Eco-Friendly Syntheses And Biological Activity Of Substituted Organic Isothiocyanates Using Copper Peroxide As Desulfurizing Agent

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Abstract:
Isothiocyanates are heteroallenic compounds. An efficient & ecofriendly process for the synthesis of substituted organic isothiocyanates is described here. In this synthesis we used copper peroxide as desulfurizing agent. This is done by reacting substituted amines with carbon disulfide in the presence of liquid ammonia and using copper peroxide. So the reported method is a step towards the sustainable and green chemistry. Synthesized Compounds were evaluated against Antimicrobial Activity .

Keywords: Copper peroxide, Carbon disulfide, organic isothiocyanates, liquid ammonia, antimicrobial activity.

Introduction:
Isothiocyanates are the most important class of organic compounds in nature.
in wasabi a Japanese spice and has also been synthesized in laboratory in the form of diisothiocyanatostilbene derivatives (DIDS)(D.X. Hou et.al. 2000 and A. Yao et.al. 2015) have proven anticancer activities. Brassicale vegetables consist of simplest form of the isothiocyanates like benzyl, allyl, phenyl ,phenylethylisothiocyantes are antitumor(T. Kasukabe et. al. 2016), anticancer[T. Kasukabe] and antibiotic[5] activities. The isothiocyanates are used in the peptide sequencing [6] and biomarkers[7] in biology and medical fields for the diagnosis purposes. Isothiocyanates are used in the synthetic organic chemistry in preparation of biologically potent scaffolds,natural products, heterocycles[8].

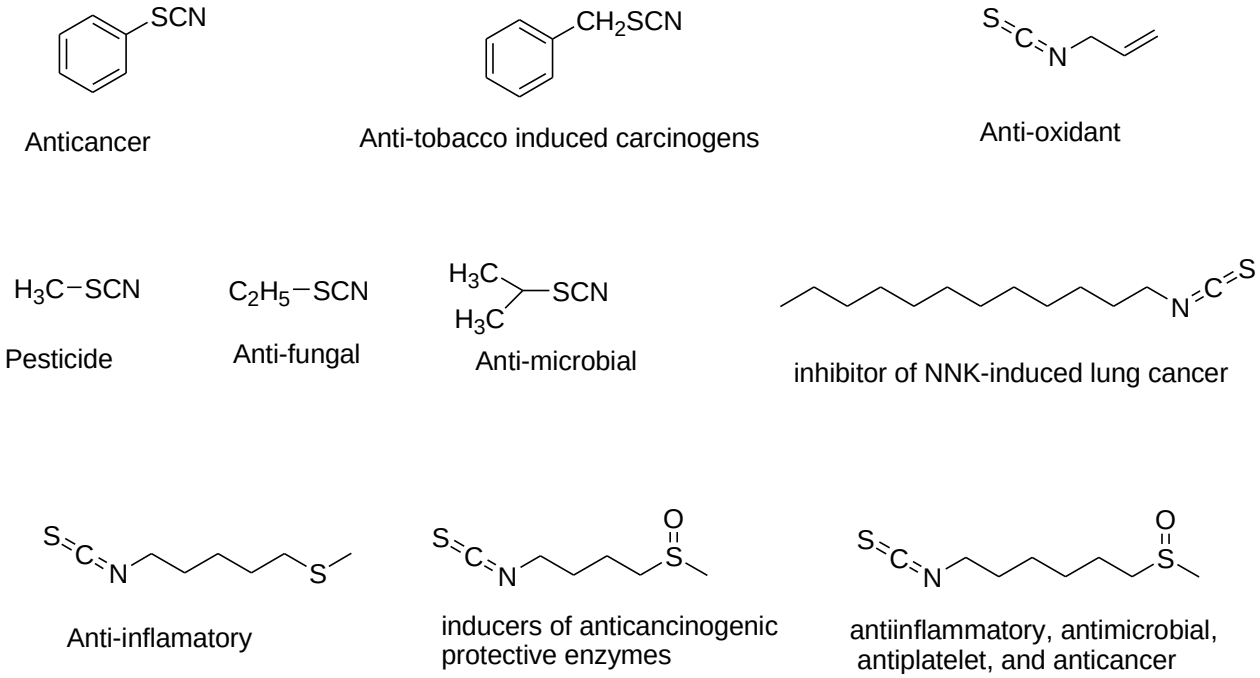
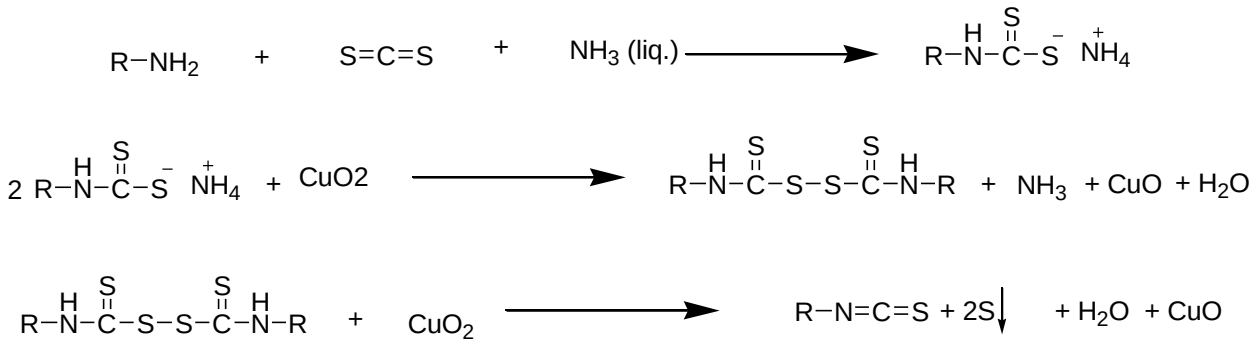


Figure 1 Structurally Diverse Biologically Potent isothiocyanates

Recognizing the versatility of the organic isothiocyantes various methods for the synthesis of such important class of compounds have been proposed all around the globe. Starting materials like thioureas[9] tertiary alcohols[10] amines[11] N-formamides[12] isocyanates[13] N-arylamino-1,2,3-thiazoles14] nitrile oxides[15] aldoximines[16] amides[17]isocyanides[18].Thiocarbonylation of amines yields isothiocyanates but the thiocrbonyl transfer agent suffer toxicity.

The treatment of the amines with the carbon disulfide is also an important and significant process but here we require some desulfurizing agent to remove sulfur from the dithiocarbamate salts to synthesize isothiocyantes. There are several desulfurizing agent which have been reported like tosyl chloride[19], hydrogen peroxide[20] ethyl chlorocarbonate[21] di-*tert*-butyl dicarbonate[22] tetrapropylammonium tribromide [23] $FeCl_3$[24] I_2[25] 2,4,6-trichloro-1,3,5-triazine[26] and chlorothionoformate[27]. The reported desulfurizing agents although helpful, but they give way to the formation of several other compounds which are not easy to separate from the desired isothiocyanates[28]. The other ways for the synthesis of isothiocyanate suffer from the lower yields [29].Thus there is an scope for an effective, greener and more convenient method for the synthesis of substituted organic isothiocyanates. We have been working with the carbon disulfide past ten years and synthesized several biologically significant scaffolds [30-33]. In the present communication we are reporting another [34] efficient process for the synthesis of organic isothiocyanates. In the present case we have employed copper peroxide as desulfurizing agent (Scheme 1).



Scheme 1. Synthesis of substituted isothiocyanates

We tested the antibodies in different solvents as shown in Table 1, but none performed better than DMSO (Part 2). When there is no solvent, the reaction does not occur.

Table 1 Reaction in different solvents

Sr.No.	Solvent	% Yield
1	Hexane	67
2	THF	71
3	Water	6
4	Ethanol	82
5	DMF	67
6	DMSO	99
7	No solvent	No reaction

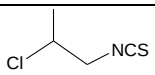
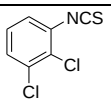
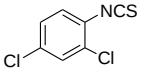
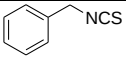
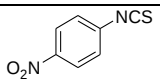
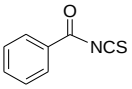
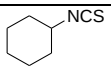
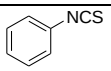
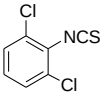
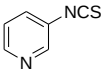
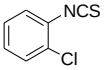
This reaction was also tested in the presence of different phase change catalysts..

Table 2:

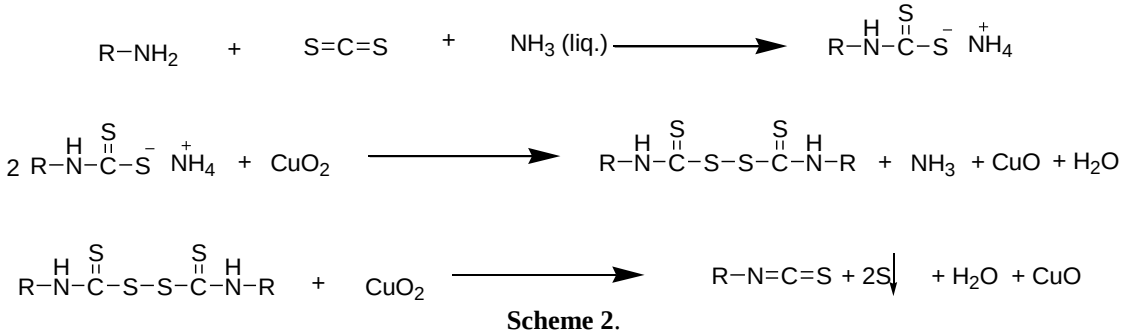
Sr.No.	Phase transfer catalyst	Time in min.	% Yield
1	TBAHC	85	60
2	TBAHS	80	72
3	TBAI	15	92
4	TMAB	75	48
5	Triton-B	75	98
6	Amberlyte-400 (basic resin)	85	62
7	No catalyst	200	10

After optimizing the reaction solvent and phase change catalyst, we studied the process structure and prepared various modified organic isothiocyanates (Table 3). Results range from good to good (76-98%), with an average of 90%.

Table 3.Substituted isothiocyanates, with reaction times and yields

Sr.No.	Substituted isothiocyanate	Time (min)	% Yield	Lit Ref
1		**20**	**97**	**33**
2		**15**	**98**	**33**
3		**15**	**98**	**33**
4		**15**	**85**	**26**
5		**15**	**82**	**26**
6		**30**	**94**	**33**
7		**40**	**88**	**25**
8		**20**	**98**	**25**
9		**15**	**95**	**33**
10		**20**	**96**	**33**
11		**15**	**94**	**33**
12		**15**	**92**	**26**

It is worthy of note that this method was also used successfully for the synthesis of alkyl isothiocyanates (Sr. No.001).



Scheme 2.

In summary**,** we present a simple**,** green method for the preparation of aromatic and aliphatic isothiocyanates in good yi elds **(**90% on average**).** This is done at low temperatures using tetrabutylammonium iodide and carbon disulphide reacte d with aliphatic and aromatic amines and using iodine as a desulfurization agent**.** We hope that our method will facilitat e the preparation and use of these important products**.**

Experimental section:
All chemicals were purchased from Fluka, Merck, Sigma-Aldrich and used without further purification. General Procedures for the Preparation of Isothiocyanates (Safety Precautions: WARNING! Carbon disulfide is toxic and should be used in a well-ventilated area, wearing personal protective clothing. All employees should be tested before testing. A small amount (1 mmol) of this process note.)

Add 1 mmol amine and 1 mmol CS_2 (dissolved in 10 mL DMSO) to a clean, dry, 100 mL round-bottom beaker. The mixture is stirred and mixed with 1 mmol of liquid. ammonia for 10 minutes. Then, with constant st irring, 1 mmol of copper peroxide was slowly added over 10 min until a yellow spot appeared in the reaction mixture. T he reaction mixture was washed with 2 mL of 10% aqueous sodium thiosulfate solution followed by 5 mL of distilled w ater. The sulfur in the mixture is filtered and the organic layer is separated, dried over anhydrous sodium sulfate, filtered , concentrated and finally purified using column chromatography (silica gel, ethyl acetate / hexane 1/10). The synthesize d compounds (4ato4p) were characterized by IR, ^{1}H NMR, ^{13}C NMR, HRMS and elemental analysis. The complete cha racteristic data of the compounds are given below:

1-Chloro-2-isothiocyanatopropane (**001**): Yield: 97 %; yellow oily liquid. ^{1} H NMR ($CDCl_3$): δ 1.54, 3.834 (t, J = 6.0 Hz, 2H), 3.70 (t, J = 6.0 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 48.3, 44.7; MS (m/z): 121.7.
Anal.calcd. % for C_3H_4NSCl: C, 29.63; H, 3.32; Cl, 29.16; N, 11.52; S, 26.37. Found: C, 29.52; H, 3.30; Cl, 29.12; S, 26.35

1,2-dichloro-3-isothiocyanato benzene (**002**): Yield:98%; yellow oily liquid. ^{1}H NMR ($CDCl_3$): δ 7.80, 7.44, 7.15, ^{13}C NMR ($CDCl_3$): δ133.4, 129.6, 129.4, 120.6, 117.8, 122.7; m/z=204.93;
Anal.calcd. % for $C_7H_3NSCl_2$: C, 41.20; H, 1.48; Cl, 34.74; N, 6.86; S, 15.71. Found: C, 41.10; H, 1.51; Cl, 34.70; N, 6.88; S, 15.71

2,4-dichloro-1-isothiocyanato benzene(**003**): Yield 98%; yellow oily liquid. ^{1}H NMR ($CDCl_3$): δ 7.35, 7.10, 6.74, ^{13}C NMR ($CDCl_3$): δ134.8, 133.2, 131.9, 128.10, 128.4, 119.8; m/z=204.93;
Anal.calcd. % for $C_7H_3NSCl_2$: C, 41.20; H, 1.48;Cl, 34.74; N, 6.86; S, 15.71. Found: C, 41.18; H, 1.46; Cl, 34.74; N, 6.90; S, 15.69

isothiobcyanatomethylbenzene(**004**):Yield 85%; yellow oily liquid. ^{1}H NMR ($CDCl_3$): δ 7.16, 7.08, 7.06, 2.36, ^{13}C NMR ($CDCl_3$): δ138.8, 128.8,127.10, 125.8, 47.6; m/z=149.03;
Anal.calcd. % for C_8H_7NS: C, 64.39; H, 4.73; N, 9.39; S, 21.49. Found: C, 64.36; H, 4.72; N, 9.36; S, 21.50

Benzoyl isothiocyanate**(006)**
Yield 94%; yellow oily liquid. ^{1}H NMR ($CDCl_3$): δ= 7.90, 7.75, 7.66, ^{13}C NMR ($CDCl_3$): δ= 174.6, 135.4, 134.7, 129.10, 129.4; m/z=163.03;
Anal.Calcd.% for C_8H_5NOS: C, 58.88; H, 3.09; N, 8.58; 19.65. Found: C, 58.57; H, 3.05; N, 8.52; S, 19.75

Isothiocyan atocyclohexane **(007)**
Yield 88%; oil**.**IR (cm^{-1}): 686, 750, 906, 928, 1072, 1452, 1476, 1490, 1580, 2042, 2160 and 3059.^{1}H NMR: δ 1.30-1.89 (m, 10 H), 3.72 (m, ^{1} H); ^{13}C NMR: δ 22.8 (coincident for two carbon), 27.7, 31.7 (coincident for two carbon), 60.0, 130.8; HRMS for [$C_7H_{11}NS+H^+$]: 141.0690 (calc), 141.0682 (obs)**.**
Anal.Calcd. % for $C_7H_{11}NS$: C, 59.53; H, 7.85; N, 9.92; S, 22.70. Found: C, 59.42; H, 7.84; N, 9.90; S, 22.66.

3-isothiocyana topyridine**(011)**
Yield 97%; oil. IR (cm^{-1}): 2022.^{1}H NMR: δ8.32, 8.46, 7.72, 7.35^{13}C NMR: δ 148.5, 146.4, 131.2, 123.6, 121.7; HRMS for [$C_6H_4N_2S$ +H^+]: 136.0126 (calc), 136.0122 (obs).
Anal.Calcd for $C_6H_4N_2S$: C, 52.92; H, 2.96; N, 20.57; S, 23.55. Found: C, 52.79; H, 2.92; N, 20.50; S, 23.59.

Antimicrobial activity: The derivatives were assessed for their antimicrobial activity against, *Candida albicans*, *Escherichia coli* and *Bacillussubtilis*. The antimicrobial assay was done by Agar-well diffusion method using Muller Hinton agar media for bacteria and Sabouraud Dextrose agar media for fungus. The examination was done using 1 mg/mL concentration of the synthesized derivatives in ethyl acetate as solvent. The antibiotic ampicillin and fluconazole were used as positive control for bacteria and fungus respectively while dimethyl sulfoxide was used as negative control. Some compounds have shown exceptional showed the antimicrobial activity against the selected strain by the showing inhibition

on the media while few compound were found inactive against the bacterial and fungal stains. The zone of inhibition obtained is listed in Table-2.

Table 2 Antimicrobial Activity of the Synthesized Compounds

Compound	Zone of Inhibition (diameter in mm)		
	C.albicans	*E.coli*	*Bacillus subtilis*
1	21	30	27
2	26	25	30
3	22	27	25
4	No activity	No Activity	No Activity
5	22	24	30
6	26	23	27
7	20	22	23
8	34	44	54
9	20	24	24
10	0	0	0
11	No activity	32	No Activity
12	42	30	50
Positive control	Fluconazole	Ampicilin	Ampicillin
Negative control	DMSO	DMSO	DMSO

Conclusion:

We have developed a novel, efficient method for the synthesis of substituted organic isothiocyanates employing the reaction between various amines and carbon disulfide using copper peroxide as desulfurizing agent and DMSO as solvent. Diverse aryl, branched, linear amines were converted to isothiocyanates in good yield. This is one pot method in which structurally diverse and biologically potent isothiocyanates were synthesized which possessed good antimicrobial activities. The biologically potent isothiocyanates synthesized can be easily purified by the column chromatography. The synthesized organic isothiocyanates have shown antimicrobial potency and some of the synthesized isothiocyanates may be further developed in the effective drugs after assessing the *in-vivo* response.

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