Annexure – VIII

UNIVERSITY GRANTS COMMISSION
BAHADUR SHAH ZAFAR MARG
NEW DELHI – 110 002

PROFORMA FOR SUBMISSION OF INFORMATION AT THE TIME OF SENDING THE FINAL REPORT OF THE WORK DONE ON THE PROJECT

1. TITLE OF THE PROJECT : Synthesis and Antimicrobial Screening of New Thiocarbamate Derivatives
2. NAME AND ADDRESS OF THE PRINCIPAL INVESTIGATOR : Dr. Mrs. Sunita D. Shirke, Department of Chemistry, Vivekanad College, Kolhapur.
3. NAME AND ADDRESS OF THE INSTITUTION :Vivkeanand College, Tarabai Park, Kolhapur
4. UGC APPROVAL LETTER NO. AND DATE: File No.47-799/09 (WRO), 13-9-2009.
5. DATE OF IMPLEMENTATION: 14 September, 2009
6. TENURE OF THE PROJECT : 2 years
7. TOTAL GRANT ALLOCATED : Rs. 1,55,000/-
8. TOTAL GRANT RECEIVED Rs. 1,12,500/-
9. FINAL EXPENDITURE Rs. 1,12,500/-
10. TITLE OF THE PROJECT : Synthesis and Antimicrobial Screening of New Thiocarbamate Derivatives

11. OBJECTIVES OF THE PROJECT
    - To study some synthetic processes catalytic reactions, cyclization and condensation reactions as well as substitution reactions.
    - To investigate improved techniques in the synthesis of new compounds by substitution reactions which are applicable in pharmaceutical and medicinal field.
    - Development of environmentally improved routes to important products by using sustainable resources.
    - Use of methodologies and tools for evaluating environmental impact.

- To study the analytical techniques for identification and confirmation of newly synthesized compounds.
- To investigate the biological activities of synthesized compounds towards gram positive and gram negative bacteria like *E.Coli, Staphylococcus aureus, S. citrus*, etc.

12. WHETHER OBJECTIVES WERE ACHIEVED : Yes
13. ACHIEVEMENT FROM THE PROJECT :

As quinazoline is the first requirement for synthesis of thiocarbamate derivatives, during this period, literature survey is done for the more convenient method of synthesis of quinazolines, which will be less time consuming, use of least number of chemicals but giving higher yield of pure product. Number of research papers, science magazines, journals, reviews, publications have been referred. Also used the internet facility for the convenient method of synthesis of same.

i) These derivatives have been prepared by using nitriles, can be converted into amides by reacting with sodium perborate (SPB) in water, in water-methanol, water-acetone or water-dioxane as solvent.

ii) Aminoquinazolines can be synthesized in micro-wave oven starting from cyanoaromatics in presence of 10% t-BuOH.

A) Quinazolines prepared by reported method using triethyl amine and carbon disulphide are analysed by IR spectroscopy (IR), spectra were recorded on a Schimadzu IR-437 spectrophotometer. Good results are obtained. All m.p. were determined in open capillary tubes and are uncorrected. Purity of compounds was checked by TLC (silica-gel- G).

B) Under next step, thiocarbamates will be synthesized by using quinazolines and following different alternate energy processes such as using water as solvent, under solvent and catalyst free conditions and using microwave oven etc.

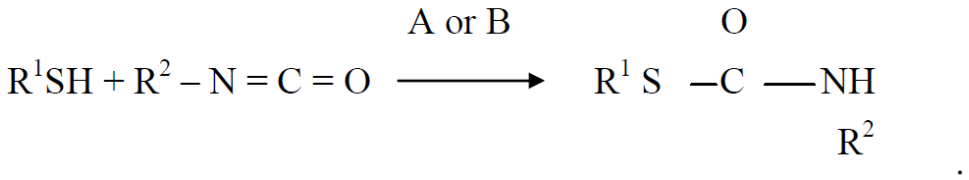
14. SUMMARY OF THE FINDINGS :

Thiocarbamates especially aryl thiocarbamates are the important class of compounds which have numerous biological effects, pesticidal, fungicidal, bactericidal, anesthetic and antiviral activity. Thiocarbamates have previously been prepared by using quinazolines, as they exhibit important physiological activities.[1] Quinazolines are synthesized by reported method i.e. by reacting substituted anilines with carbon disulphide in presence of triethylamine.[2] Alkyl thiocarbamates have been prepared by reaction of carbamoyl chlorides with thiols in presence of pyridine[3] or by reaction of alkyl chlorothioformate (RSCOCl) with amines.[4] They have also been prepared by acid catalysed reaction of alcohols with alkyl and aryl thiocyanate.[5] Several other methods have been reported for the preparation of thiocarbamates. They have been prepared from asymmetrical disulphides. In recent report, a synthesis of thiocarbamates from isocyanate and quinazoline in solvent free conditions at 25-70^{0}C is discussed. Condensation of thiols with isocyanate under various conditions (acidic or basic) and in presence of solvents have been reported. However, several disadvantages such as long reaction times, use of harmful solvents, low or high temperature, use of costly catalysts, low to moderate yields etc. are encountered in the reported methodologies. Hence the development of new more efficient and convenient method necessitate. From an ecological point of view the best solvent is without a doubt no solvent.

The experimental procedure for the reaction is very simple i.e. an equimolar amount of isocyanate was added to liquid or molten quinazoline and reaction mixture stirred at 25-70^{0}C temperature for 30-300 min. as required to complete the reaction, it is monitored by TLC.

A series of quinazolines (containing electron releasing and electron withdrawing groups) and isocyanate were used. The structures of all the products established from their physical and spectral (IR, 1HNMR) data. The thiocarbamates are obtained as the sole products in the moderate to high yields. The results are compared with those obtained in solution, in minimum amount of dichloromethane (CH_2Cl_2). There are appreciable differences both in reaction time and isolated yields, between the results obtained in solution. Thus by omitting the solvent the reaction time was significantly reduced and need for solvent is thus avoided.

Thus the procedure provides a powerful and versatile method for the preparation of thiocarbamates. This method is endowed with unique merits like simplicity of operation. Mild reaction conditions avoiding hazardous organic solvents, toxic and expensive reagents, short reaction times and high product yields



A : Catalyst and solvent free, 25-70^{0}C

B : Catalyst free; CH_2Cl_2, 25^{0}C

Scheme

Experimental :

The experimental procedure for the reaction is very simple . An equimolar quantities of isocyanate and quinazoline , this reaction mixture stirred at 25-70 C temperature for 30-300 min. as required to complete the reaction which is monitored by TLC. A series of quinazolines (containing electron withdrawing and electron donating groups) and isocyanates were used.

All products were characterized by their physical and spectral data with those of known samples. IR spectra (KBr) were obtained on Schimadzu IR-437 and NMR (DMSO-d6) were recorded on Perkin Elmer R-32 spectrophotometer using TMS as standard. Melting points were determined by open capillary method. Purity of compounds was checked by TLC (silica gel-G).

Preparation of 3-Aryl-2-thioxo-4 (3H)-quinazoline-4-one :

A mixture of substituted aniline in ethanol (10 g, 0.1 mol) and anthranilic acid (-15 g, 0.1 mol) was refluxed on a steam bath for 5 hrs. The excess solvent was removed under reduced pressure. The separated solid was redissolved in ethanolic NaOH, filtered and filtrate on neutralization with dil. HCl gave a solid which was recrystallised from ethanol (88.7%) m.p. 265^0C.

Preparation of 3-Aryl-2-thioxo-4(SH) Quinazolo-N – Phenylthiocarbamates – Under solvent free conditions

Phenyl isocyanate (1.0 mmol, 100 mg) was added to 100 mg molten quinazoline (1 mmol) and the whole mixture was stirred at 50-70^0C for 15 min. as indicated by TLC for completion of reaction. The reaction mixture was allowed to cool at room temperature followed by preparative TLC of crude product over silica gel plate.

Preparation of 3-Aryl-2-thioxo-4 (3H) quinazolo – N –Phenylthiocarbamate :

Dichloromethane was added (100 mg) to 100 mg phenylisocyanate (1.0 mmol) and the mixture was stirred for 50 min. at 70^0C. After completion of the reaction (monitored by TLC) the solvent was evaporated and crude product was purified by TLC (silica-gel- G) to obtain the pure thiocarbamate.

The results are compared with those obtained in solution in minimum amount of dichloromethane. There are appreciable differences both in reaction time and yields obtained in two methods. Thus the procedure provides a powerful versatile preparation method for thiocarbamates.

Table 1. :Elemental and Spectral Analysis of substituted aryl -2- Thioxo – 4 (3H) – quinazolin – 4- ones synthesized

Compd. No.	R	% Yield	M.P. ^{0}C	Molecular Formula	Found (Calcd)			IR V_{max} kBr
					C	H	N	
i)	o-OCH_3	88.7	262	$C_{15}H_{12}O_2N_2S$	55.40 (55.55)	5.11 (5.13)	11.92 (11.97)	3311(NH),1639(C=O), 1600 (C=C)cm^{-1}
ii)	o-Cl	85.2	245	$C_{14}H_9ON_2S.Cl$	58.20 (58.33)	3.10 (3.12)	9.70 (9.71)	3320(NH),1660(C=O), 1600 (C=C)cm^{-1}
iii)	p-Cl	82.0	284	$C_{14}H_9ON_2S.Cl$	58.25 (58.23)	3.10 (3.12)	9.70 (9.75)	3210(NH),1661(C=O), 1591 (C=C)cm^{-1}
iv)	o-CH_3	89.3	272	$C_{15}H_{12}ON_2S$	67.15 (67.11)	4.48 (4.50)	10.32 (10.32)	3300(NH),1660(C=O), 1600 (C=C)cm^{-1}
v)	p-CH_3	86.9	280	$C_{15}H_{12}ON_2S$	67.10 (67.08)	4.50 (4.47)	11.00 (10.98)	3291(NH),1620(C=O), 1600 (C=C)cm^{-1}
vi)	--	90.0	130	$C_{14}H_{10}ON_2S$	66.14 (66.14)	3.93 (3.94)	11.00 (11.02)	3280(NH),1622(C=O), 1600 (C=C)cm^{-1}

Table 2 : Summary of Thiocarbamates synthesis under catalyst free conditions

Sr. No.	R^1	R^2	Product	Temp ^{0}C	Solvent free Time(min)/Yield	Solvent Time (min)/Yield
1.	o-OCH_3	Ph	Quin.o-OCH_3.S CONHPh	50	60 (90)	120 (92)
2.	o-Cl	Ph	Quin.o-Cl.S CONHPh	50	50 (87)	128 (81)
3.	p-Cl	Ph	Quin.p-Cl..S CONHPh	70	80 (92)	180 (87)
4.	p-CH_3	Et	Quin.p-CH_3.S CONHPh	70	75 (80)	270 (77)
5.	--	Et	Quin.p-CH_3.S CONHEt	70	40 (89)	150 (83)

Conclusions :

- In this project some synthetic processes catalytic reactions, cyclization and condensation reactions as well as substitution reactions were carried out. The results are encouraging.
- The improved techniques in the synthesis of new compounds by substitution reactions have been investigated, which are applicable in pharmaceutical, medicinal and other fields. These techniques are environmentally improved route to important products by using the sustainable resources.
- The reactions taking place in the presence of catalyst/solvent, in the absence of catalyst/solvent are studies. It is observed that the reactions taking place in solvent free conditions give good yield of products than the reaction in the presence of solvent. Therefore the method developed here is highly efficient, powerful and versatile one for preparation of thiocarbamates.
- The reported technique avoids handling of hazardous, toxic and expensive organic solvents and reagents. Thus the technique developed is eco-friendly as well as economic way of synthesis.
- The synthesis was found to be very simple as far as operations are concerned and requires short time period. The yield due to synthesis is better.
- The analytical techniques for identification and confirmation of newly synthesized compounds were attempted.
- The biological activities of synthesized compounds towards gram positive and gram negative bacteria like *E.Coli, Staphylococcus aureus, S. citrus*, were

investigated. The newly synthesized compound show good antibacterial properties. The study reveals that there is a good scope to extend the work.

- In this project, a simple and efficient procedure was developed for the synthesis of thiocarbamate under solvent free conditions without use of catalyst. The significant features of this method are : a) operation simplicity, b) mild reaction conditions, c) short reaction times, d) solvent free conditions, d) high product yields.

15. CONTRIBUTION TO THE SOCIETY : Thiocarbamates especially aryl thiocarbamates are the important class of compounds which have numerous biological effects, pesticidal, fungicidal, bactericidal, anesthetic and antiviral activity. The work undertaken will be useful in the area of pharmaceutical science.
16. WHETHER PH.D. ENROLLED OR PRODUCED OUT OF THE PROJECT : No.
17. NO. OF PUBLICATIONS OUT OF THE PROJECT : One article prepared.

PRINCIPAL INVESTIGATOR

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