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SYNTHESIS, REACTIONS AND BIOLOGICAL ACTIVITY OF ISOTHIOCYANATES DERIVATIVES

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Abstract
Isothiocyanates reacted with primary and secondary amines to yield the corresponding thiourea, that can undergo heterocyclization to give pyrimidine or thiazine depending upon the condition and the nature of isothiocyanate. The reaction of cyclohexylideneacetyl isothiocyanate with aryl amines afforded aryl-4-oxo-1, 3-diazaspiro-5`, 5`undecan. This conversion involved nucleophilic addition to heterallene and subsequent intermolecular Michael reaction. Diphenylamine reacted with to give 5-cyano-2-diphenyl amino-4-oxo-1-thia-3-azaspiro [5, 5]undecene **.**

Key words: Isothiocyanates, synthesis, reactions and biological activity.

Introduction

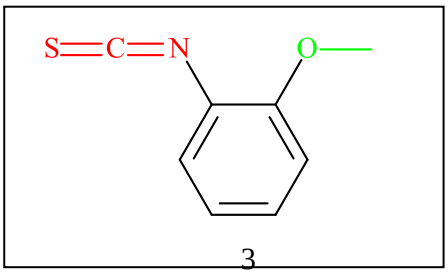
Isothiocyanates are an important building unit to prepare a wide class of nitrogen, sulfur and oxygen heterocycles and organometallic compounds. Heteroallenes show enhances reactivity in nucleophilic and cycloaddition reactions. They are placed at high list of important organic functional group **[I]** [II, III]. Isothiocyanates are the sulfur analogous of isocyanate **1** as isomeric with the thiocyanates **2**, aliphatic and aromatic isothiocyanates colorless liquids possing irritating odour and sharp test.

R-N=C=O R-S=C≡N
1 2

In plant isothiocyanates isolated from seeds of black mustared and roots of horseradish **[**[IV].

2. Spectroscopy of isothiocyanates:

U.V spectroscopy of Alkyl isothiocyanates are marked by single absorption in region (244 – 248 nm) but aromatic isothiocyanate absorbs at higher wavelength. The infrared spectroscopy of alkyl isothiocyanates show strong dispersed and splitted band in the region 2100 – 2000 cm^{-1} due to stretching vibration of N=C-S[V-VII]. IR has been made for the liquid sample 2-methoxyphenyl isothiocyanate **3**, The 2100 cm^{-1} region in the IR is dominated by the asymmetric stretching mode of the isothiocyanate with a doublet structure having frequencies at 2034 and 2112 cm^{-1} [VIII].



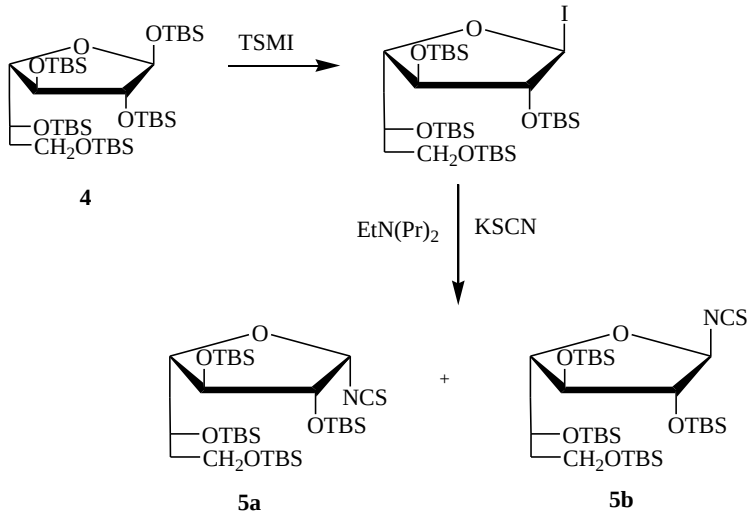
3

1. Synthesis of isothiocyanates

There are several methods to prepare isothiocyanates, the choice depend upon the target molecule.

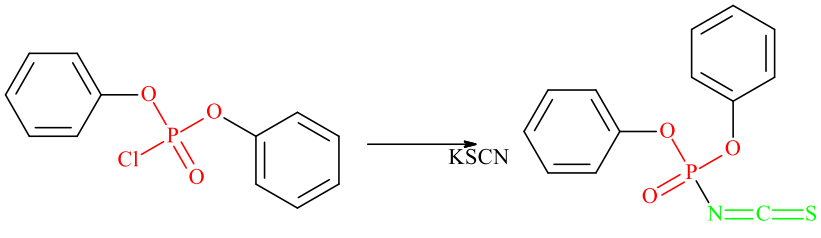
1-Substitution of thiocyanic acid or its salts:

2, 3, 5, 6-Tetra-O-tert-butyldimethylsilyl-α,β-D-galactofuranosyl isothiocyanate (**5a,b**) was synthesized by the reaction of per-O-TBS-*β* -*D*-galactofuranose **4** with KSCN [IX].



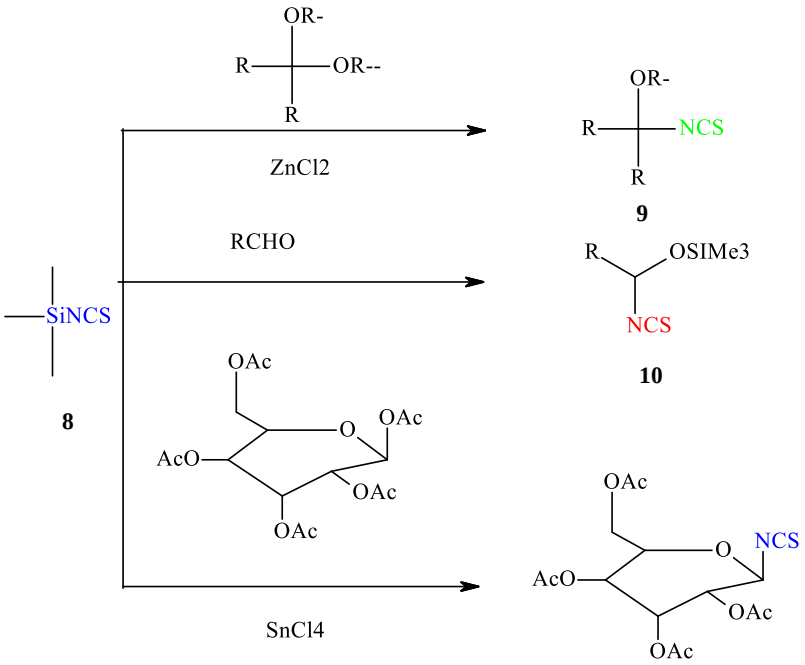
4 **5a** **5b**

Diphenylphosphoryl isothiocyanate (DPPITC) **7** was prepared by adding diphenyl chlorophosphate (DPPCl) **6** to a magnetically stirred solution of reaction of Potassium thiocyanate [X].

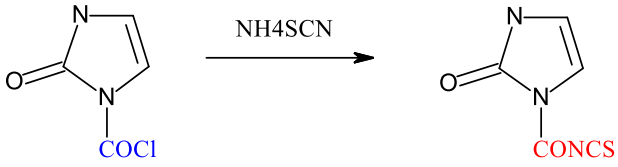


6 **7**

Trimethylsilyl isothiocyanate (TMSNCS) **8** is a versatile reagent in organic chemistry, since it easily undergoes many important reactions such as reaction with acetals and aldehydes to give **9, 10** [XI] and with acetylated hexoses to give **11** [XII].

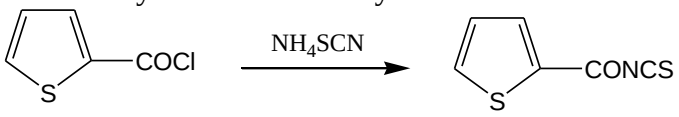


2-Oxa-4-imidazoline-1-carbonyl chloride **12** was reacted with ammonium thiocyanate in boiling acetone to give 2-oxoimidazolinyl-carbonyl isothiocyanate **13** [XIII].



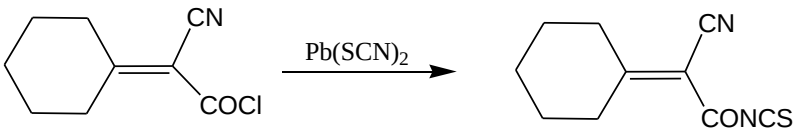
12 **13**

Acyl and aroyl halides gave the corresponding isothiocyanates on heating with metal thiocyanates or ammonium thiocyanate. 2-thienoyl isothiocyanate **15** was obtained by interaction of ammonium thiocyanate and 2-thinoylchlride **14** [XIV].



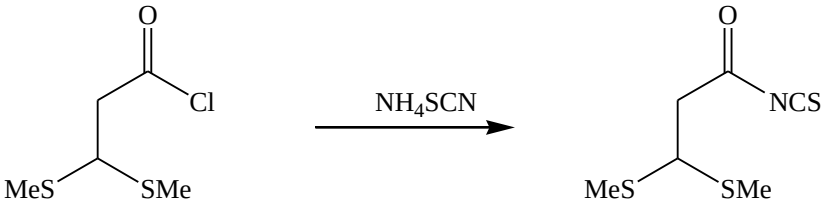
14 **15**

2-Cyanocyclo hexyliden acetyl isothiocyanate **17** was prepared by treatment of 2-cyanocyclohexylidene acetyl chloride **16** with freshly prepared lead thiocyanate in benzene [XV].



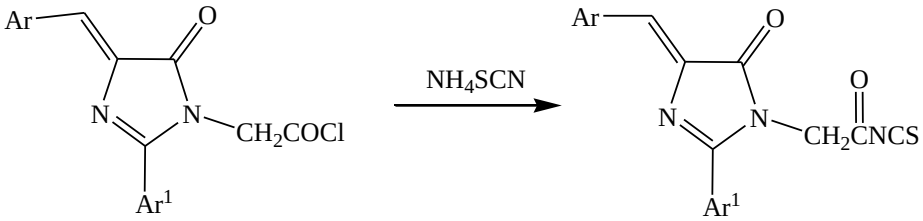
16 **17**

3, 3-Dimethylthioacrylolylchloride **18** reacted with ammonium thiocyanate in benzene yielded the corresponding to acroyl isothiocyanate derivatives **19** [XVI].



18 **19**

1-Acetylisothiocyanates 4- arylidene-2-imidazoline-5-ones **21** were prepared by reacting compounds **20** with ammonium thiocyanate [XVII, XVIII].



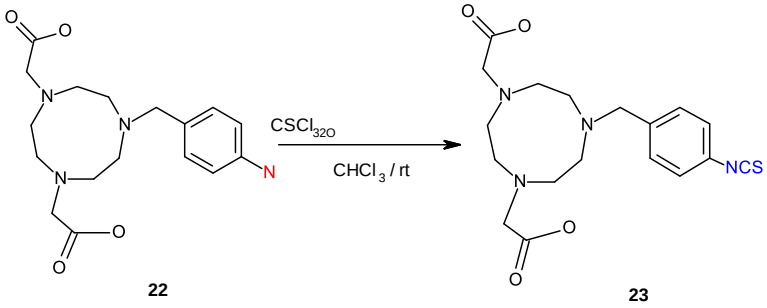
20 21

a, Ar = Ar[1] = Ph
b, Ar = Ar[1] = p_OCH3Ph

1. Reaction of amines

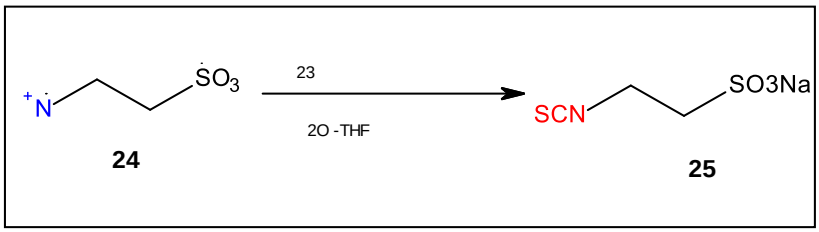
4.1 Primary amine:

4,7-Bis(carboxymethyl)-1-(4-isothiocyanato-benzyl)-1,4,7-triazanonane **23** was prepared by reaction of compound **22** with thioposhgen in the solvents mixture [XIX].



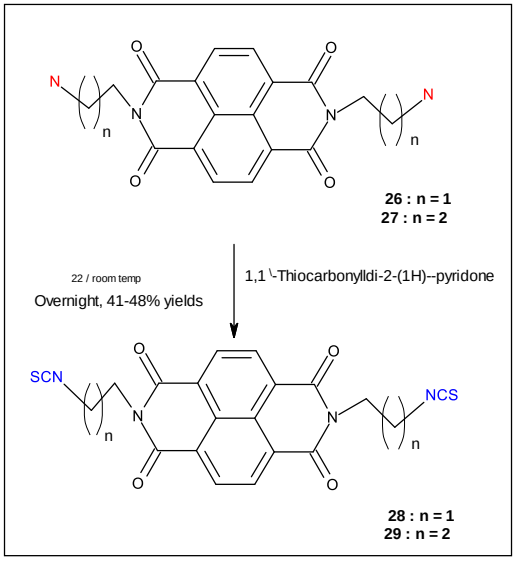
22 **23**

Preparation of crystalline isothiocyanate **25** in quite an effective and operative fashion by the treatment of taurine **24** with thiophosgene in aqueous THF in the presence of $NaHCO_3$ as a mild base [XX].

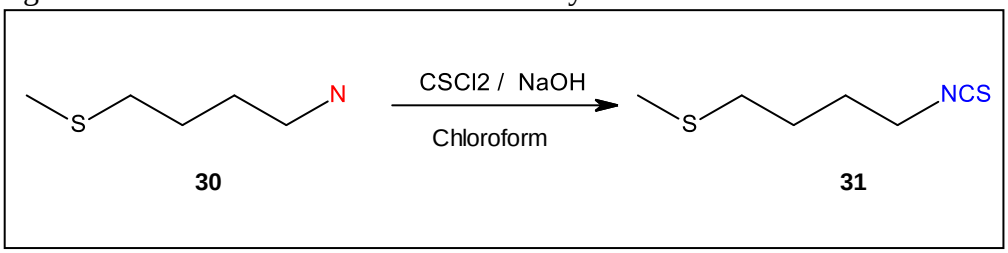


24 **25**

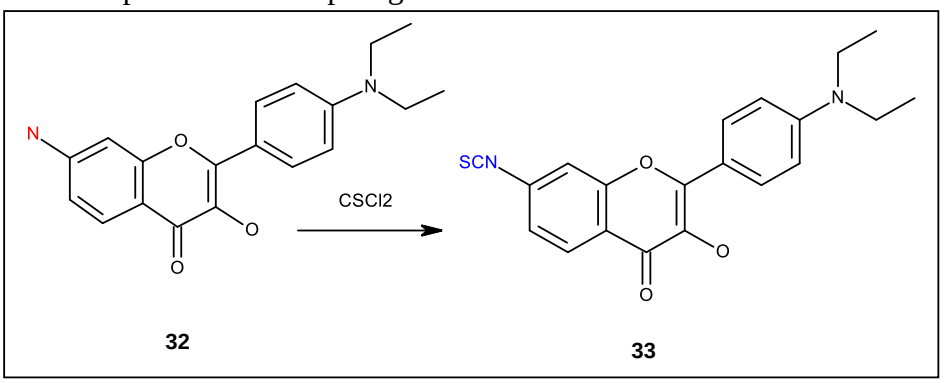
Compounds **26** and **27** [21] were reacted with commercially available 1,1`-thiocarbonyldi-2(1H)-pyridone [XXI] to provide the corresponding isothiocyanates **28** and **43** .



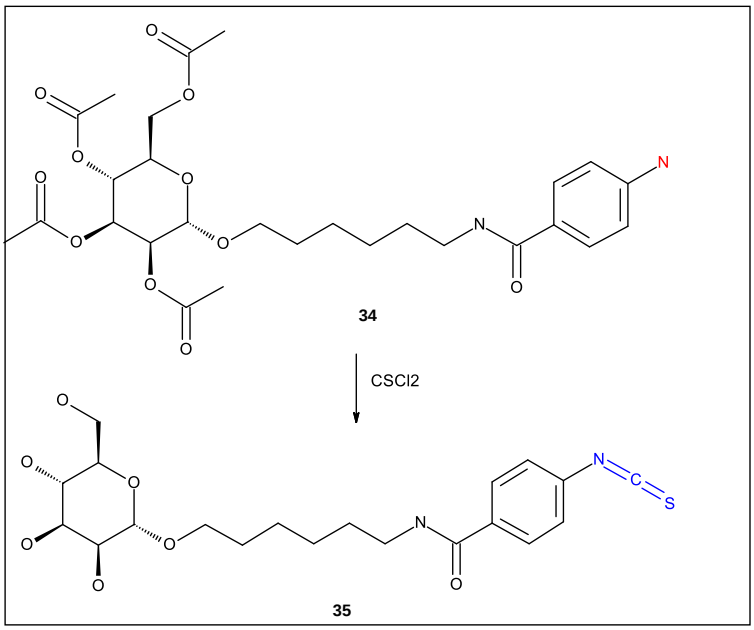
Thiophosgene used to convert amines **30** to isothiocyanates **31** [XXII].



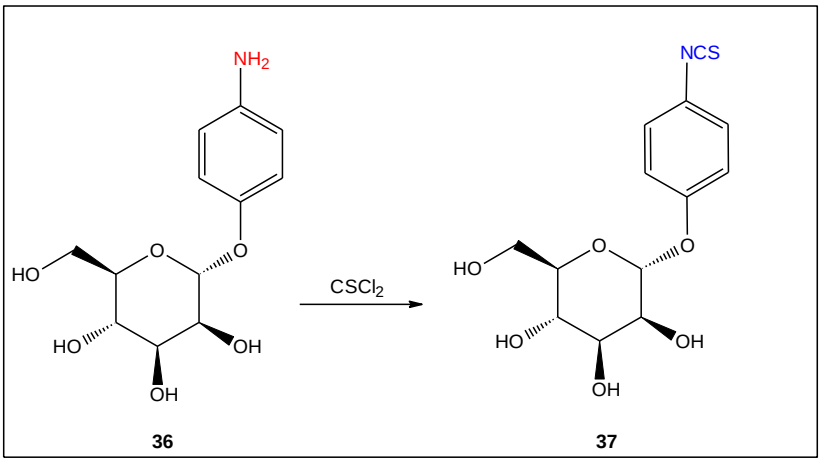
7-amino-4_-diethylamino-3-hydroxyflavone **32** was converted into a 7-isothiocyanate derivative **33** in the presence of thiophosgene [XXIII].



6-(4-Isothiocyanatobenzamido) hexyl α-D-mannopyranoside **34** was prepared by adding Thiophosgene to a magnetically stirred solution of of 6-(4-amino-benzamido)hexyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside **35** [XXIV, XXV].

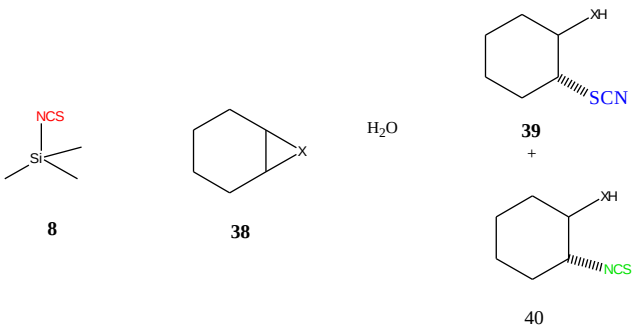


Isothiocyanatophenyl α-D-mannopyranoside **37** was prepared by adding excess of thiophosgene to a magnetically stirred solution of 4-aminophenyl α-D-mannopyranoside36 in 80% ethanol/water mixture [XXVI-XXVII].



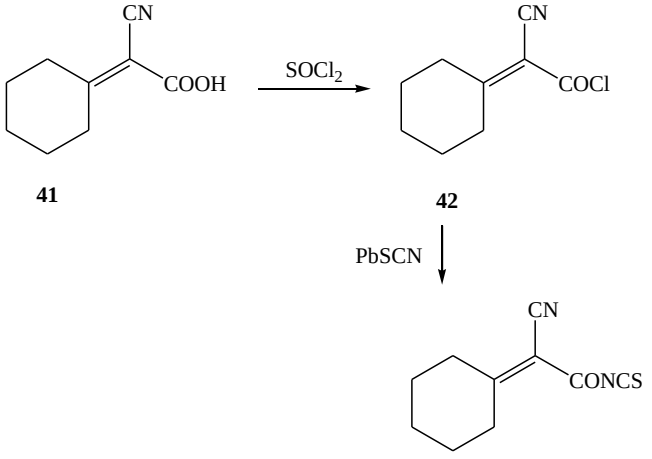
4.2 Secondary and tertiary amines:

Trimethylsilyl isothiocyanate **8** was reacted with aziridines and oxiranes **38** to give isothiocyanate **40** [XXVIII].

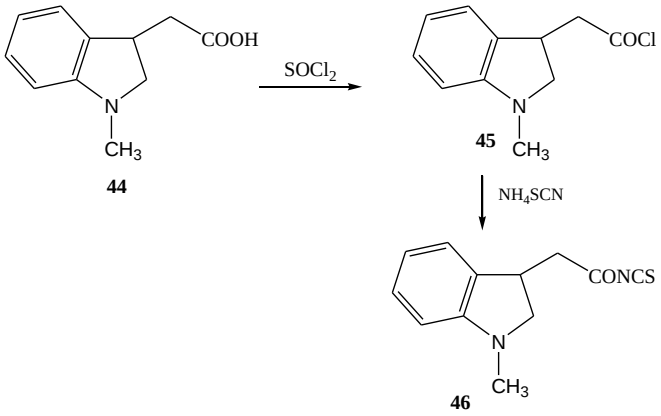


4.3 Acid chlorides:

When 2-cyanocyclohexylidene acetyl chloride **42** prepared from acid derivative **41** and thionyl chloride was treated with freshly prepared lead thiocyanate in anhydrous benzene it afforded the corresponding acyl isothiocyanate **43** [XXIX].

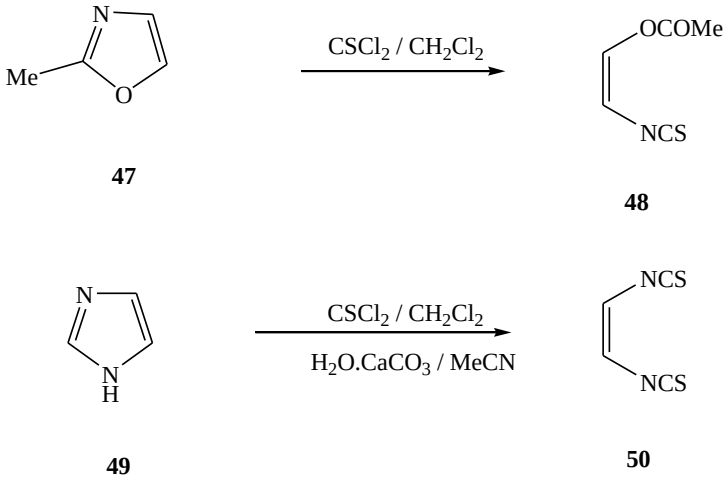


2-(1-Methylindolin-3-yl)ethanoyl isothiocyanate **46** was prepared by reacting of 2-(1-methylindolin-3-yl)acetyl chloride **45**with ammonium thiocyanate. [XXX].

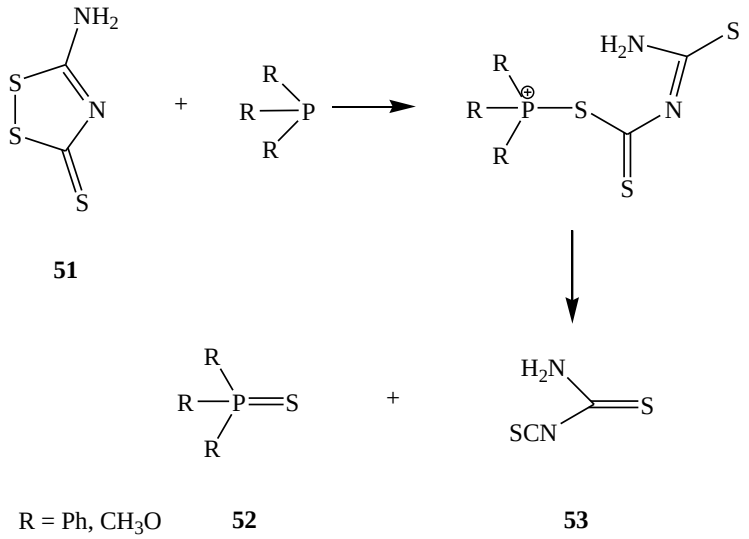


4.4. Ring cleavage reactions:

The adduct of 2-methyloxazol **47** and imidazole **49** with thiophosgene underwent hydrolytic cleavage to the corresponding isothiocyanates **48** and **50** [XXXI-XXXII].



Nucleophilic attack of the phosphorus at sulfur next to the thiocarbonyl group of 3-Amino-1,2,4-dithiazole-5-thione **51** and subsequent decomposition of the phosphonium intermediate formed into triphenylphosphine sulfide or trimethyl thiophosphate **52** and thiocarbamoyl isothiocyanate **53** [XXXIII].

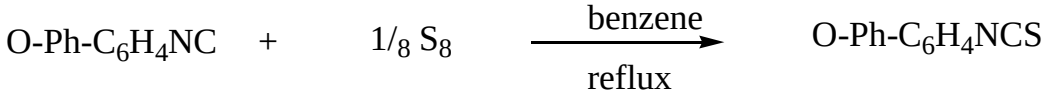


51 **52** **53**

R = Ph, CH_3O

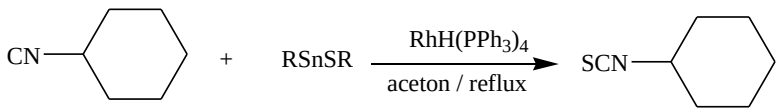
4.5. Sulfuration of cyano compound:

Treatment O-biphenyl isocyanide **54** with elemental sulfur under reflux for 64 hr in benzene gave O-biphenyl isothiocyanate **55** [XXXIV].



54 **55**

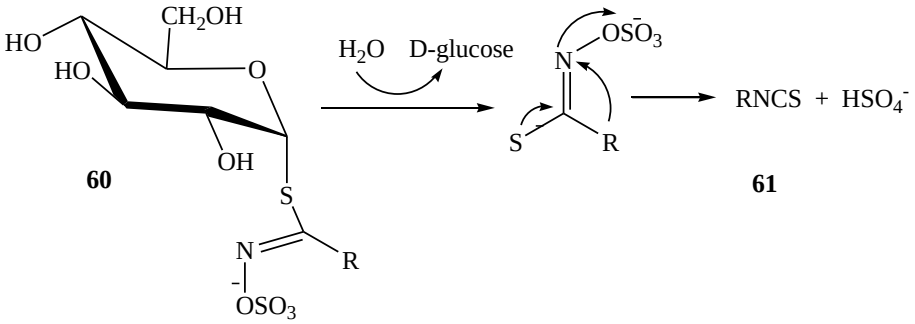
To a mixture of $RhH(PPh_3)_4$ in acetone was added cyclohexyl isonitrile **56** and sulfur giving cyclohexyl isothiocyanate **57** in 91% yield [XXXV].



56 **57**

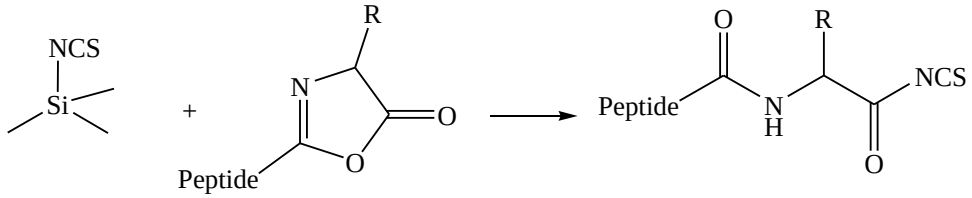
4.7. Miscellanoeus synthesis of isothiocyanates:

The isothiocyanates **61** are therefore an important group of breakdown products derived from glucosinolates **60** [XXXVI].



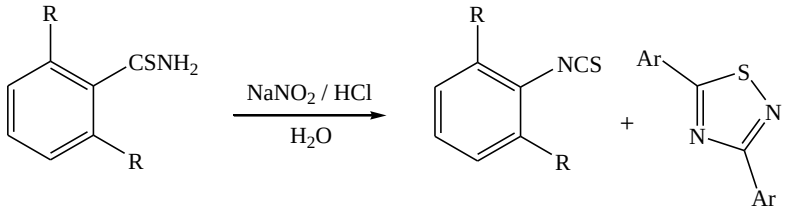
60 **61**

Trimethylsilyl isothiocyanate **8** was reacted with the peptide **62** to give isothiocyanate **63** [XXXVII].



8 **62** **63**

Oxidation of 2, 6 dihalothiobenzamide **64** with dilute HNO_2 lead to a mixture of 2, 6 dihalophenyl isothiocyanate **65** and 3, 5 diaryl(1,2,4)thiadiizoles **66** [XXXVIII-XXXIX].



64 **65** **66**

R = Cl, Br

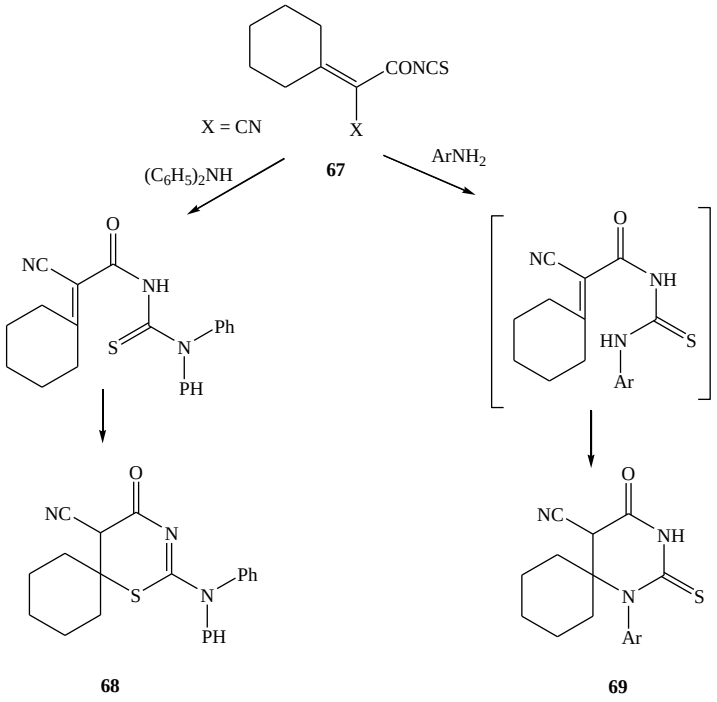
5. Reaction of isothiocyanates

5.1. Reaction of isothiocyanate with nitrogen nucleophiles.

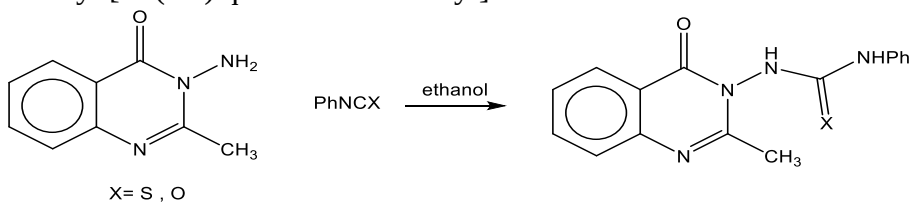
The reaction of isothiocyanates with compounds carrying an active hydrogen give adducts which undergo cyclization spontaneously or by addition of external reagents to yield heterocycles. Ring closure of the intermediate depends on the presence of compatible functionality at appropriate position within the molecule and on the reaction condition. In the case of intermediates from acyl isothiocyanate any one of the three heteroatoms of the heterallene moiety can participate in heterocyclization step [XL]. And in case of aroyl isothiocyanate, the strong electron attracting power of their aroyl group enhances the reactivity of the adjacent isothiocyanato-function and promotes nucleophilic addition at this center. Simultaneous or subsequent cyclization of the adducts gives access to a variety of 5- or 6-memgered heterocyclic structures, including bicyclic condensed ring-systems [XLI-XLII].

5.2.Reaction with amines:

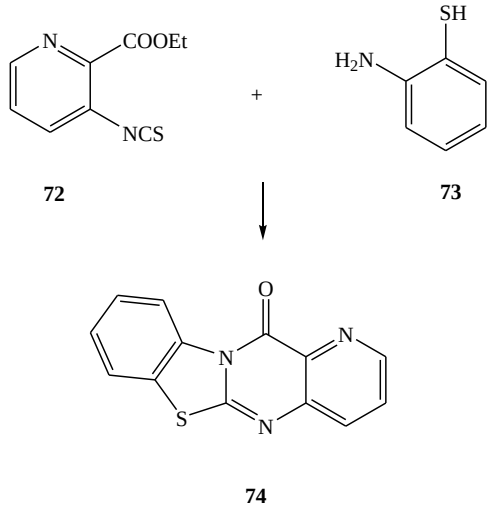
Isothiocyanates reacted with primary and secondary amines to yield the corresponding thiourea, that can be undergo heterocyclization to give pyrimidine or thiazine depending upon the condition and the nature of isothiocyanate. The reaction of cyclohexylideneacetyl isothiocyanate **67** with aryl amines afforded aryl-4-oxo-1,3-diazaspiro-5`,5`undecan **69**. This conversion involved nucleophilic addition to heterallene and subsequent intermolecular Michael reaction. Diphenylamine reacted with **67** to give 5-cyano-2-diphenyl amino-4-oxo-1-thia-3-azaspiro [5,5]undecene **68** [XLIII].



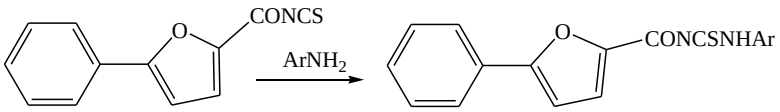
When aminoquinazolinone **70** was treated wirh phenyl isothiocyanate in refluxing ethanol gave N-phenyl-3-methyl [4` (3H) quinozolinone-3`-yl]-aminocarbothinide **71** [XLIV].



The reaction of ethyl-3-isothiocyanatopridine-2-carboxylate **72** and different amines (e.g **73**) produced 3-substituted pyrido[3,2-d]pyrimidine derivative **74** [XLV].



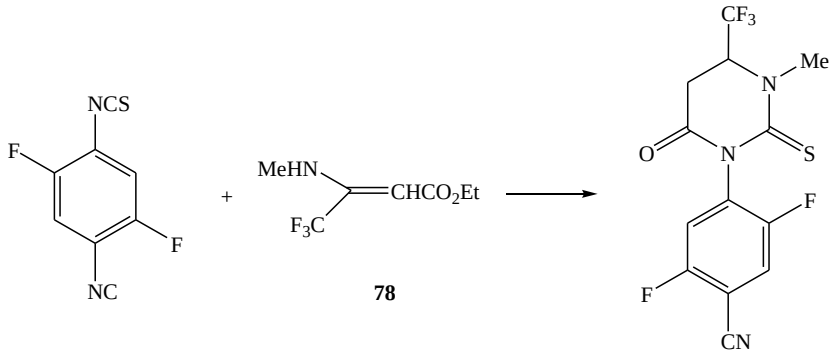
Furanoyl isothiocyanate derivative **75** reacted with arylamines to produce the corresponding thiourea derivatives **76a, b** [XLVI].



75 76

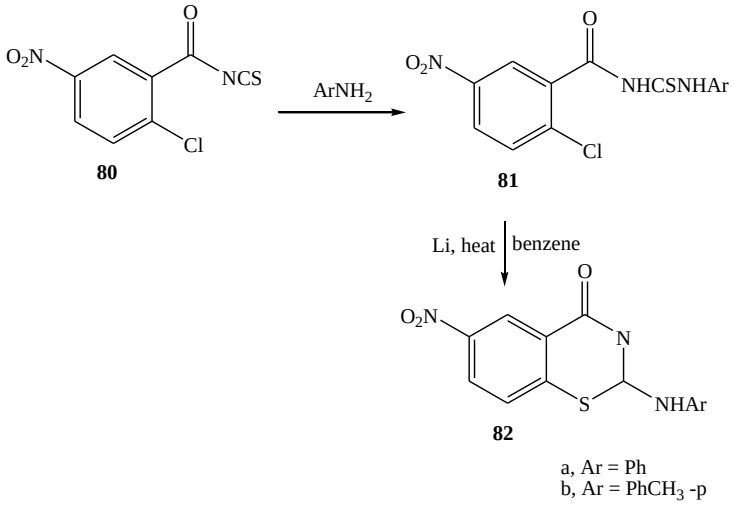
a, Ar = Ph
b, Ar = $PhCH_3$ -p

Condensation of isothiocyanate derivative **77** with methyl aminoacrylate derivative **78** gave pyrimidine derivative **79** [XLVII].



77 **78** **79**

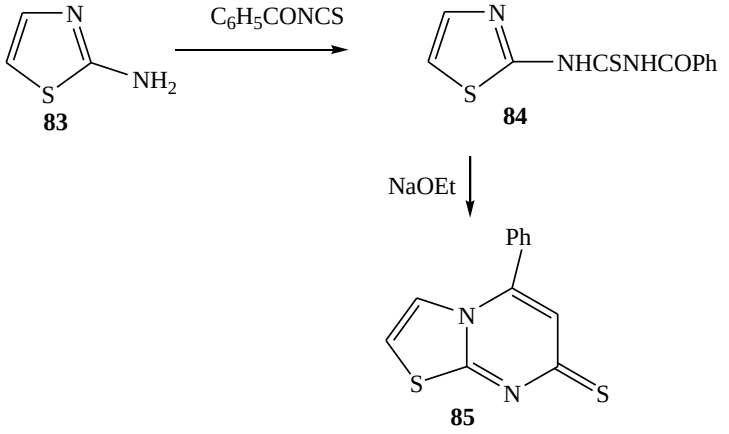
Reaction of 2-chloro-5-nitrobenzoyl isothiocyanate **80** with primary amines afforded thiorea deruvatives **81** which cyclized by heating with lithium to give benzothiazine-4-ones **82** [XLVIII].



80 **81** **82**

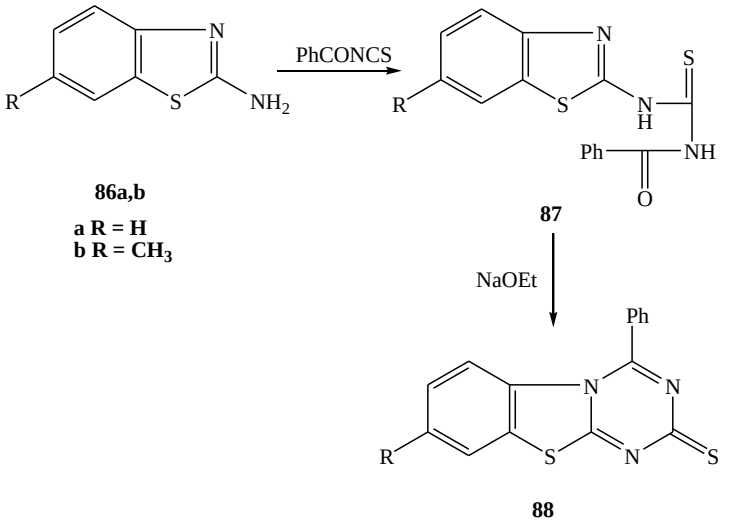
a, Ar = Ph
b, Ar = $PhCH_3$ -p

The reaction of 2-aminothiazole **83** with benzoyl isothiocyanate lead to N-benzoyl-N-[thiazole-2-yl]thiourea **84**, that cyclized by NaOEt afforded thiazolotriazine **85** [XLIX].



83 **84** **85**

Benzoyl isothiocyanate reacted with 2-aminobenzothiazole derivatives **86**[L] gave the corresponding thiourea derivative **87** which cyclized by NaOEt to benzothiazolo[3,2-b]triazine **88** [LI-LII].

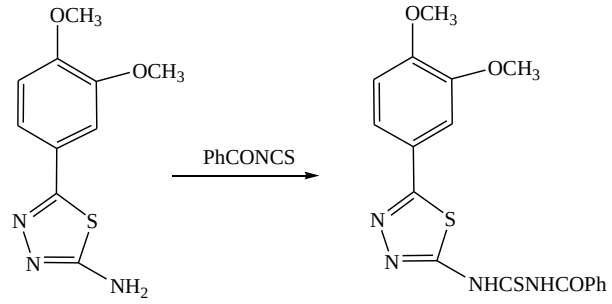


86a,b

a R = H
b R = CH_3

87 **88**

Benzoylisothiocyanate reacted with 2-amino-5-(3,4-dimeth-oxyphenyl)-1,3,4-triazole **89** afforded N-[5(2,4-dimethoxyphenyl)-1,3,4-triadiazol-2-yl]-N-benzoyl thiourea **90** [LIII].

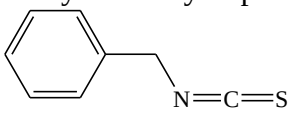


89 **90**

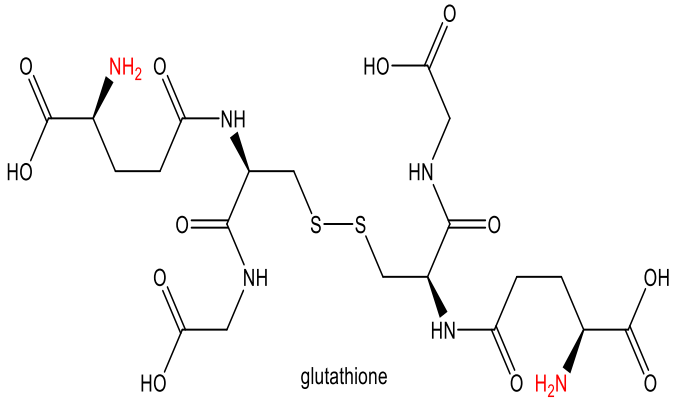
Biological activity of isothiocyanate:

Organic isothiocyanates (ITCs) 1 are chemopreventive compounds occurring in a wide variety of cruciferous vegetables as glucosinolates. Damage to plant cells, such as from cutting and chewing, releases myrosinase which catalyzes the hydrolysis of glucosinolates and the

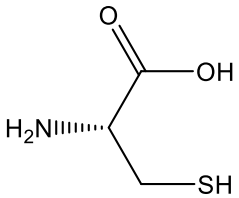
formation of ITCs by a Lossen rearrangement [LIV]. Benzyl isothiocyanates (BITC) exerts its cancer chemo preventive activities through mechanisms involving reactive oxygen species (ROS)-dependent induction of phase II detoxification enzymes, induction of mitochondrial death pathway-dependent apoptosis, G2/M cell cycle arrest-dependent apoptosis through the MAP kinase pathway, and its selective cytotoxicity to precancerous cells **[LV].**



Application of the developed method to an extract of isothiocyanates ITC-treated human colon cancer HCT116 cells, thiocarbamoylation of cysteine residues **92** of glutathione **91**, and the N-terminal proline residues from macrophage migration inhibitory factor were successfully identified as one of the intracellular targets of isothiocyanates ITCs **[LVI]**.



91

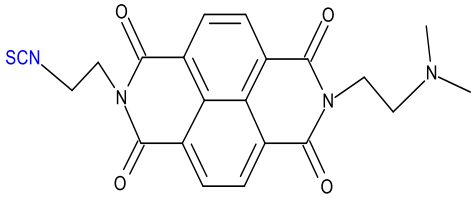


cysteine

92

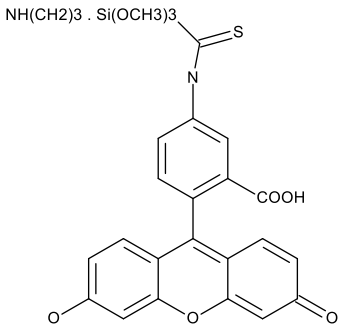
Cytotoxic terpenes containing isocyano or isothiocyanato substituents are characteristic metabolites from marine sponges and associated mollusks [LVII]. The potentials of sulforaphane and phenethyl isothiocyanate as functional food ingredients against hematological malignancies were evaluated on the intracellular targets of these antiangiogenic compounds in CEM/C2 T leukemia cells. CEM/C2 cells were seeded and incubated with various concentrations of sulforaphane or phenethyl isothiocyanate for 24 or 48 h. Sulforaphane at 0–30 lmol/L dose-dependently suppressed CEM/C2 cell growth and proliferation and caused cell death by apoptosis with down-regulation of bcl-2 and increased release of cytochrome c within 48 h [LVIII].

From sulforaphane (SFN), a well-known anticancer natural product, were reported. The most interesting compound of the series was **93** [LIX].



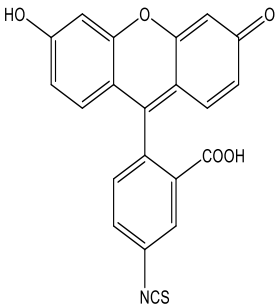
93

A novel type of core-shell fluorescein isothiocyanate (FITC)-doped[LX] fluorescent silica nanoparticle **94** was synthesized and used as an intracellular pH sensor [LXI].

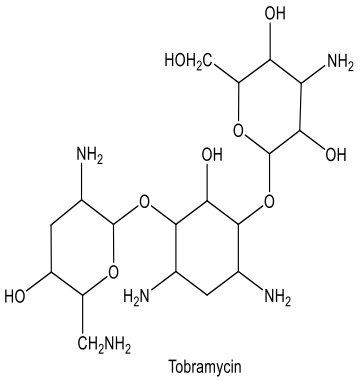


FITC-APTMS
94

For the determination of tobramycin **95** in spiked human urine following FITC pre-column derivatisation **96** has been developed [LXII-LXIII].



95



Tobramycin
96

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