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ECOFRIENDLY SYNTHESIS OF 2-PHENYL-3,5-DITHIO-7-SUBSTITUTEDIMINO-6-[2,4-DICHLORO-1,3,5-TRIAZ-6-YL]-1,2,4,6-THIATRIAZEPINE

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ABSTRACT

Recently in this laboratory a novel series 2-phenyl-3,5-dithio-7-substitutedimino-6-[2,4-dichloro-1,3,5-triaz-6-yl]-1,2,4,6-thiatriazepines (IIIa-e) were successfully synthesized by the interactions of 2,4-dichloro-6-[2,4-dithio-5-phenyl-biureto]-1,3,5-triazines (I) with substituted isothiocarbomoyl chloride (IIa-e) in 1:1 molar ratio in acetone-ethanol medium. A new route was developed for the synthesis of thiatriazepines to increase the yield of product by maintaining the purity of the product, at the same time it was also thought to decrease the time span of the reaction. The achievement of this research work that we developed a new route for the synthesis of substituted-1,2,4,6-thiatriazepines by maintaining the purity as well as their is increases in the yield of the product. During synthesis two parameters of Green Chemistry are maintained hence, this is eco-friendly reaction. The justification and identification of the structure of these newly synthesized compounds had been established on the basis of chemical characterization, elemental analysis and through spectral data.

Keywords: Eco-friendly synthesis, 1,2,4,6-Thiatriazepines, 1,3,5-Triazines, Biurete, Acetone-ethanol.

INTRODUCTION

1,3,5-triazino and 1,2,4,6-thiatriazepino nucleus containing drugs created their own identity, importance and significances in Pharmaceutical, Medicinal, Biochemical, Industrial and Agricultural sciences [1-4]. These drugs showed antimicrobial [5-8] properties / activities. The literature survey reveals that a very few work was done on the synthesis of 1,2,4,6-thiatriazepine. Up till now the synthesis of 1,2,4,6-thiatriazepines from 2,4-dichloro-6-[2,4-dithio-5- phenyl- biureto]- 1,3,5-triazines (I) with substituted isothiocarbomoyl chloride (IIa-e) is stills lacking. The literature survey also showed that the synthesis of 1,2,4,6-thiatriazepine was generally carried out by oxidative cyclization [9]. In some synthesis acetone medium was used and it required five hours for the completion of reaction.

As a wider programme of this laboratory in the synthesis of nitrogen, nitrogen and sulphur containing heteroacycles and their cyclization in to 5,6 and 7 member heterocycles viz. 1,2,4-thiadiazols, 1,2,4-dithiazols, 1,3,5-thiadiazines, 1,3,5-dithiazines, 1,3,5-triazines etc. synthetic applications of isocyano dichloride, cyanoguanidine, thiocarbamoyls and biuretes have been explored in sufficient details [10]. Therefore it was thought interesting to synthesize 2-phenyl-3,5-dithio-7-substitutedimino-6-[2,4-dichloro-1,3,5-triaz-6-yl]-1,2,4,6-thiatriazepines (IIIa-e) by the interactions of 2,4-dichloro-6-[2,4-dithio-5-phenyl-biureto]-1,3,5-triazines (I) with substituted isothiocarbamoyl chloride (IIa-e) which is heither to unknown. As coated in literature the 1,2,4,6-thiatriazepines were synthesize by oxidative cyclization in which iodine is used during the synthesis [9]. Iodine is dangerous, while in another route acetone medium is used during refluxtion and it take five hours [10] for the completion of reaction and the yield obtain is only 52%. Hence, the various attempts were made for the developing of new route for the synthesis of 1,2,4,6-thiatriazepines by changing the solvent and reaction condition during the synthesis.

We developed new route for this synthesis in

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which the time span of the reactions decreases which maintain the green chemistry parameters i.e. we used 80% acetone-ethanol mixture. As a medium in which the percentage of acetone is only 20% which help one green chemistry parameter and we reduce the time span of the reactions by 6 hours this is another parameter of green chemistry. At the same time yield of product is also increase by maintaining purity of product.

Experimental: The melting points of the synthesized compounds were recorded using hot paraffin bath. The carbon and hydrogen analysis were carried out on Carlo-Ebra 1106 analyzer. Nitrogen estimation was carried out on Colman-N-analyzer-29. IR spectra were recorded on Perkin Elmer Spectrometer in range 4000-400 cm^{-1} in KBr pellets. PMR spectra were recorded on Brucker Ac 400 F Spectrometer with TMS as internal standard using $CDCl_3$and DMSO-d_6 as a solvents. The purity of compound was checked on silica Gel-G Pellets by TLC with layer thickness of 0.3 mm. All chemicals were used of AR-grade.

2-phenyl-3,5-dithio-7-substitutedimino-6-[2,4-dichloro-1,3,5-triaz-6-yl]-1,2,4,6-thiatriazepines (IIIa-e) was synthesized by the known method[11].

2-phenyl-3,5-dithio-7-ethylimino-6-[2,4-dichloro-1,3,5-triaz-6-yl]-1,2,4,6-thiatriazepines (IIIa):- A mixture of 2,4-dichloro-6-[2,4-dithio-5-phenyl-biureto]-1,3,5-triazines (I), ethyl-isothiocarbomoyl chloride (IIa) and ethanol-acetone (80%, 15 ml) was refluxed on boiling water bath for 2 hours. During boiling suspended 2,4-dichloro-6-[2,4-dithio-5-phenyl-biureto]-1,3,5- triazines (I) went into the solution and the new product was found to be gradually separated out by the elimination of HCl gas. It was filtered in hot condition and crystallized with aqueous ethanol to obtain (IIIa), yield 87%, melting point 188^0C.

Properties:

It is yellow, crystalline solid having melting point 188^0C. It gave positive test for nitrogen, sulphur and chlorine. Desulphurised by alkaline plumbite solution. It formed picrate, melting point 170^0C.

Elemental analysis:

C [(found 36.79 %) calculated 38.00], H [(found 2.15 %) calculated 2.48], N [(found 22.00 %) calculated 22.17], S [(found 21.63 %) calculated 21.71].

IR Spectra:

The IR spectra was carried out in KBr pellets and the important absorption can be correlated as (cm^{-1}) 3212 (N-H stretching), 3049 (C-H stretching), 1332 (C-N stretching), 1405 (C=S stretching), 1688 (C=N stretching), 1946 (S=C=N stretching), 743 (C-Cl stretching).

PMR Spectra:

The spectrum was carried out in $CDCl_3$ and DMSO-d_6. This spectrum distinctly displayed the signals at δ3.1493-4.5387 ppm are due to N-H proton, signals at δ0.8502-1.3813 ppm are due to $-CH_3$ protons, signals at δ2.1061-2.5457 ppm are due to $-CH_2$ protons, signals at δ6.7293-7.8476 ppm are due to Ar-H proton at m-position attached to 1,2,4,6-thiatriazepine ring, signals at δ8.1439-9.9036 ppm are due to Ar-H proton at p-position attached to 1,2,4,6-thiatriazepine ring, signals at δ10.9212-11.1940 ppm are due to Ar-H proton at o-position attached to 1,2,4,6-thiatriazepine ring.

Same reactions were carried out in various solvents and percent ratio of solvents for improving the yield and purity of the products as well as to maintain green chemistry parameters. The results are depicted in table 1.

In isopropanol, benzene and dioxane medium product contain impurities of both reactants with product. 80% Ethanol-acetone mixture is the best medium for the synthesis of 1,2,4,6-thiatriazepine, in which the yield is 87% and the medium required for the condensation is only 15 ml while the reaction is completed in 2 hours.

Similarly 2-phenyl-3,5-dithio-7-p-chloro pheny limino -6-[2,4-dichloro-1,3,5-triaz-6-yl]-1,2,4,6-thiatri azepine, 2-phenyl-3, 5- dithio-7-methylimino-6-[2,4-dichloro-1,3,5-triaz-6-yl]-1,2,4,6-thiatriazepine, 2-phenyl-3,5-dithio-7-t-butylimino-6-[2,4-dichloro-1,3,5-triaz-6-yl]-1,2,4,6-thiatriazepine, 2-phenyl-3,5-dithio-7-phenylimino-6-[2,4-dichloro-1,3,5-triaz-6-yl]- 1,2,4,6- thiatriazepine were synthesize by reacting I with IIb-e respectively by the above mentioned method.

Table 1. Reactions and percent ratio of solvents for improving the yield and purity of the products

Sr. No.	Solvents	Quantity(ml)	Time Span (hours)	Yield (%)	Melting Point (^{0}C)
1	Water	50	No reaction	- -	- -
2	Acetone*	50	8	52	188
3	Ethanol	50	8	47	188
4	Methanol	50	No reaction	- -	- -
5	Isopropanol	50	8	35	187
6	Benzene	50	10	25	182
7	Dioxane	50	10	20	179
8	Acetone-ethanol(20%)	30	7	60	188

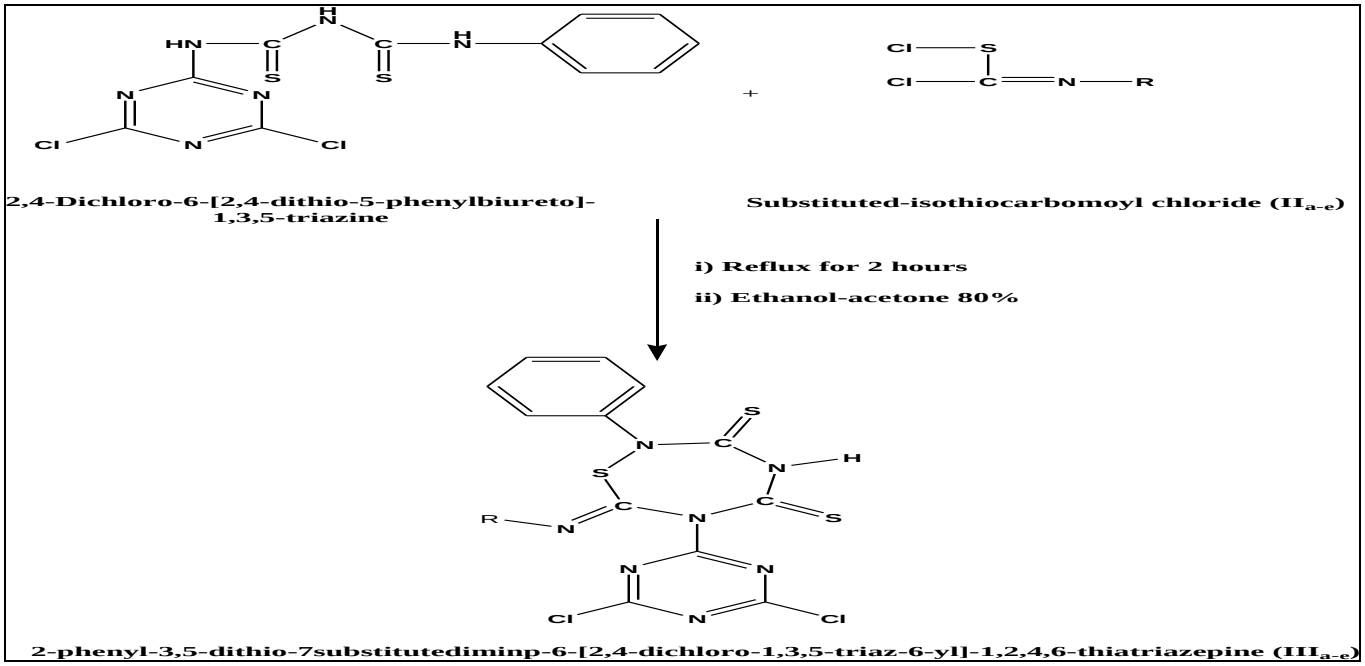
9	Acetone-ethanol(40%)	30	5	65	188
10	Acetone-ethanol(60%)	30	4	71	188
11	Acetone-ethanol(80%)	30	2	87	188

* - Known literature solvent.

Table 2. Shown the results are obtained

Sr. No.	Expt. No.	2-phenyl-3,5-dithio-7-substitutedimino-6-[2,4-dichloro-1,3,5-triaz-6-yl]-1,2,4,6-thiatriazepines	Yield (%)	Melting Point (^{0}C)
1	2	2-phenyl -3,5-dithio-7- p-chlorophenylimino-6-[2,4-dichloro-1,3,5-triaz-6-yl]-1,2,4,6-thiatriazepine	78	127
2	3	2-phenyl -3,5-dithio-7- methylimino-6-[2,4-dichloro-1,3,5-triaz-6-yl]-1,2,4,6-thiatriazepine	83	98
3	4	2-phenyl -3,5-dithio-7- t-butylimino-6-[2,4-dichloro-1,3,5-triaz-6-yl]-1,2,4,6-thiatriazepine	67	110
4	5	2-phenyl -3,5-dithio-7- phenylimino-6-[2,4-dichloro-1,3,5-triaz-6-yl]-1,2,4,6-thiatriazepine	85	142

Scheme:



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