediated toxicity of phenoliclactive hydrogen compounds.

MICROREVIEWS: This feature introduces the readers to the author's research through a concise overview of the selected topic. Reference to important work from others in the field is included.

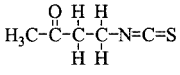
Frequent consumption of cruciferous vegetables that contain organosulfur compounds such as isothiocyanates decreases the risk of various types of cancer. This may be due to blocking of the metabolic activation of the carcinogens through alteration of the enzymes involved in the process, induction of apoptosis and detoxification of the enzymes.[40] The mechanisms of the chemopreventive effects of isothiocyanates are of great importance not only due to their blocking of the formation of a wide variety of carcinogen-induced tumors in rodents, but also because these isothiocyanates and their glucosinolate precursors are widespread in human dietary systems and are consumed in substantial quantities. To what extent these substances contribute to the protective effects of vegetables against cancer is unclear.[41] The mechanism of the anticarcinogenic activity of isothiocyanates is thought to involve two distinct pathways, tandem and cooperating mechanisms: (i) suppression of carcinogen activation by cytochromes P-450, probably by a combination of down-regulation of enzyme levels and direct inhibition of their catalytic activities, which hence lower the levels of carcinogens ultimately formed, and (ii) induction of phase II enzymes such as glutathione transferases and NADPH (quinone oxidoreductase), which detoxify any residual electrophilic metabolites generated by phase I enzymes and thus destroy their ability to damage DNA.[9] Recent studies on the mechanism of cancer chemopreventive action of isothiocyanates have suggested that the isothiocyanates are absorbed across intestinal cell membranes by diffusion and bind reversibly to plasma protein thiols by thiocarbamoylation. Free isothiocyanate enters into the cells and is converted into the glutathione conjugate by glutathione S-transferases. The glutathione conjugate has been exported from cells by multidrug resistance proteins and metabolized in the mercapturic acid pathway to the corresponding mercapturic acid.[42]

Because of the antimicrobial activity of isothiocyanates, they are useful for food preservation, such as in the extension of the shelf life of cooked rice by treatment with allyl isothiocyanate in combination with acetic acid.[22] The quality of pickles is also maintained by use of allyl isothiocyanate.[43] Proliferation of microorganisms in air conditioners can also be effectively prevented for a long period by use of allyl isothiocyanate.[44] Tribenzylsilyl isothiocyanate (TBS ITC) has been used for the sequencing of C-terminal peptides and proteins and successfully applied to the sequencing of six C-terminal residues of mouse apomyoglobin and a synthetic peptide at low nmol levels.[45] The chemistry involves activation with acetic acid anhydride, derivatization with tribenzylsilyl isothiocyanate (TBS ITC), and cleavage of the derivatized C-terminal amino acid thiohydantoin with sodium hydroxide. The tribenzylsilyl moiety is a bulky, electron-donating group and is also a good leaving group. It facilitates the nucleophilic attack of the −NCS group in the coupling reaction. Guanidinium isothiocyanate has proved to be a novel choice in the isolation of *Mycobacterium tuberculosis* DNA.[46]

The chemistry of 3-oxobutyl isothiocyanate (OB ITC) has acquired increased importance due to its wide application in the synthesis of heterocycles of biological importance, such as antiinflammatory,[47,48] analgesic,[48] antiamoebic,[48] anti-HIV,[49] antibacterial,[49] and antifungal agents.[49] The main aim of this review is to provide comprehensive coverage of the use of OB ITC in the construction of various heterocycles. No attempt has been made to compile all the literature falling within the scope of this review; the emphasis has instead been laid on all those publications that should aid in the presentation of a broader perspective of the role of this isothiocyanate in the synthesis of heterocycles.

II. Synthesis of 3-Oxobutyl Isothiocyanate (OB ITC)

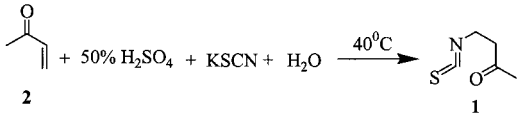
The reaction between methyl vinyl ketone and ammonium thiocyanate in the presence of sulfuric acid for the synthesis of OB ITC (**1**) was first attempted by Murata et al.,[50] in 1957, but at that time he assigned its structure as 1-thiocyanato-3-butanone. Later on, in 1965, Unkovskii et al.[51] studied the reaction between methyl vinyl ketone and thiocyanic acid (generated in situ from potassium thiocyanate and sulfuric acid) and confirmed that the product was 3-oxobutyl isothiocyanate (OB ITC) on the basis of its IR spectrum and investigation of its reaction products.



1 (OB-ITC)

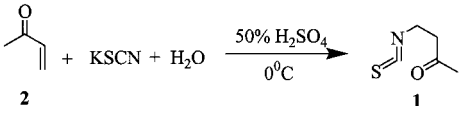
A number of synthetic methods for the synthesis of OB ITC (**1**) have been developed; these are as follows:

Method A:[51] A mixture of 50% concd. sulfuric acid in water and methyl vinyl ketone (**2**) was treated with a solution of potassium thiocyanate in water at 40 °C to give OB ITC (**1**) after 2 h.



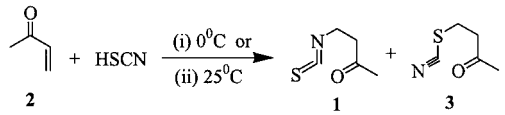
2 **1**

Method B:[52,53] Aqueous sulfuric acid (50%) was added to a mixture of methyl vinyl ketone (**2**) and a solution of potassium thiocyanate at 0 °C and immediately worked up to provide OB ITC (**1**) in 60% yield.



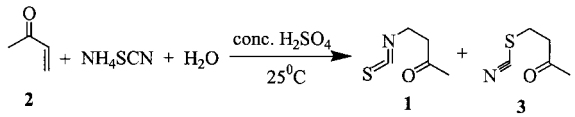
2 **1**

Method C:[54] Addition of HSCN to methyl vinyl ketone (**2**) at 0 °C gave a 95% yield of 1-thiocyanato-3-butanone (**3**) and 5% of OB ITC (**1**); with an excess of HSCN, the 1-thiocyanato-3-butanone (**3**) rearranged slowly at 25 °C to give, after 24 h, a 64:36 mixture of **1/3**.



2 1 3

Method D:[55] Addition of thiocyanic acid, generated in situ from ammonium thiocyanate and concd. sulfuric acid, to methyl vinyl ketone (**2**) at 25 °C and maintenance of the temperature for 30 min resulted in the formation of a mixture of OB ITC (**1**) and 1-thiocyanato-3-butanone (**3**) in 50%:50% ratio.

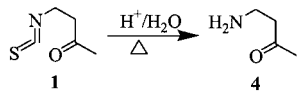


2 1 3

III. Reactions between OB ITC (1) and

A. Acids

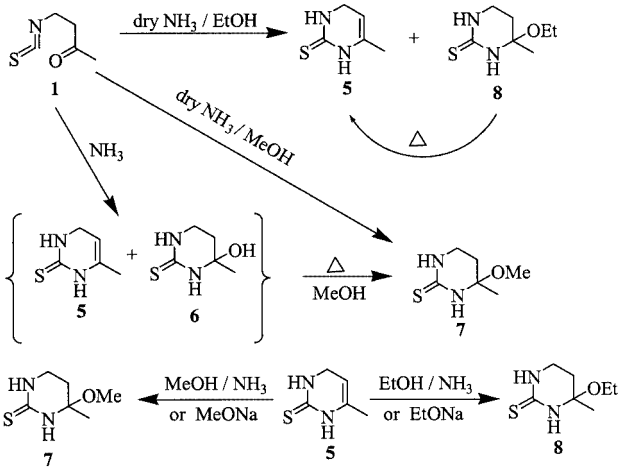
Acidic hydrolysis of OB ITC (**1**) gave 4-amino-2-butanone (**4**).[51]



1 4

B. Ammonia

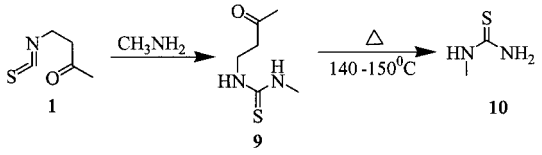
Treatment of OB ITC (**1**) with an ammonia solution of $AgNO_3$ in EtOH gave Ag_2S.[51] Treatment of OB ITC (**1**) with ammonia solution gave 6-methyl-3,4-dihydropyrimidine-2(1*H*)-thione (**5**) and 4-hydroxy-4-methyl-3,4,5,6-tetrahydropyrimidine-2(1*H*)-thione (**6**). A mixture of **5** and **6** with methanol gave 4-methoxy-4-methyl-3,4,5,6-tetrahydropyrimidine-2(1*H*)-thione (**7**). Treatment of OB ITC (**1**) with dry ammonia gas in methanol and of 6-methyl-3,4-dihydropyrimidine-2(1*H*)-thione (**5**) with methanol in the presence of catalytic amounts of ammonia or sodium methoxide also gave 4-methoxy-4-methyl-3,4,5,6-tetrahydropyrimidine-2(1*H*)-thione (**7**). Similarly, treatment of OB ITC (**1**) with dry ammonia in ethanol formed 6-methyl-3,4-dihydropyrimidine-2(1*H*)-thione (**5**) and another product, 4-ethoxy-4-methyl-3,4,5,6-tetrahydropyrimidine-2(1*H*)-thione (**8**), which on heating was transformed into **5**. When an ethanolic solution of **5** was treated with ammonia or a catalytic amount of sodium ethoxide, it gave 4-ethoxy-4-methyl-3,4,5,6-tetrahydropyrimidine-2(1*H*)-thione (**8**)[52,53] (Scheme 1).



Scheme 1

C. Aliphatic Amines

Treatment of OB ITC (**1**) with methylamine gave only *N*-methyl-*N*′-(3-oxobutyl)thiourea (**9**), which could not be cyclodehydrated under a variety of both acidic and basic conditions.[51,52] On heating at 140−150 °C, compound **9** decomposed to give methyl thiourea (**10**)[52] (Scheme 2).



1 9 10

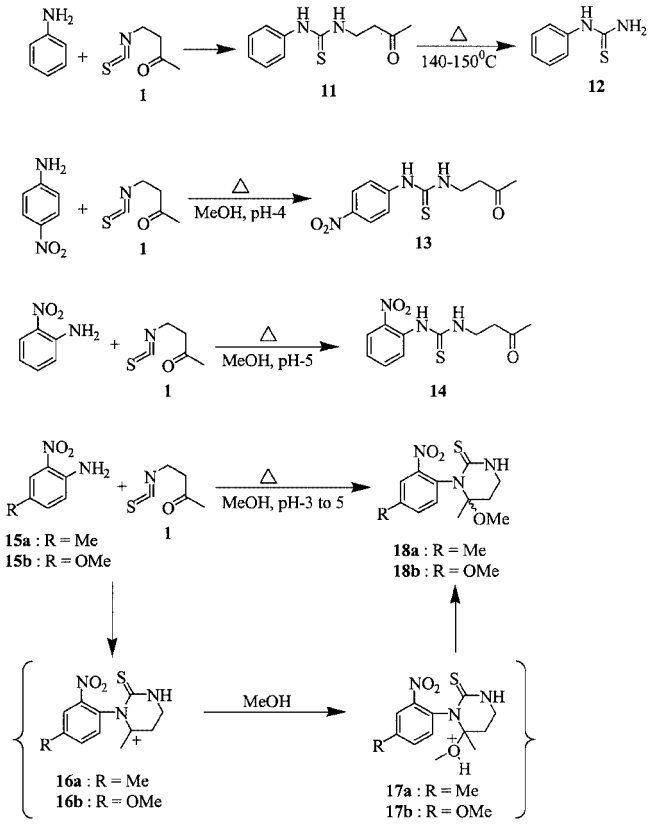
Scheme 2

D. Aromatic Amines

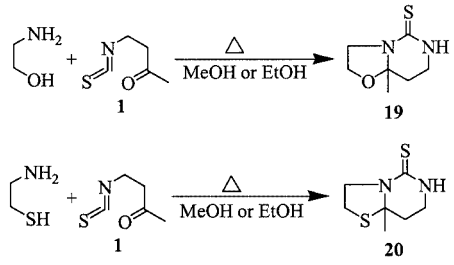
Aniline reacts with OB ITC (**1**) similarly to methylamine, giving only *N*-(3-oxobutyl)-*N*′-phenylthiourea (**11**), which could not be cyclodehydrated under a variety of acidic and basic conditions.[51,52] On subjection to heating at 140−150 °C, compound **11** decomposed and gave phenylthiourea (**12**).[52] Treatment of OB ITC (**1**) with *p*-nitroaniline in the presence of methanol and at pH = 4 gave only *N*-(4-nitrophenyl)-*N*′-(3-oxobutyl)thiourea (**13**) and this did not cyclize to form a pyrimidine ring.[47] *o*-Nitroaniline, on condensation with OB ITC (**1**) under reflux in methanol at pH = 5, gave *N*-(2-nitrophenyl)-*N*′-(3-oxobutyl)thiourea (**14**).[48] However, coupling of OB ITC (**1**) with 4-methyl-2-nitroaniline and 4-methoxy-2-nitroaniline in the presence of methanol and at pH = 3−5 gave the cyclized products 6-methoxy-6-methyl-1-(4-methyl-2-nitrophenyl)tetrahydropyrimidine-2-thione (**18a**) and 6-methoxy-1-(4-methoxy-2-nitrophenyl)-6-methyltetrahydropyrimidine-2-thione (**18b**), respectively[47,56] (Scheme 3).

E. Amino Alcohol and Amino Thiol

Condensation between OB ITC (**1**) and 2-aminoethanol in the presence of methanol or ethanol as the solvent gave the cyclized product 8a-methylhexahydrooxazolo[3,2-*c*]pyrimidine-5-thione (**19**). Similarly, 2-mercaptoethylamine condensed with OB ITC (**1**) in the presence of methanol or ethanol as the solvent to provide 8a-methylhexahydrothiazolo[3,2-*c*] pyrimidine-5-thione (**20**)[57,58] (Scheme 4).



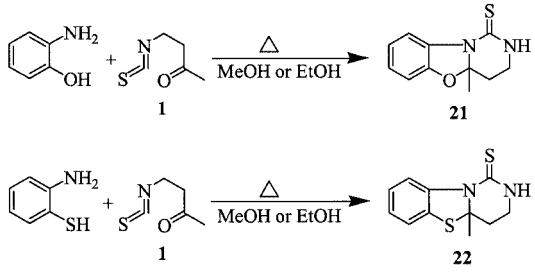
Scheme 3



Scheme 4

F. Aminophenol and Aminothiophenol

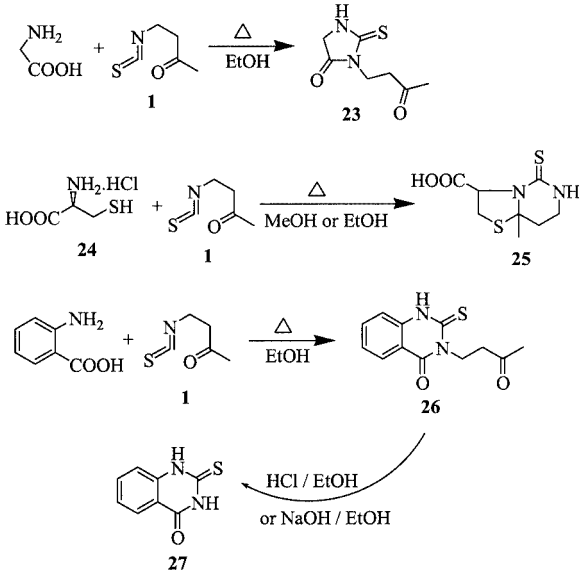
Condensations between OB ITC (**1**) and *o*-aminophenol or *o*-aminothiophenol in the presence of methanol or ethanol as solvent gave the tricyclic heterocycles 4a-methyl-2,3,4,4a-tetrahydropyrimido[6,1-*b*]benzoxazole-1-thione (**21**) and 4a-methyl-2,3,4,4a-tetrahydropyrimido[6,1-*b*]-benzothiazole-1-thione (**22**), respectively[57] (Scheme 5).



Scheme 5

G. Amino Acids

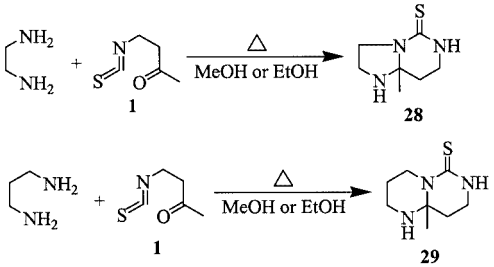
When a solution of glycine and OB ITC (**1**) was heated at reflux in ethanol, 3-(3-oxobutyl)-2-thioxoimidazolidin-4-one (**23**) was produced.[59] Cysteine hydrochloride (**24**), when condensed with OB ITC (**1**) in methanol or ethanol as solvent, gave a cyclic product 8a-methyl-5-thioxohexahydrothiazolo[3,2-*c*]pyrimidine-3-carboxylic acid (**25**).[57] Condensation between anthranilic acid and OB ITC (**1**) in ethanol gave 3-(3-oxobutyl)-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one (**26**), which underwent both acid- and base-catalyzed β-elimination to form 2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one (**27**)[59] (Scheme 6).



Scheme 6

H. Aliphatic Diamines

The condensation reaction between OB ITC (**1**) and ethane-1,2-diamine in methanol or ethanol as the solvent gave the cyclized product 8a-methylhexahydroimidazo[1,2-*c*]pyrimidine-5-thione (**28**).[57,58] Similarly, propane-1,3-diamine gave 9a-methyloctahydropyrimido[1,6-*a*]pyrimidine-6-thione (**29**)[57] (Scheme 7).

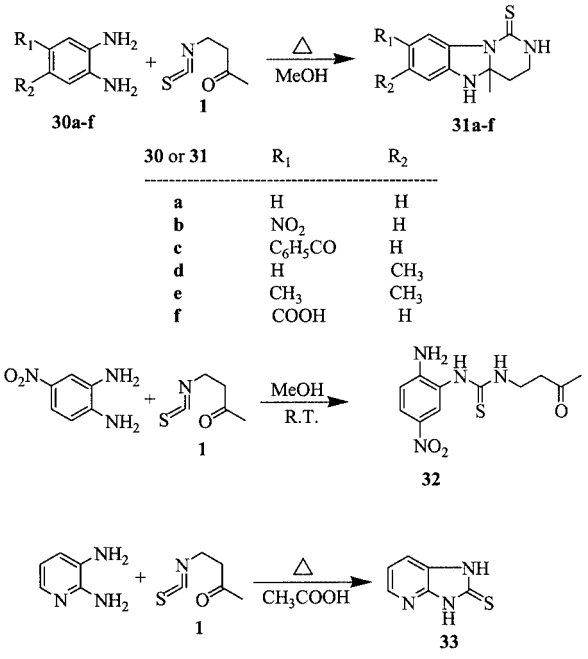


Scheme 7

I. Aromatic Diamines

o-Phenylenediamine, 4-nitro-1,2-phenylenediamine, 3,4-diaminobenzophenone, 3,4-diaminotoluene, 4,5-dimethyl-

phenylenediamine, and 3,4-diaminobenzoic acid (**30a−f**) when condensed with OB ITC (**1**) in methanol as solvent and at pH = 5, gave the pyrimidobenzimidazole derivatives 4a-methyl-3,4,4a,5-tetrahydropyrimido[1,6-*a*]benzimidazole-1(2*H*)-thione (**31a**), 4a-methyl-8-nitro-3,4,4a,5-tetrahydropyrimido[1,6-*a*]benzimidazole-1(2*H*)-thione (**31b**), (4a-methyl-1-thioxo-1,2,3,4,4a,5-hexahydropyrimido[1,6-*a*]-benzimidazol-8-yl)phenylmethanone (**31c**), 4a,7-dimethyl-3,4,4a,5-tetrahydropyrimido[1,6-*a*]benzimidazole-1(2*H*)-thione (**31d**), 4a,7,8-trimethyl-3,4,4a,5-tetrahydropyrimido[1,6-*a*]benzimidazole-1(2*H*)-thione (**31e**), and 4a-methyl-1-thioxo-1,2,3,4,4a,5-hexahydropyrimido[1,6-*a*]benzimidazole-8-carboxylic acid (**31f**), respectively. Condensation between 4-nitro-1,2-phenylenediamine and OB ITC (**1**) in methanol as solvent and at room temperature gave *N*-(2-amino-5-nitrophenyl)-*N*′-(3-oxobutyl)thiourea (**32**). 2,3-Diaminopyridine, on condensation with OB ITC (**1**) in acetic acid as solvent, gave 1,3-dihydroimidazo[4,5-*b*]pyridine-2-thione (**33**)[48] (Scheme 8).



Scheme 8

IV. Conclusion

3-Oxobutyl isothiocyanate (OB ITC) has been shown to be an important starting material for the synthesis of heterocycles with promising potential in medicinal chemistry. For example, compounds **31b** and **31d** showed good antiinflammatory and analgesic activities, whereas compound **31b** exhibited antiamoebic activity similar to that of the standard drug meteronidazole.[48] Therefore, it is clear that more study of the reactions between OB ITC (**1**) and new substrates should be carried out.

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