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Synthesis of Isothiocyanates: A Review

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Abstract: Naturally occurring isothiocyanates are limited in number. These have been found to be present in some species of Cruciferae as progenitors, called glucosinolates, and are released from the injured plant by the enzyme myrosinase. On the other hand, there is a large number of synthetic isothiocyanates which constitute an important class of compounds. It is apparent that the chemistry of isothiocyanates has burgeoned over the years, and it continues to be a blossoming field. The attraction of isothiocyanates as synthons is obviously due to their diverse reactions and also due to their easy availability. It would not be out of place to record that, in comparison to isocyanates, their sulfur analogues, isothiocyanates, are less unpleasant and to some extent less hazardous to work with. In one of our investigations during 1984, we had to abandon the use of isocyanates as cyclocondensing agents because of the reluctance of a research scholar who was in the grip of a fear complex caused by the tragic death and crippling of a large number of Bhopal citizens due to the devastating accident in a chemical plant using methyl isocyanate. Since then we became interested in isothiocyanates. The purpose of this review is to present highlights of the various synthetic schemes to obtain the various kind of isothiocyanates.

Keywords: Isothiocyanate, Thiourea, Dithiocarbonate, Thiophosgene.

Introduction

Isothiocyanates are heteroallenic compounds which are abundantly found in cruciferous vegetables. These are formed by substitution of oxygen in the isocyanate group with sulphur. These are popularly used as antimicrobial [1], anti parasitic [2-3] and anti tumour agents [4]. They exist in nature as marine sesquiterpenes [5]. They are actively used as anti-proliferative [6], enzyme

inhibitors for HIV virus [7], biological assays of DNA and proteins [8-9] and pharmaceutical products [10].

They are used as synthetic intermediates in nucleophilic and cycloaddition reactions [11]. They are popularly used as starting materials in synthesis of sulphur and nitrogen containing compounds [12]. They are used as chemo selective electrophiles in bio conjugate chemistry because of their tolerance towards aqueous reaction conditions [13], also they are key intermediates in synthesis of sulphur containing heterocycles [14-23].

They have been proposed as counterattack reagents since many of their adducts with compounds carrying an active hydrogen atom undergo cyclization spontaneously and can be manipulated to form heterocycles [24]. They have contributed to the importance of coumarin chemistry due to their varied biological properties [25]. Caumarinyl isothiocyanates are synthesized and used for synthesis of heterocycles like quinazolinones, thiohydatoins, thiazolodinone, benzooxazole, benzothiazole[26], thiopyrimidones, thioquinazolones, mercaptoimidazoles, thioimidazolones, pyridinethiones, pyrrolodines, benzothiazines [27]. They have industrial, medical and analytical applications [28-30]. They are used for antifungal and anthelminic activities [31]. They are important reagents for amide ligitation [32] and Edman peptide sequencing [33]. They are used to synthesize unsymmetrical thioureas [34-37] and in preparation of irreversible inhibitors [38].

A variety of the biologically active compounds which have been synthesized by using isothiocyanates are reported in several literature. Triapine, a tridentate α-N-pyridyl thiosemicarbazone is a potent RR inhibitor currently undergoing phase I and II clinical trials [39] (Fig. 1). Substitution on the terminal nitrogen (N4) of the thiosemicarbazone moiety was reported to increase toxicity of thiosemicarbazone derivatives which were synthesized from isothiocynates [40-41]. The terminally dimethylated thiosemicarbazone (di-2-pyridylketone-4,4,-dimethyl-3-thiosemicarbazone), derived from isothiocynates (Dp44mT, Figure 1) has even been shown to exhibit a paradoxical hypertoxicity against the P-gp-overexpressing cervix carcinoma cell line KB-V1 as compared to its parental cell line KB-3-1 [42-43]. In particular, there is a strong link between the thiosemicarbazone backbone, derived from isothiocynates and MDR selective toxicity, as exemplified by several isatin-βthiosemicarbazones including NSC73306 (Figure 1), NSC658339, NSC716765, NSC716766, NSC716768, NSC716771 and NSC716772 [44-45]. In addition to these thiosemicarbazones, the pharmacogenomic approach also identified a benzothiazole (NSC693630, Figure 1), derived from isothiocynates as a candidate MDRselective agent [46]. The pyrimidinylhydrazone VP035 (Figure 1, upper right panel) has also been reported to show selective toxicity towards MDR cell lines, yet in a P-gp independent manner [47].

Over the past years, various methods have been encountered for symmetrical, cyclic and acyclic isothiocyanate synthesis. The present review gives an insight to discuss various synthetic protocols for synthesis of isothiocyanates.

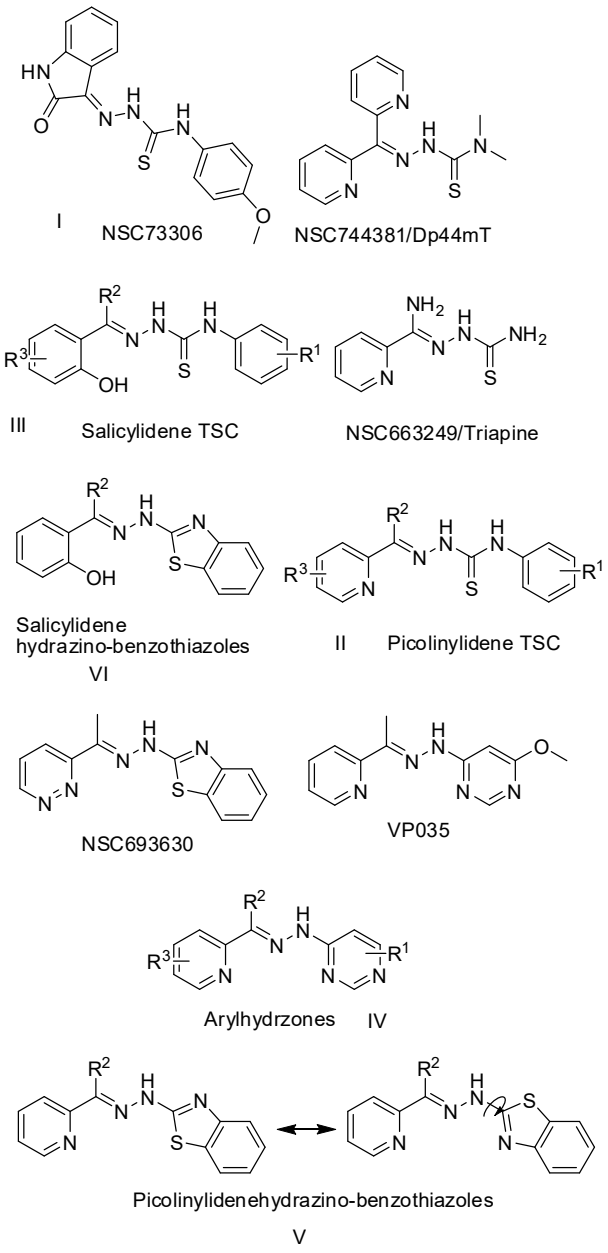


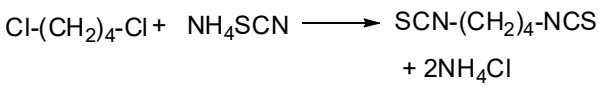
Fig.1 Bioactive compounds derived from isothiocynates

Synthesis of Isothiocyanates

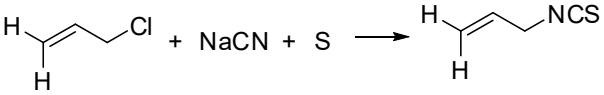
1) **From alkyl halides and metal thiocyanates, rearrangement of thiocyanates:** Although this reaction is one of the oldest methods of preparing isothiocyanates, it cannot be predicted a priori whether the reaction of an alkyl halide with a metal or ammonium salt of thiocyanic acid will result in the formation of a normal thiocyanate or the corresponding isothiocyanate. The experimental conditions employed determine which isomer will be formed and mixtures of both isomers often result. It appears that the iso thiocyanate is more thermally-stable compound and thiocyanates or mixtures thereof can be converted to pure isothiocyanates at elevated temperatures especially in the presence of cadmium iodide or zinc chloride. The salts of thiocyanic acid most commonly employed are potassium, ammonium, and less frequently silver thiocyanate, tetramethylene diisothiocyanate [48] is a typical example shown below:

2)

Scheme 1



Chlorides directly react with sulphur and sodium cyanide in methanol as shown in the equation

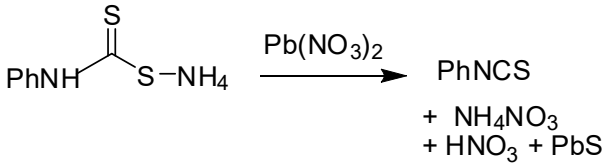


3) **From salts of dithiocarbamic acid:** Salts of dithiocarbamic acid, readily obtained by the reactions of carbon disulfide and alkali hydroxides or ammonia with primary amines, are smoothly cleaved to isothiocyanates by heavy metal salts chloroformate esters, phosgene, sodium hypochlorite, or iodine [49-52]. Each of these methods fail, of course, if the amine is too weakly basic to form a dithiocarbamate salt.

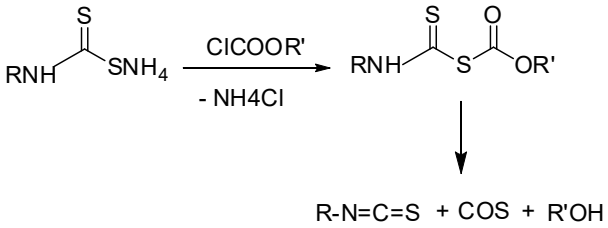
Although the alkali metal or ammonium salts of dithiocarbamic acid derived from primary amines are relatively stable, the corresponding heavy metal salts are easily decomposed to form isothiocyanates. A typical preparation is that of phenyl isothio cyanate [53] from ammonium phenyldithiocarbamate via the lead

salt intermediate

Scheme 2



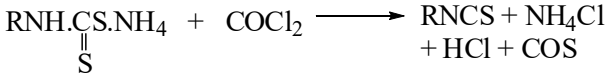
And research [54] observed that the reactions of aliphatic dithiocarbamate salts with chloroformate esters yield the corresponding aliphatic isothiocyanates in good yield. The reaction has been interpreted as shown below:



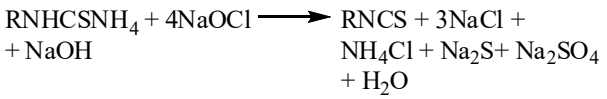
The method is not generally applicable for the preparation of aryl isothiocyanates for in addition to the expected product, large quantities of diaryl ureas are formed under the experimental conditions. These by-products arise from the cleavage of the four membered ring intermediate to carbon disulfide and aryl isocyanates [55], which are then converted to diaryl ureas in the presence of water. A recent modification of the method permits preparation of aryl isothiocyanates in good yield in aqueous solution. A possible mechanism for the reaction is also discussed.

Reactions of dithiocarbamate salts with phosgene [56] proceed smoothly

Scheme 3

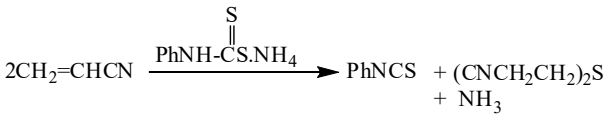


Yields, even in the preparation of complex aryl isothiocyanates are excellent. Primary and secondary isothiocyanates can be prepared readily by oxidation of dithiocarbamate salts with sodium hypochlorite. [57]



Delaby and co-workers have described the reaction of acrylonitrile with dithiocarbamate salts to form isothiocyanates and bis-2-cyano-ethyl sulphide.

Scheme 4



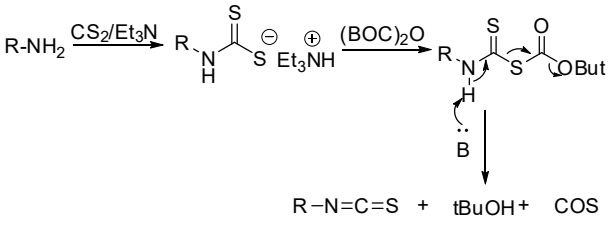
*Alkyl and aryl amines are converted smoothly to corresponding isothiocyanates via dithiocarbamates in excellent yields using di-ter butyl dicarbonate(Boc_2O) and 1-3% of DMAP (4-Dimethylaminopyridine) or DABCO (1,4-Diazabicyclo[2.2.2]octane) as catalyst. Most of the by-products are volatile hence; workup requires simple evaporation of the reaction mixture.

Although the previous methods are efficient, there was a need of clean work up procedure avoiding use of chromatography. Di-ter butyl dicarbonate (Boc_2O) is a suitable agent for desulphurisation as this reagent may involve CO_2 and COS during the reaction. Residual CS_2 and ter-butanol together with the solvent should be removed easily by evaporation. As the formation of dithiocarbamate in the case of most amines proceeds rapidly, isothiocyanates can be synthesized directly from the amine in the presence of excess carbon disulphide.

It was observed that a catalytic amount of DMAP or DABCO (1-3%) increased the reaction rate significantly resulting in formation of isothiocyanates from corresponding amines in minutes with visible evolution of gas from

reaction mixture. In the stepwise reaction, the electrophile Boc_2O reacts with dithiocabamate with evolution of CO_2 to form an unstable mixed dithiocarbamate/carbonate adducts that rapidly decomposes to the isothiocyanates, COS and ter-butanol (scheme1). One equivalent of triethyl amine was used for stabilization and complete formation of dithiocarbamate as reported earlier [58]. The reaction is carried out in polar conditions ethanol, or methanol though it proceeds well in non polar solvents as DCM (dichloromethane), THF (tetrahydrofuran) or in dipolar solvents as DMF (N,N-dimethyl formamide) and acetone. Boc_2O was added in almost stoichiometric amounts (0.99equiv) to avoid formation of residual di-tert-butyl dicarbonate as a by-product. Although the reaction can proceed via various pathways such as Boc protection of amine or amine's conversion to isothiocyanate, these reactions are rarely observed [59]. However, Boc-protected amine formation was observed to be upto 14% in GCMS in case of 1-adamantyl amine and poorly soluble aryl amines along with the case of deactivated aryl amines as para-bromoaniline(8%).

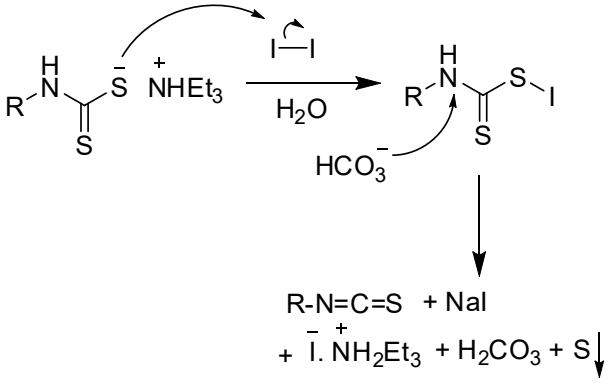
Scheme 5



An improved procedure for the synthesis of isothiocyanates from the corresponding dithiocarbamic acid salts via a desulphurization strategy using molecular iodine and sodium bicarbonate in water/ethyl acetate biphasic medium. The reagents used are easily available, non-toxic and cheap. This method is accepted due to its environmental acceptability of reagents, cost effectiveness.

During the process the dithiocarbamic acid salt is easily converted into the corresponding isothiocyanate by treating it with iodine in presence of sodium bicarbonate in water/ethyl acetate biphasic medium in good to excellent yields in shorter time (15 minutes). The water/ethyl acetate has potential advantages. The coexistence of water with ethyl acetate helps in extracting the isothiocyanate to the organic layer leaving behind the impurities in the aqueous layer which in turn facilitates an easy work up process. Iodine is soluble in ethyl acetate and on stirring, dissolves and gets delivered at water/ethyl acetate interface for desulphurization. The water phase dissolves the base sodium bicarbonate over organic bases offer a mild and effective green approach towards synthesis of isothiocyanates.

Scheme 6



Various dithiocarbamic salts of aryl amines with electron withdrawing groups in both ortho and para positions afford excellent yields [60]. Aromatic ring containing two fluro groups in ortho and para positions gave isothiocyanates in excellent yields. Isothiocyantaes were obtained in very high yields from their corresponding dithiocarbamate salts containing high electron withdrawing substituents in meta and para positions. This methodology worked well with substrates having electron withdrawing groups. Similar results were obtained while preparing aliphatic isothiocyanates of n-butyl, dodecayl

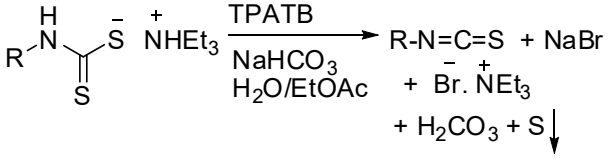
and cyclohexyl dithiocarbamates. The method was effective as well with dithiocarbamate salts of bezyl piperonyl and homoveratrylamines.

The reactions were clean and thioureas and other by-products were not obtained during the preparation of isothiocyanates.The reactions were fast and facile at room temperatures. The products were obtained in high yields is pure without requiring any further purification.

*A highly efficient and simple protocol for the synthesis of isothiocyanates and cyanamides from their respective amines have been developed in the presence of a mild, efficient, and non-toxic reagent tetrapropylammonium tribromide (TPATB).High environmental acceptability of the reagents, cost effectiveness and high this methodology viable.

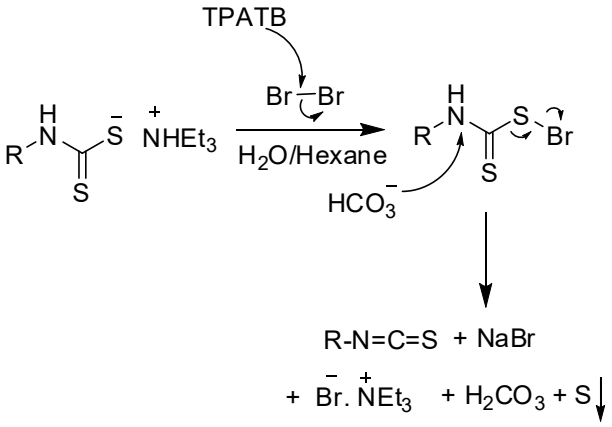
Although many synthetic methods for the preparation of isothiocyanates have been reported to date [61–67] most methods suffer from the employment of highly toxic reagents. Thus, there is still need for a commercially viable and environmentally acceptable protocol for the synthesis of isothiocyanates. The synthesis of isothiocyanates via TPATB(tetrapropylammonium tribromide)-mediated decomposition of dithiocarbamate salt in the presence of sodium bicarbonate in water/ethyl acetate biphasic solvent system at room temperature (Scheme 7) emerged as an effective method.

Scheme 7



The water/ethyl acetate biphasic solvent system has several important advantages. In addition to the versatile character of both water and ethyl acetate, the presence of both water with ethyl acetate helps in the extraction of isothiocyanate to the organic layer leaving behind the impurities in the aqueous layer which brings about an easy workup. TPATB (tetrapropylammonium tribromide) is soluble in ethyl acetate and on stirring dissolves, thus diffuses to the water-ethyl acetate interphase for desulfurization. Moreover, the water phase dissolves the base sodium bicarbonate and keeps the dithiocarbamic acid salt in aqueous layer. The use of sodium bicarbonate over organic bases offers a mild and effective green approach towards the synthesis of isothiocyanates. The mechanism of the present transformation is given in Scheme 8.

Scheme 8

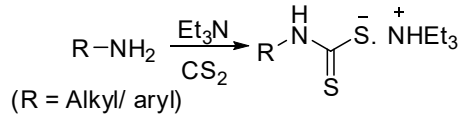


In conclusion a general, economical and environmentally novel method for the preparation of isothiocyanates and cyanamides from their corresponding dithiocarbamic acid salts has been developed. The use of non-toxic and eco-friendly reagents and solvents without the formation of any side products has rendered this methodology potentially useful. The yield could in fact be considered as very good if not excellent.

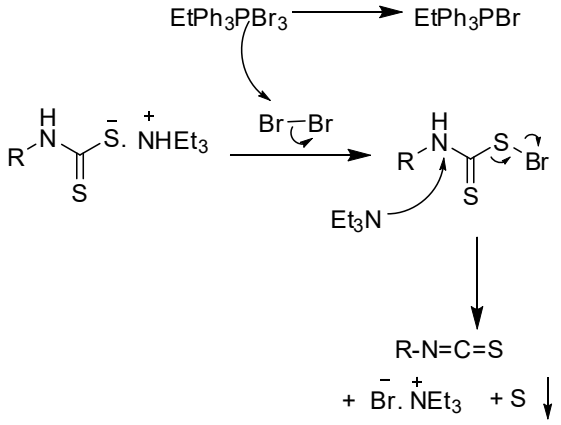
*Synthesis of isothiocyantes from ethyl triphenyl phosphonium tribromide (ETPPTB), the analysis of its reactivity profile and its efficacy in various reactions like bromination, acylations etc. In this method, it was observed that ETPPTB (ethyl triphenyl phosphonium

tribromide) works well as desulphurizing agent for synthesis of isothiocyanates from corresponding dithiocarbamate precursor. The dithiocarbamic acid salts were prepared following a modified procedure which is represented in scheme.

Scheme 9



Scheme 9(a). Preparation of dithiocarbamate salt.



Scheme 9(b). Proposed mechanism for formation of isothiocyanate.

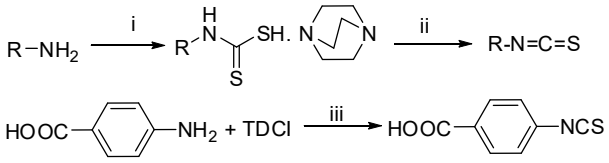
ETPPTB (ethyl triphenyl phosphonium tribromide) has been synthesized and its reactivity studied. Its ease of preparation,

Mildness and efficacy in organic reactions such as bromination, acylation and isothiocyanate preparation shows that the reagent could be a useful addition to the existing lot of reagents.

*Dithiocarbamate salts were prepared by reaction of triethylenediamine and carbamodithioic acids which were formed by treatment of aromatic amines with carbon disulphide. Isothiocyanates were then obtained by treated dithiocarbamate salts with BTC (bis(trichloromethyl) carbonate). 4-isothiocyanates were then obtained by treated dithiocarbamate salts with BTC (bis(trichloromethyl)carbonate). 4-isothiocyanatebenzoic acid was prepared by reaction of 4-aminobenzoic acid with TCDI (1,1'-Thiocarbonyldiimidazole) in the presence of TEA (triethyl amine).

4-Thiazolidinones and their analogs were prepared according to the routes [68-79] depicted in scheme 2. Aryl isothiocyanates were treated with active methylene compounds and potassium hydroxide in DMF to provide ketene-N,S-acetal salts. These salts were further reacted with 2-chloroacetyl chloride, 3-bromopropanoyl chloride or 1,2-dibromoethane to give compounds 5-11 or 13-31.Compound 12 was prepared by de-protection of compound 11 with TFA (trifluoroaceetic acid) in DCM. Reaction of isothiocyanate with 2-mercaptoacetic acid offered an intermediate 2-(carbamothioylthio) acetic acid, which was subsequently cyclised to produce the additional analogues.

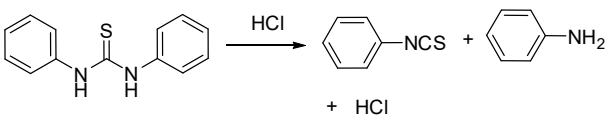
Scheme 10



A strategy for preparation of isothiocyanates via diacetoxy iodobenzene (DIB) mediated decomposition of dithiocarbamate salts.

3) Isothiocyanates from thioureas: The cheap and readily available diarylthioureas are easily cleaved by hot mineral acids to aryl isothiocyanates and salts of aryl amines.

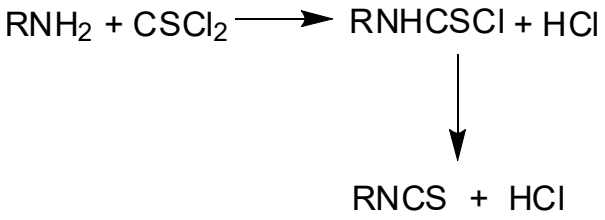
Scheme 11



If unsymmetrical disubstituted thioureas are used both possible isothiocyanates are formed. According to a method described monoarylthioureas can be cleaved by extended heating in a suitable inert solvent. Aryl isothiocyanates result in good yield with the liberation of ammonia.

4) Isothiocyanates from primary amines and thiophosgene; The reaction of thiophosgene with primary amines to form isothiocyanates has long been known, and proceeds smoothly in most cases. Although the reaction appears to be analogous to the commercially important phosphgenation of amines to form isocyanides, thiophosgene and isothiocyanates are relatively insensitive to water in cold and the reaction can be conducted in aqueous media. Hydroxyl, carboxyl, thiol or sulfamide groups on the amine decrease the water sensitivity even further and in contrast to the preparation of isocyanates do not appear to interfere with the formation of isothiocyanates. It has been shown that the reaction proceeds via the thiocarbamyl chloride, which eliminates hydrogen chloride to form the isothiocyanate.

Scheme 12

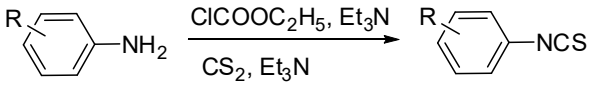


Thus, the amine salts, as well as the free amines, can be thiophosgenated are preferred, since the side reactions of isothiocyanates with free amine to form symmetrical thiourea can materially lower the yields unless thiophosgene is always present in excess. Aromatic amines are exception and are generally employed as the free bases because of their weakly basic character.

Also, isothiocyanates were synthesized starting from proper amines like 2-napthylamine and Commercialized substituted thiophenol obtained from p-chlorophenol and p-nitrophenol in presence of alcoholic solution of hydrochloric acid. 34-78% isothiocyanates obtained were crystalline. Yields of derivatives with bulkier groups were lower as compared to the ones having more remote acetyl group.

*Aryl isothiocyanates with strong electron withdrawing fluorine were prepared by a more straight forward and convenient synthetic route in one step and good yield (Scheme 13). Reaction of flurophenyl amines with carbon disulphide in presence of triethylamines gave ethyl chloroformate in ice bath, flurophenyl isothocyanates were obtained in the range of 40-89%. [80-87]

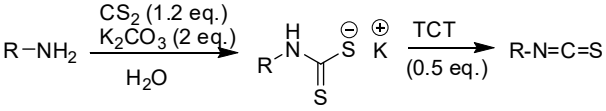
Scheme 13



R= 2-F, 4-F, 2,4-F_2, 2,6-F_2, 2-CF_3, 3-CF_3

*A general and facile one pot synthesis of a broad range of alkyl and aryl isothiocyanates have been developed from their corresponding primary amines under aqueous conditions. This two step process synthetic process involves an in situ generation of a dithiocarbamate salt from the amine substrate by reacting it with CS_2 in presence of a base followed by elimination to form this isothiocyanate product with cyanuric acid as the desulphurylation agent.

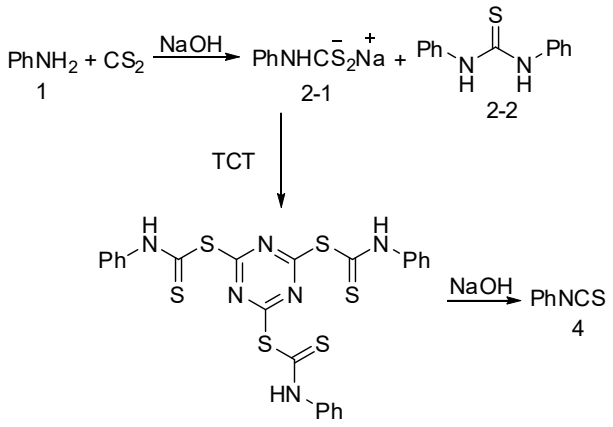
Scheme 14



These methods were successful with substrates having highly electron withdrawing groups as CF_3, CN, CH_3CO, NO_2. From previous methods,

considering that TCT (2,4,6-trichloro-1,3,5-triazine) is an efficient desulphurylation reagent, it was speculated that it can be used for desulphurylation of dithiocabamates to form isothiocyanates. Initialy, the method begins with aniline to prepare phenyl isothiocyanate(Scheme 15) via N-phenyl dithiocarbamate followed by desulphurylation with TCT (2,4,6-trichloro-1,3,5-triazine). As inorganic bases were more efficient for the conversion of arylamines to N-aryl dithiocarbamates in aqueous systems, inorganic bases were chosen to screen the optimum reaction conditions for the one pot synthesis.

Scheme 15



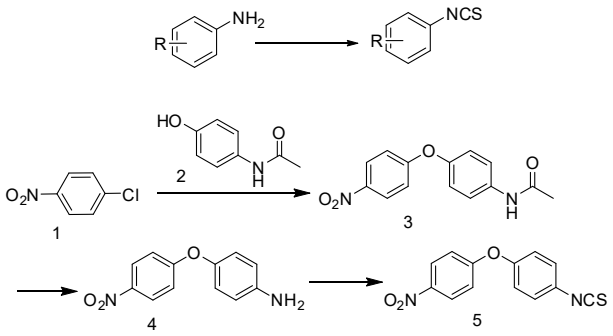
As per the literature N-phenyl dithiocarbamate was generated by mixing aniline and CS_2 in water in presence of NaOH at room temperature. After the aniline disappeared completely, the mixture was cooled to 0˚C and TCT (2,4,6-trichloro-1,3,5-triazine) in CH_2Cl_2 was added. This biphasic mixture was stirred for 30 minutes and further treated with NaOH to form a clear solution. The workup yielded 61% phenyl isothiocyanate along with small amount of N,N'-diphenyl urea as a by-product. Moreover, under this condition, the by-product TMT was easily soluble in water to form a clear solution and thus, convenient to the layers separation during the workshop. Under optimal conditions, an overall yield of phenyl isothiocyanate from aniline was obtained up to 98%. It should be noted that choosing K_2CO_3 as the reaction base was crucial. It was found out that dithiocarbamate could form a clear aqueous solution while the corresponding sodium salt was much less soluble and the ammonium salt was almost insoluble and difficult to stir. Although the isolation of intermediate 3 was not successful (scheme 1), the fact that the formation of the side product TMT was observed strongly indicated the presence of this intermediacy.

The newly developed method could convert a wide range of primary alkyl and arylamines into their corresponding isothiocyanates in excellent yields and provides promise for further scale-up activities. Moreover, this method is advantageous over many other methods for the synthesis of highly electron-deficient aromatic isothiocyanates. [88- 116]

*An efficient, mild, chemo selective and convenient protocol for synthesis of isothiocyanate derivatives. The protocol was applied successfully in the novel synthesis of anthelmintic drug 4-isothiocyanato-4' nitrodiphenyl ether and its analog. Here, the conversion of amines to isothiocyanates is done in presence of a different base, ferrous sulphate as novel catalyst.

Amine, carbon disulphide and acetone were stirred at room temperature to form dithiocarbamate salt which was subsequently treated with triethyl amine and ferrous sulphate to secure isothiocyanates. This reaction can't be completed without ferrous sulphate to secure isothiocyanates, thus it is used as catalysts. The purified product was isolated using n-hexane. [117] A broad range of structurally diverse aromatic amines have been used.

Scheme 16

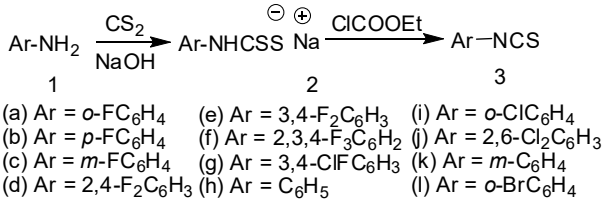


This method is further used for synthesis of anthelminic drug 4-isothiocyanato-4'-nitrodiphenyl ether scheme 16.

This is a simple novel method for synthesis of isothiocyanates with relatively short reaction times, utilization of cheap and readily available reagents and high yields of products are some of the advantages of the present protocol. These are advantageous for modern day large scale operations.

*A straight forward and convenient synthesis of aryl isothiocyanates from aryl amines on the basis of Kaluza method as shown in the following equation.[118-121] Aryl amines readily react with carbon disulphide and sodium hydroxide in water to give sodium aryl dithiocarbamates which were treated directly with ethyl chloroformate at 35˚-45˚C to give aryl isothiocyanates.

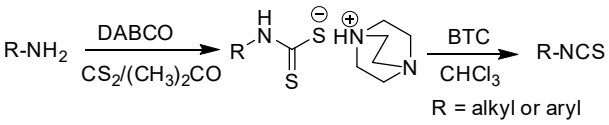
Scheme 17



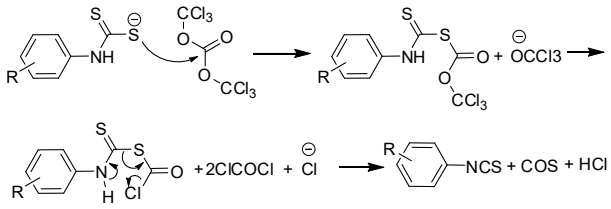
*A mild and efficient method for the conversion of alkyl and aryl amines to isothiocyanates via dithiocarbamates has been developed using$(CH_3)_2CO$-CS_2 as a co solvent and triphosgene as dehydrosulfurization reagent. High yields, mild reactions conditions and excellent functional group compatibility make it become a versatile synthetic method for the preparation of isothiocyantes compared with reported methods. A series of isothiocyantes were prepared in good yields by decomposition of dithiocarbamates using cholorosilanes such as MiSiCl, Me_2SiCl_2, $MeSiCl_3$ and $SiCl_4$. [122-138]

Bis(trichloromethyl)carbonate (BTC) usually called triphosgene or solid phosgene, being a substitute for phosgene and diphosgene in synthesis is safe and convenient to be used with good selectivity and yields under mild conditions. The use of triphosgene as a dehydrosulphurization reagent in the preparation of isothiocyanate has been reported by Chaskar and co-workers. Most isothiocyanates bearing electron-withdrawing groups were obtained in good yields by their methods. Though, it is not suitable for anilines bearing strong electron withdrawing groups as cyano and nitro groups. It is well known that some strong electron-withdrawing substituents are important pharmacophores and pharmaceuticals.

Scheme 18



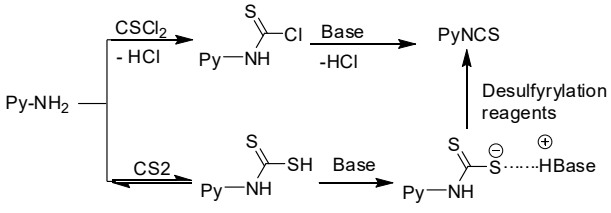
In the exploratory studies, a strong electric-withdrawing amine, p-nitro aniline selected to investigate the effect of solvents. P-Nitro aniline and CS_2 in the presence of 1,4-diazabicyclo[2.2.2]-Octan(DABCO) reacted in different solvents at room temperature. The was even no precipitation of product (b) in ethanol after 24 hrs.



In other solvents, the reaction didn't complete in 24 hrs and only a little precipitation was afforded. The yield with toluene was good but was not optimal due to toxicity and pungent smell. Acetone was less efficient than toluene but its dissolution capacity was much better for p-nitro aniline. It was found that yield increased upto 90% when $(CH_3)_2CO$-CS_2 in ratio 1:5 was used as co-solvent in formation of isothiocyanate.

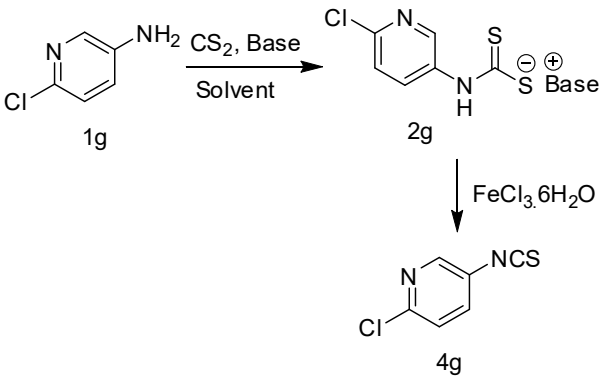
*A pot synthesis of pyridyl isothiocyanates from the corresponding amines has been developed. This method involves aqueous iron(III) chloride mediated desulphurization of a dithiocarbamate salt that is generated in situ by treatment of an amine with carbon disulphide in the presence of DABCO or sodium hydride. The choice of base is of importance for the dithiocarbamate salts. This one pot process works well for a wide range of pyridyl isothiocyanate. Utilizing this protocol some highly electron deficient pyridyl and aryl isothiocyanate are obtained in moderate to good yields. There are two main methods to convert substituted aminopyridines into the corresponding isothiocyanate analogue (Scheme 19).

Scheme 19



The most well known method is based on thiophosgene and later refinements of thiocarbonyl transfer reagents such as thiocarbonyl diimidazole and dipyridyl thionocarbonate [139-163]. The high toxicity and incomparability of thiophosgene with many functional groups limit its general use furthermore these thiocarbonyl transfer reagents are not readily available and often do not work as desired due to formation of thiourea by-products. Another two step approach, based on reagent promoted decomposition of dithiocarbamate salts into isothiocyanates was proposed by Le Count. The intermediate dithiocarbamate salts are generated by treatment of amine with carbon disulphide and Et_3N.Although some desulphurylating reagents for this approach wer developed. In first step, preparing the N-pyridyl dithiocarbamate salts was neglected. Most of these methods are efficient only for electron rich pyridyl isothiocyanate as electron deficient aminopyridines are less reactive to form dithiocarbamate salt, resulting in low yield.

Le count's work, iron(III)chloride has been proved to be effective for decomposition of dithiocarbonate salts was investigated, so its important to improvise the preparation as once dithiocarbamates were obtained as desulphurylation process proceeds gradually. Initially, 3-amino-6-chloropyridine was chosen as model substrate to prepare isothiocyanate in a one pot process. Initially, the effect of various bases was evaluated by performing the model reaction in tetrafuran when inorganic bases and organic bases were employed, the conversion of thiocarbamate salts were low, even after 12 hrs, the yield was less than 30%. Trimethyl amine and potassium tert-butaoxide was used for 12 hrs, resulting in formation of large amount of thiourea. With DABCO as a base, the conversion took 4 hrs and resulted excellent yields. However THF is a non polar solvent with low dielectric constant, the corresponding ammonium salts in non polar solvents are present entirely as ion pairs.

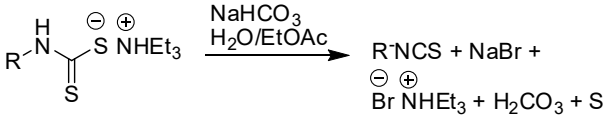


A mechanism for formation of pyridyl dithiocarbamate salts is proposed. Step one, amine attacks on carbon disulphide leads to formation of dithiocarbamic acid, which is reversible. The driving force of reaction is most importantly the reaction of base with dithocarbamic acid to bring about stable dithiocarbamate salts. A greater ion pair basicity corresponds to tighter ion pair, which eases the generation of dithiocarbamates, the ion pair basicities of Et_3N and DABCO suit with observed different reactivity. When DABCO is used as a base, it has been found that THF was the best solvent among DMF, acetone, MeCN,EtOH,CH_2Cl_2.Next step, with suitable conditions, on addition of $FeCl_3$ to unpurified one pot reaction for complete conversion for 1 hr at room temperature.

*A highly efficient yet simple protocol for synthesis of isothiocyanates from respective amines in presence of a mild, non-toxic reagent, tetrapropylammonium tribromide(TPATB) is proposed. High environmental acceptance of reagent, good yield adds to this method.

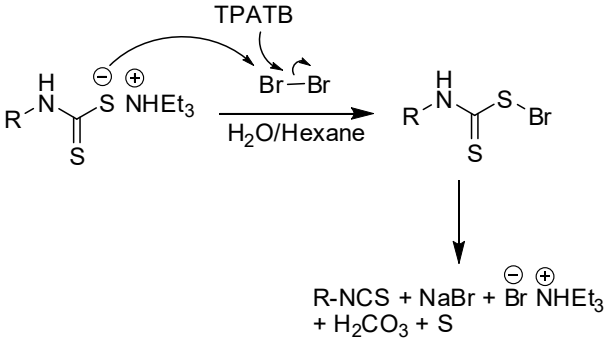
The dithiocarbamic acid salt is converted into a corresponding isothiocyanate treating it with TPATB in presence of sodium bicarbonate in water/ethyl acetate biphasic medium in good to excellent yields in shorter time as shown in the scheme1.

Scheme 20



Preparation of isothiocyanate from dithiocarbamate salt

The water/ethyl acetate biphasic medium is potential solvent system as it helps in extracting the isothiocyanate to the organic layer leaving behind the impurities in aqueous layer which facilitates an easy work up. TPATB is soluble in ethyl acetate and dissolved on stirring, thus getting delivered to water-ethyl acetate interphase for desulphurylation. The water phase dissolves the base sodium carbonate and retains dithiocarbamic acid salt in aqueous layer. The use of sodium bicarbonate over organic bases offers a mild and effective green approach towards the synthesis of isothiocyanates. Thus the method offers an economically as well as ecologically viable process for the preparation of isothiocyanates. The reaction was performed on freshly prepared dithiocarbamate salts synthesized from variety of alkyl and aryl amines.



Mechanism of the formation of isothiocyanate from dithiocarbamate salt

Substrates containing activating substituents gave the expected products efficiently as also did substrates containing deactivating

substituents. Trisubstituted substrates as well as highly hindered substrates gave corresponding isothiocyanates in higher yields. Benzyl substrate and aliphatic substrates also gave their expected products in excellent yields.

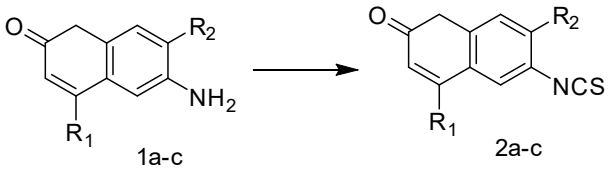
5)Miscellaneous Preparations of Isothiocyanates: When the, reaction is conducted under pressure at 12Q-130°C, elemental sulfur adds to the carbon nitrogen double bond of methylene aniline to form phenyl isothiocyanate and other compounds.

• Isonitriles similarly add sulphur and isocyanic acid- adds to the carbon-carbon double bond of olefinic compounds according to Markownikoff's rule, yielding secondary or tertiary isothiocyanates. [164-167]

Carbodi-imides, phosphinimines, and phosphoni-mines are cleaved by carbon disulfide at elevated temperatures to form isothiocyanates and other products. Isocyanates are readily converted to isothiocyanates by heating under pressure in the presence of phosphorous penta-sulfide, or carbon disulfide.

*Coumarinyl isothiocyanates are prepared from 6-amino coumarins with carbon disulphide and iodine in pyridine.Condensation of anthranilic acid. [168-171]

Scheme 21



Conclusion:

Isothiocyanates remain very important starting materials for the construction of heterocycles. Notwithstanding the prolific use of addition-cyclization approach for this purpose, its scope continues to be enormous. Carbon bases and organometallic compounds, particularly those hitherto unexplored, can provide adducts suitable for heterocyclic synthesis. Therefore, reactions of isothiocyanates with new substrates should be studied with this perspective in mind. Also, search for novel isothiocyanates and investigation of their photochemistry and cycloaddition reactions would be rewarding. Furthermore, the possibility of desulfurization of isothiocyanate-derived products could be profitably exploited in the preparation of diverse compounds, particularly those having carbonyl in place of thiocarbonyl groups which would obviate the use of harmful isocyanates. In conclusion, it should be added that a judicious application of the knowledge gained over the years in the further exploration of this area would pay dividend.

References:

1. (a)Drobmica, L.; Zemanova M.; Nemac, P.;Kristian, P.; Antos, K.; Hulka, A.Appl. Microbiol. 1967, 15, 710-717; (b) Carter, G.A.; Garraway, J. L.; Spencer, D. M.; Wain, R.L. Ann. Appl. Bio. 1963, 51, 135-151. Posher, G.H.S.; Cho,C.G.: Green,J.V.; Zhang, Y.; Talalay, P. *J. Med.Chem.* 1994, 37, 170-176.
2. Arnold, J. T.; Wikinson, B.P.; Sharma, S.;Steele, V.E. *Cancer Res.* 1995, 55, 537-543.
3. Posher, G.H.S.; Cho, C.-G.; Green, J.V.;Zhang, Y; Talalay, P. J. Med. Chem. 1994, 37, 170-176; (b)Arnold, J. T.; Wilkinson, B.P.; Sharma, S,; Steele, V.E. Cancer Res. 1995, 55, 537-543; (c) Pintao, A. M.; Pais, M. S. ; Coley, H.; Kelland, L. R.; Judson, I. R, Planta Med. 1995, 61, 233-236; (d)Adsule, S.; Banerjee, S.; Ahmed, F.; Padhye, S.; Sarkar, F. H. *Bioorg. Med.Chem.Lett*. 2010, 20, 1247-1251.
4. Nastruzzi C. Cortesi R.E Mengegatti, E.; Leoni, O.:Iori,R,; Palmiery, S . *J. Agric.Food Chem.*2000, 48, 3572-3575.
5. Nastruzzi C. Cortesi R.E Mengegatti, E.; Leoni, O.:Iori,R,; Palmiery, S . *J. Agric.Food Chem.*2000, 48, 3572-3575.
6. (a)Bian, G.; Shan, W,;Su,W. J. Chem. Res. Synop.2005, 2005, 585-586; (b)Zhang, X.; Neamati, N,; Lee, Y.k.;Orr,A.;Brown, R.D.;Whitaker, N.; Pommier, Y.; Burke,T.R. Bioorg.Med.Chem.2001,9, 1649-1657
7. (a)Heckl,S,; Sturzu, A,; Regenbogen, M,;Beck, A.;Feil, G,;Gharabaghi,A,;Echner, H.Med. Chem. 2008, 4, 348-354; (b) Dong, S.;Roman, M. J. Am.Chem. Soc. 2007, 129, 13810-13811; (c) Lerchen, H.-G; Baumgarten, J.; Piel, N.;

Kolb-Bachofen, V. Angew. Chem., Int. Ed. 1999, 38, 3680-3683
8. Edman,P . Arch. Biochem. Biophys.1949,22 , 475-476.
9. (a) Xiao, D.; Powolny, A. A.; Singh, S. V. J. Biol. Chem. 2008, 283, 30151–30163; (b) Cuddihy, S. L.; Brown, K. K.;Thomson, S. J.; Hampton, M. B. Cancer Lett. 2008, 271, 215–221; (c) Wang, L. G.; Liu,X. M.; Fang, Y.; Dai, W.; Chiao, F. B.; Puccio, G. M.; Feng, J.; Liu, D.; Chiao,J. W. Int. J. Oncol. 2008, 33, 375–380.
10. Ferna´ndez, J. M. G.; Mellet, C. O.; Blanco, J. L. J.; Mota, J. F.; Gadelle, A.; Coste Sarguet, A.; Defaye, J. Carbohydr. Res. 1995, 268, 57–71.
11. Mukerjee, A. K.; Ashare, R. Chem. Rev. 1991, 91, 1–24.
12. Stephensen, H.; Zaragosa, F. J. Org. Chem. 1997, 62, 6096–6097.
13. Ratke, A. Chem. Ber. 1872, 5, 799.
14. Dyson, G. M.; George, H. J. J. Chem. Soc. 1924, 125, 1702–1708.
15. Larsen, C.; Stelliou, K.; Harpp, D. N. J. Org. Chem. 1978, 43, 337–339.
16. Larsen, C.; Harpp, D. N. J. Org. Chem. 1981, 46, 2465–2466.
17. Kim, S.; Yi, K. Y. Tetrahedron Lett. 1985, 26, 1661–1664.
18. Boas, U.; Jakobsen, M. H. J. Chem. Soc., Chem. Commun. 1995,1995–1996.
19. Boas, U.; Pedersen, B.; Christensen, J. B. Synth. Commun. 1998, 28,1223–1228.
20. Boas, U.; Pedersen, H. G.; Christensen, J. B.; Heegaard, P. M. H.Tetrahedron Lett. 2004, 45, 269–272.
21. Molina, P.; Alajarin, M.; Tamiaki, H. Synthesis 1982, 596–597.
22. Jochims, J. C.; Seeliger, A. Angew. Chem. 1967, 79, 151.
23. Mukherjee A.K.& Ashare R, Chem Rev, 91, 1991, 1-24.
24. Berdy J, Heterocyclic Antibiotics,(CRC Press, Boca Ranton), 1981,570.
25. Gold H., in The Chemistry of Synthetic Dyes, Vol 5, edited by K. Venkataraman (Academic Press, New York) 1971, Chap.8. Lockhart I.M., Chem Heterocycl. Comp,31,1977,440.
26. Mukherjee A.K.& Ashare R, Chem Rev, 91, 1991, 1-24.
27. Berdy J, Heterocyclic Antibiotics,(CRC Press, Boca Ranton), 1981,570.
28. Gold H., in The Chemistry of Synthetic Dyes, Vol 5, edited by K. Venkataraman (Academic Press, New York) 1971, Chap.8.
29. Jochims, J. C.; Seeliger, A. Angew. Chem. 1967, 79, 151.
30. Kim J.N.;Jung,K.S;Lee,H.J.; Son, J.S. *Tetrahedron Lett.* 1997, 38, 1597-1598.
31. Crich.D; Sasaki, K.Org.Letters, 2009,11, 3514-3517.
32. Edman,P . *Arch. Biochem. Biophys.*1949,22 , 475-476.
33. Li J, Tan Z, Tang S, Hewlett I, Pang R, He M, He S, Tian B, Chen K, Yang M. Bioorg Med Chem. 2009;17:3177–3188.
34. Ashish Bhatt, Rajesh K. Singh, Bhupendra K. Sarma, Ravi Kant, Tetrahedron Letters, 2019, 60(36), 151026
35. Ashish Bhatt, Rajesh K. Singh, Ravi Kant, Tetrahedron Letters, 2019, 60(16), 1143-1147
36. Ashish Bhatt, Rajesh K. Singh, and Ravi Kant, Synthetic Communications, 2019, 49(1), 22 – 31.
37. Ashish Bhatt, Rajesh K. Singh, Ravi Kant, Bhupendra K. Sarma, SYNTHESIS, 2019, 51, 3883-3890.
38. Burke, T.R.;Bajwa, B.S.;Jacobson,A.E.;Rice.K.C.;Streaty R.A.;Klee.W.A.;J.Med.Chem. 1984, 27,1570.
39. C.R. Kowol, R. Berger, R. Eichinger, A. Roller, M.A. Jakupec, P.P. Schmidt, et al., J. Med. Chem. 2007, 50, 1254–1265.
40. Y. Yu, J. Wong, D.B. Lovejoy, D.S. Kalinowski, D.R. Richardson, Clin. Cancer Res. 2006, 12, 6876–6883.
41. C.M. Nutting, C.M.L. van Herpen, A.B. Miah, S.A. Bhide, J.-P. Machiels, J. Buter, et al., Ann. Oncol. 2009, 20, 1275–1279.
42. G. Rappa, A. Lorico, M.-C. Liu, G.D. Kruh, A.H. Cory, J.G. Cory, et al., Biochem. Pharmacol. 1997, 54, 649–655.
43. M.D. Hall, N.K. Salam, J.L. Hellawell, H.M. Fales, C.B. Kensler, J.A. Ludwig, et al., J. Med. Chem. 2009, 52, 3191–3204.
44. C.R. Kowol, R. Trondl, P. Heffeter, V.B. Arion, M.A. Jakupec, A. Roller, et al., J. Med. Chem. 2009, 52, 5032–5043.
45. P.V. Bernhardt, P.C. Sharpe, M. Islam, D.B. Lovejoy, D.S. Kalinowski, D.R. Richardson, J. Med. Chem. 2009, 52, 407–415.
46. P.J. Jansson, T. Yamagishi, A. Arvind, N. Seebacher, E. Gutierrez, A. Stacy, et al., J. Biol. Chem. 2015, 290, 9588–9603.
47. Henry L. Wheeler, Henry F. Merriam *J. Am. Chem. Soc.*1901,23,5283-299
48. S.Sharma .Sulp.Reports,1987, 327-454 |
49. T. Isoda, K. Hayashi, S. Tamai, T. Kumagai, Y. Nagao, *Chem. Pharm. Bull.* **2006**, *54*, 1616–1619.
50. Kneeland, D. M.; Ariga, K.; Lynch, V. M.; Huang, C.-Y.; Anslyn, E.V. J. Am. Chem. Soc. 1993, 115, 10042–10055
51. Stetter, H.; Wulff, C. Chem. Ber. 1962, 95, 2302–2304.
52. Spurlock, L. A.; Porter, R. K.; Cox, W. G. J. Org. Chem. 1972, 37,1162–1168.
53. Yamasaki, T.; Kawaminami, E.; Uchimura, F.; Okamoto, Y.;Okawara, T.; Furukawa, M. J. Heterocycl. Chem. 1992, 29, 825–829.
54. Bolsen, C. E.; Hartshorn, E. B. J. Am. Chem. Soc. 1923, 45, 2349–2355.;Mull, R. J. Am. Chem. Soc. 1955, 77, 581–583.
55. Bolsen, C. E.; Hartshorn, E. B. J. Am. Chem. Soc. 1923, 45, 2349–2355.;Mull, R. J. Am. Chem. Soc. 1955, 77, 581–583.
56. J. N. Kim, K. S. Jung, H. J. Lee, J. S. Son, *Tetrahedron **Lett.*** **1997,** ***38***, 1597–1598.
57. Krishna Srivastava, Ashish Bhatt, Ravi Kant, Deepa Lakhmani, Chemical Biology Letters, 2019, 6(2), 46-54.
58. (a) Frentzel, J. Chem. Ber. 1883, 16, 743–746; (b)

Kneeland, D. M.; Ariga, K.; Lynch, V. M.; Huang, C.-Y.; Anslyn, E.V. J. Am. Chem. Soc. 1993, 115, 10042–10055. (c) Spurlock, L. A.; Porter, R. K.; Cox, W. G. J. Org. Chem. 1972, 37,1162–1168.
59. (a) Munch, H.; Hansen, J.S.; Pittelkow, M.; Christensen,J.B.; Boas, U. Tetrahedron Lett. 2008, 49, 3117-3119. (b) Hodgkins, J.E.; Reeves, W.P. J. Org. Chem. 1964, 29,3098-3099. (c) Li, G.; Tajima, H.; Ohtani, T. J. Org. Chem. 1997, 62,4539-4540.
60. Toshimitsu, S. Uemura, M. Okano, N. Watanabe, *J. Org. Chem.* **1983**, *48*, 5246–5251.
61. D. Albanese, M. Penso, *Synthesis* **1991**, 1001–1002.
62. W. G. Shan, G. F. Bian, W. K. Su, X. R. Liang, *Org. Prep. Proced. Int.* **2004**, *36*, 283–286.
63. J. N. Kim, E. K. Ryu, *Tetrahedron Lett.* **1993**, *34*, 8283–8284.
64. J. N. Kim, K. S. Jung, H. J. Lee, J. S. Son, *Tetrahedron Lett.* **1997**, *38*, 1597–1598.
65. W. Adam, R. M. Bargon, S. G. Bosio, W. A. Schenk, D. Stalke, *J. Org. Chem.* **2002**, *67*, 7037–7041.
66. M. Arisawa, M. Ashikawa, A. Suwa, M. Yamaguchi, *Tetrahedron Lett.* **2005**, *46*, 1727–1729.
67. L. Valette, S. Poulain, X. Fernandez, L. Lizzani-Cuvelier, *J. Sulfur Chem.* **2005,** *26*, 155–161.
68. T. Isoda, K. Hayashi, S. Tamai, T. Kumagai, Y. Nagao, *Chem. Pharm. Bull.* **2006**, *54*, 1616–1619.
69. B. Zhong, R. S. Al-Awar, C. Shih, J. H. Grimes Jr., M. Vieth, C. Hamdouchi, *Tetrahedron Lett.* **2006**, *47*, 2161–2164.
70. W. J. Neely, *Aust. J. Chem.* **1960**, *13*, 341–346.
71. M. Bollini, J. J. Casal, D. E. Alvarez, L. Boiani, M. Gonzalez, H. Cerecetto, A. M. Bruno, *Bioorg. Med. Chem.* **2009**, *17*, 1437–1444.
72. E. Dyer, T. B. Johnson, *J. Am. Chem. Soc.* **1932**, *54*, 777–
73. G. M. Dyson, T. Harrington, *J. Chem. Soc.* **1942**, 374–375.
74. J. C. Jochims, A. Seeliger, *Tetrahedron* **1965**, *21*, 2611–2616.
75. R. Gottfried, *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 963–964.
76. C. Larsen, K. Steliou, D. N. Harpp, *J. Org. Chem.* **1978**, *43*, 337–339.
77. C. Larsen, D. N. Harpp, *J. Org. Chem.* **1981**, *46*, 2465–2466.
78. S. Kim, K. Y. Yi, *J. Org. Chem.* **1986**, *51*, 2613–2615.
79. S. Kim, K. Y. Yi, *Tetrahedron Lett.* **1985**, *26*, 1661–1664.
80. K. H. Chaudhuri, U. S. Mahajan, D. S. Bhalerao, K. G. Akamanchi, *Synlett* **2007**, 2815–2818.
81. J. Nath, B. Patel, L. Jamir, U. B. Sinha, K. V. V. V. Satyanarayana, *Green Chem.* **2009**, *11*, 1503–1506.
82. Munier-Lehmann, H. l. n.; Lucas-Hourani, M.; Guillou, S.; Helynck, O.; Zanghi, G.; Noel, A.; Tangy, F. d. r.; Vidalain, P.-O.; Janin, Y. L. *J. Med. Chem.* 2015, 58, 860-877.
83. Sykes, David B.; Kfoury, Youmna S.; Mercier, François E.; Wawer, Mathias J.;Law, Jason M.; Haynes, Mark K.; Lewis, Timothy A.; Schajnovitz, A. et. al. *Cell* 2016, 167, 171-186.
84. Bar-Or, A.; Pachner, A.; Menguy-Vacheron, F.; Kaplan, J.; Wiendl, H. *Drugs* 2014, 74, 659-674.
85. Brunetti, L.; Wagner, M. L.; Maroney, M.; Ryan, M. *Ann. Pharmacother.* 2013,47, 1153-1160.
86. I Keen, H.; Conaghan, P. G.; Tett, S. E. *Expert. Opin. Drug. Saf.* 2013, 12,581-588.
87. X.-Y. Xu, X.-H. Qian, Z. Li, G.-H. Song,W.-D. Chen, J. Fluor. Chem. 2004, 125, 1159–1162.
88. X.-H. Qian, X.-Y. Xu, Z.-B. Li, Z. Li, G.-H. Song, J. Fluor. Chem. 2004, 125, 1609–1620.
89. C.-X. Liu, X.-Y. Xu, Z. Li,W.-D. Chen, Q.-C. Huang, X.-H. Qian, J. Fluor.Chem. 2005, 126, 53–58.
90. Ashish Bhatt, Rajesh K. Singh, and Ravi Kant, Synthetic Communications, 2019, 49(8), 1083-1091.
91. S. Kawamura, K. Izumi, J. Sato, Y. Sanemitsu, T. Hamada, H. Shibata, R. Sato, US 5244863 (1993).
92. J.E. Harris, J.A. Gagne, J.E. Fischer, R.R. Sharma, K.A. Traul, J.D. Scott, F.G. Hess, in: D.L. Shaner, S.L. O'Connor (Eds.), TheImidazolinone Herbicides, CRC Press, Boca Raton, FL, 1991, pp. 179–190.
93. Ashish Bhatt, Rajesh K. Singh, and Ravi Kant, ARKIVOC, 2018, 7, 236-247.
94. Ashish Bhatt, Rajesh K. Singh, and Ravi Kant, Journal of Heterocyclic Chemistry, 2019, 56(2), 696-702.
95. Ashish Bhatt, Rajesh K. Singh, Ravi Kant, Chemistry of Heterocyclic Compounds, 2018, 54(12), 1111–1116.
96. Isoda T, Hayashi K, Tamai S, Kumagai T, Nagao Y. Chem Pharm Bull. 2006, 54, 1616–1619.
97. Zhong B, Al-Awar R S, Shih C, Grimes J H, Jr, Vieth M, Hamdouchi C. Tetrahedron Lett. 2006, 47, 2161–2164.
98. Neely W J. Aust J Chem. 1960, 13, 341–346.
99. Jochims J C, Seeliger A. Tetrahedron. 1965, 21, 2611–2616.
100. Gottfried R. Angew Chem, Int Ed Engl. 1966;5:963–964.
101. Larsen C, Steliou K, Harpp D N. J Org Chem. 1978;43:337–339.
102. Ashish Bhatt, Ravi Kant and Rajesh K Singh, Medicinal Chemistry (Los Angeles), 2016, 6(4), 257-263.
103. Kim S, Yi K Y. J Org Chem. 1986;51:2613–2615.
104. Kim S, Yi K Y. Tetrahedron Lett. 1985;26:1661–1664.
105. Grayson J I. Org Process Res Dev. 1997;1:240–246.
106. Hodgkins J E, Ettlinger M G. J Org Chem. 1956;21:404–405.
107. Hodgkins J E, Reeves W P. J Org Chem. 1964;29:3098–3099.
108. Shibanuma T, Shiono M, Mukaiyama T. Chem Lett. 1977;6:573–574.
109. Kondo K, Komamura C, Murakami M, Takemoto K. Synth Commun. 1985;15:171–177.
110. Ashish Bhatt, Rajesh Kumar Singh, Ravi Kant, Chemical Biology Letters, 2017, 4(2), 73-80.
111. Ashish Bhatt, Rajesh Kumar Singh, Ravi Kant, Chemical

Biology Letters, 2016, 3(2), 38-43.
112. Ashish Bhatt, Rajesh Kumar Singh and Ravi Kant, Der Pharmacia Lettre, 2016, 8 (6), 182-187.
113. Boas U, Gertz H, Christensen J B, Heegaard P M H. Tetrahedron Lett. 2004, 45, 269–272.
114. Li G, Tajima H, Ohtani T. J Org Chem. 1997;62:4539–4540.
115. (a) Isobe T. J Org Chem. 1999;64:6984–6988. (b) Bian G, Shan W, Su W. J Chem Res. 2005:585–586.
116. Chaskar A C, Yewale S, Bhagat R, Langi B P. Synth Commun. 2008;38:1972–1975.
117. Wong R, Dolman S J. J Org Chem. 2007, 72, 3969–3971. Bian G, Qiu H, Jiang J, Wu J, Lai G. Phosphorus, Sulfur Silicon Relat Elem. 2007, 182, 503–508.
118. Ravi Kant, Ashish Bhatt, Krishna Srivastava, Chemical Biology Letters, 2019, 6(2), 55-61.
119. Munch H, Hansen J S, Pittelkow M, Christensen J B, Boas U. Tetrahedron Lett. 2008, 49, 3117–3119.
120. Chaskar A C, Bandgar B P, Modhave R K, Patil A B, Yewale S. Synth Commun. 2009, 39, 992–1001.
121. Nath J, Ghosh H, Yella R, Patel B K. Eur J Org Chem. 2009:1849–1851.
122. Chaskar, A. C.; Yewale, S.; Bhagat, R.; Langi, B. P. Triphosgene: An efficient catalyst for synthesis of isothiocyanates. Synth. Commun. 2008, 38, 1972–1975.
123. J. E. Hodgkins and W. P. Reeves, *J. Org. Chem., 1964,* 29,3098.
124. (a) J. Segawa, M. Kitano, K. Kazuno, M. Tsuda, I. Shirahase, M. Ozaki, M. Matsuda and M. Kise, *J. Heterocyl. Cheni., 1992,* 29, 1117 (b) Y. Jinbo, H. Kondo. Y. Inoue, M. Taguchi, H. Tsujishita, Y. Kotera. F. Sakamoto and G Tsukamoto, *J. Med. Chem., 1993,* 36,2621.
125. S**.** Sakai, T. Aizawa and T. Fujinami, J. *Org. Chem.. 1974,* 39, 1970.
126. T. Rasschaert and G. Benoy, *Ind. Chim. Belge. 1967,* 32, 106.
127. (a) Nasser, I.; Habib, F.; Najmeh, N. Tetrahedron 2006, 62, 5498–5501; (b) Nasser, R.; Habib, F.; Batool, A. Synthesis 2004, 1, 92–96; (c) Hideyoshi, M.; Yuichin, N.; Mitsuru, S. Chem. Lett. 2006, 35, 1262–1263.
128. (a) Chaskar, A. C.; Bandgar, B. P.; Modhave, R. K.; Patil, A. B.; Yewale, S. Synth. Commun. 2009, 39, 992–1001; (b) Rince, W.; Sarah, J. D. J. Org. Chem. 2007, 72, 3969–3971; (c) Harashadas, M. M.; Srinivas, D.; Yadav, J. S. Tetrahedron Lett. 1997, 38, 8743–8744; (d) Grzegorz, B. Liebigs Ann. Chem. 1982, 10, 1927–1932; (e) Shizuyoshi, S.; Tatsuo, F.; Toshiyuki, A. Bull. Chem. Soc. Jpn. 1975, 48, 2981–2982; (g) Shibanuma, T.; Shiono, M.; Mukaiyama, T. Chem. Lett. 1977, 6, 573–574; (i) Molina, P.; Alajarin, M.; Arques, A. Synthesis 1982, 7, 596–597.
129. (a) Jae, N. K.; Eung, K. R. Tetrahedron Lett. 1993, 34, 8283–8284; (b) Jae, N. K.; Keum,S. J.; Hong, J. L. Tetrahedron Lett. 1997, 38, 1597–1598; (c) Jae, N. K.; Jong, H. S.; Eung,K. R. Synth. Commun. 1994, 24, 1101–1105.
130. (a) Fujiwara, S.; Shin-ike, T. Tetrahedron Lett. 1991, 32, 3503–3506; (b) Fujiwara, S.; Shin-ike, T. Tetrahedron Lett. 1992, 33, 7021–7024; (c) Adam, W.; Bargon, A. M.; Bosio, S. G.; Schenk, W. A. J. Org. Chem. 2002, 67, 7037–7041.
131. Valette, L.; Poulain, S. Fernandez, X. J. Sulfur Chem. 2005, 26, 155–161.
132. Eckert, H.; Forster, B. Angew. Chem., Int. Ed. Engl. 1987, 26, 894–895.
133. Mayekara, S. A.; Chaskara, A. C.; Mulwada, V. V. Synth. Commun. 2010, 40, 46–51.
134. Bian, G.; Qiu, H.; Jiang, J.; Wu, J.; Lai, G. Phosphorus, Sulfur Silicon Relat. Elem. 2007,182, 503–508.3350
135. Boas, U.; Gertz, H.; Christensenb, J. B.; Heegaard, P. M. H. Tetrahedron Lett. 2004, 45, 269–272.
136. Cotarca, L.; Delogu, P.; Nardelli, A.; Sunjic, V. Synthesis 1996, 5, 553–576.
137. Chaskar, A. C.; Yewale, S.; Bhagat, R.; Langi, B. P. Synth. Commun. 2008, 38, 1972–1975.
138. Munch, H.; Hansen, J. S.; Pittelkow, M.; Christensen, J. B.; Boas, U. Tetrahedron Lett. 2008, 49, 3117–3119.
139. (a) Huang, C.; Yin, Q.; Zhu, W.; Yang, Y.; Wang, X.; Qian, X.; Xu, Y. Angew. Chem. Int.Ed. 2011, 50, 7551–7556; (b) Chen, Z.; Wang, W.; Zhu, W.; Xu, Y.; Qian, X. J. Med. Chem. 2011, 54, 3732–3745.
140. Yella, R.; Ghosh, H.; Murru, S.; Sahoo, S. K.; Patel, B. K. Synth. Commun. 2010, 40, 2083–2096.
141. (a) Urleb, U.; Stanovnik, B.; Ti_sler, M. J. Heterocycl. Chem. 1990, 27, 407–412; (b) Cee,V. J.; Frohn, M.; Lanman, B. A. ACS Med. Chem. Lett. 2010, 2, 107–112; (c) Louie, M.-W.; Fong, T. T.-H.; Lo, K. K.-W. Inorg. Chem. 2011, 50, 9465–9471.
142. (a) Fawzy, N. M.; Swelam, S. A. Pharm. Chem. 2009, 1, 52–62; (b) Brown, A.; Brown, T.B.; Calabrese, A. Bioorg. Med. Chem. Lett. 2010, 20, 516–520.
143. (a) Li, Z.; Qian, X.; Liu, Z.; Li, Z.; Song, G. Org. Prep. Proced. Int. 2000, 6, 571–573; (b)Degorce, S.; Jung, F. H.; Harris, C. S.; Koza, P.; Lecoq, J.; Stevenin, A. Tetrahedron Lett. 2011, 52, 6719–6722; (c) Varaprasad, C. V. N. S.; Barawkar, D.; El Abdellaoui, H.; Chakravarty, S.; Allan, M.; Chen, H.; Zhang, W.; Wu, J. Z.; Tam, R.; Hamatake, R.; Lang, S.; Hong, Z. Bioorg. Med. Chem. Lett. 2006, 16, 3975–3980.
144. Nath, J.; Ghosh, H.; Yella, R.; Patel, B.K. *Eur. J. Org. Chem.* **2009**, *2009*, 1849–1851.
145. Wong, R.; Dolman, S.J. *J. Org. Chem.* **2007**, *72*, 3969–3971.
146. Munch, H.; Hansen, J.S.; Pittelkow, M.; Christensen, J.B.; Boas, U. *Tetrahedron Lett.* **2008**, *49*, 3117–3119.
147. Sun, N.; Li, B.; Shao, J.-P.; Mo, W.-M.; Hu, B.-X.; Shen, Z.-L.; Hu, X.-Q. *J. Org. Chem.* **2012**, *8*, 61–70.
148. Liu, P.-F.; Li, C.-Y.; Zhang, J.-W.; Xu, X.-Y. *Synth. Commun.* **2013**, *43*, 3342–3351.
149. Li, Z.-Y.; Ma, H.-Z.; Han, C.; Xi, H.-T.; Meng, Q.; Chen,

X.; Sun, X.-Q. *Synthesis* **2013**, *45*, 1667–1674.
150. Zhang, Z.; Wu, H.-H.; Tan, Y.-J. *RSC Adv.* **2013**, *3*,16940–16944.
151. Pronin, S.V.; Reiher, C.A.; Shenvi, R.A. *Nature* **2013**, *501*, 195–199.
152. Zhong, B.; Al-Awar, R.S.; Shih, C.; Grimes, J.H.; Vieth, M.; Hamdouchi, C. *Tetrahedron Lett.* **2006**, *47*, 2161–2164.
153. Ibrahim, M.A.; Yusof, M.S.M.; Amin, N.M. *Molecules* **2014**, *19*, 5191–5204.
154. Burkett, B.A.; Fu, P.; Hewitt, R.J.; Ng, S.L.; Toh, J.D.W. *Eur. J. Org. Chem.* **2014**, *2014*, 1053–1058.
155. Kobayashi, K.; Kobayashi, A.; Ezaki, K. *Tetrahedron* **2013**, *69*, 7936–7942.
156. Fujiwara, S.; Shin-Ike, T.; Sonoda, N.; Aoki, M.; Okada, K.; Miyoshi, N.; Kambe, N. *Tetrahedron Lett.* **1991**, *32*, 3503–3506. *Molecules* **2014**, *19* **13642**
157. Larsen, C.; Steliou, K.; Harpp, D.N. Organic sulfur chemistry. 25. Thiocarbonyl transfer reagents.*J. Org. Chem.* **1978**, *43*, 337–339.
158. Kim, S.; Yi, K.Y. Di-2-pyridyl thionocarbonate. *Tetrahedron Lett.* **1985**, *26*, 1661–1664.
159. Le Count, D.J.; Dewsbury, D.J.; Grundy, W. *Synthesis* **1977**, 582–583.
160. Ding, F.-Z.; Smith, J.M.; Wang, H.-B. *J. Org. Chem.* **2009**, *74*, 2679–2691.
161. Streitwieser, A.; Kim, Y.-J. *J. Am. Chem. Soc.* **2000**, *122*, 11783–11786.
162. Cecchi, L.; de Sarlo, F.; Machetti, F. *Eur. J. Org. Chem.* **2006**, *2006*, 4852–4860.
163. Ashish Bhatt, Rajesh Kumar Singh, Ravi Kant, Pramod Kumar Chauhan, Chemistry & Biology Interface, 2016, 6(5), 357-365.
164. Haynes, W.M. *Crc Handbook of Chemistry and Physics*, 95th ed.; Lide, D.R., Ed.; CRC Press/Taylor and Francis: Boca Raton, FL, USA, 2014.
165. Nair, V.; Kim, K.H. *J. Heterocycl. Chem.* **1976**, *13*, 873–876.
166. L'abbé, G.; Allewaert, K.; Toppet, S. *J. Heterocycl. Chem.* **1988**, *25*, 1459–1462.
167. Ramachandran, S.; Shahul H.P.; Srivastava, A.; Shanbhag, G.; Morayya, S.; Rautela, N.; Awasthy, D.; Kavanagh, S.; Bharath, S.; Reddy, J.; *et al. J. Med. Chem.* **2014**, *57*, 6642–6652.
168. Altenbach, R.J.; Bai, H.; Brioni, J.D.; Carroll, W.A.; Gopalakrishnan, M.; Gregg, R.J.; Holladay, M.W.; Huang, P.P.; Kincaid, J.F.; Kort, M.E.; *et al.* Potassium Channel Openers. U.S. Patent 2002/0028836A1
169. Sommen G, Comel A & Kirsch G, Synlett, 2001, 1731.
170. Sommen G, Comel A & Kirsch G, Tetrahedron 59, 2003, 1557.
171. Krylsky D V, Shilkhaliev K S & Solovyev A S, Chem Heterocyclic compound, 2001, 37, 52.