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ECOFRIENDLY AND ENVIRONMENTALLY BENIGN SYNTHESIS OF 2-(2-AMINO-1, 3-OXAZOL-4-YL)-4-SUBSTITUTEDNAPHTHALEN-1-OL IN PEG 400 MEDIUM

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ABSTRACT

New oxazole derivative of substitutednaphthol were ecofriendly and efficiently be synthesized like 2-(2-amino-1, 3-oxazol-4-yl)-4-substitutednaphthalen-1-ol (5) by cyclization of 1-[2-(4-Substituted-1-hydroxynaphthalen-2-yl)-2-oxoethyl]thiocarbamide (4) by utilizing elemental sulphur as a chief, easily available, non toxic catalyst. All the reactions were carried out in ecofreindly solvent medium PEG 400 in a short period of time. The synthesized compounds were characterized by IR, NMR, Mass spectral and C, H, N elemental analysis.

Keywords *– Elemental sulphar;Naphthol;Non-toxic;Ecofriendly;Oxaole*

1. INTRODUCTION

Substituted oxazole have versatile application in the preparation of various biological, medicinal and agriculture compounds as well as in the industrial fields.[1-3] the oxazole ring is present in large number of pharmaceutical products such as antibiotics[4] and antiproliferative[5]. The wide range of biological activities of oxazoles includes anti-inflammatory[6], analgesic [7], antibacterial, antifungal[8], hypoglycemic[9], antiproliferative[10], anti-tuberculosis[11], muscle relaxant[12] and HIV inhibitor activity[13]. In addition, oxazole derivatives are useful synthetic intermediates and can be used as diversity scaffolds in combinatorial chemistry[14] and also as peptidomimetics[15].

Substituted oxazole can be synthesized by robinson gabrial synthesis method from alpha-acylamino ketones in the presence of dehydrating reagents H_2SO_4, $POCl_3$ and $(CF_3SO_2)_2O$[16-18]

Another method for synthesis of substituted oxazole involve the Catalytic decomposition of a-diazocarbonyl compounds in nitriles.[19-21] it can also be synthesisized by the reaction of (acyloxy)vinyl azides with triethyl phosphate.[22] reaction of benzoin carboxylates with formamide[23] and decarboxylation of *N*-acylisoxazol-5-ones by means of photolysis or pyrolysis.[24-25] Highly substituted synthesis of 1,3-Oxazole can be done by utilizing the synthetic intermediates such as alpha-diazo ketones[26-28], alpha-halo ketones[29-30], alpha-sulfonyloxy ketones[31], and iodonium ylides of ketones.[32]

In spite of these ways of interest, due to the biological and medicinal importance of oxazole Innovation of inexpensive and green catalyst is still in demand. So, it is necessary to develop new environmentally benign and clean method of syntheses. To overcome the

environmental aspect and applying green chemical approach there is need to replace the hazardous catalyst and solvent. Unique advantages of Polyethylene glycol (PEG) and its monomethyl ethers like high thermal stability, negligible vapor pressure, no toxicity, and recyclability attracted the attention of organic chemists in recent years[33]. They are also widely used as media for phase-transfer catalysts[34-38]. A variety of methods are now available for synthesis of substituted oxazole. Most of them have certain demerits such as use of expensive, toxic catalyst, long reaction times, harsh reaction conditions and non satisfactory yield of the desire products. With increasing environmental concerns and the regulatory constraints, the development of environmentally benign organic reactions has become a crucial and demanding area in modern organic chemical research. We wish to report a practical and convenient method for the preparation of newly substituted oxazole, using elemental sulphur as cyclising catalyst in PEG 400 a green and ecofreindly solvent medium.

2. MATERIALS AND METHOD

All chemicals used were of AR grades. The melting points of all the synthesized compounds were recorded using hot paraffin bath. The Carbon and Hydrogen analysis was carried out on Carlo-Ebra 1106 analyser. Nitrogen estimation was carried out on Colman-N-analyzer-29. IR spectra were recorded on Lambda Scientific Pvt Ltd spectrometer in the range 4000-400 cm^{-1} in KBr pellets. PMR spectra were recorded on Brucker AC-500F spectrophotometer with TMS as internal standard using $CDCl_3$ and DMSO-d_6 as solvent. The purity of compound was checked on silica Gel-G plates by TLC with layer thickness of 0.3 mm.

2.1 General Procedure for Synthesis of 2-(2-amino-1,3-oxazol-4-yl)-4-bromonaphthalen-1-ol (5a)

1-[2-(4-bromo-1-hydroxynaphthalen-2-yl)-2-oxoethyl]thiocarbamide (4a) (1.0 mmol), Sulphur (50 % mmol) and PEG (25 mL) was Taken in a 100 ml Round bottom flask and refluxed the reaction mixture on oil bath for 6 hour between temperature 150^0 to 160^0C completion of the reaction was monitored by Thin Layer Chromatography (N-Hexane: Ethyl acetate 80:20). The hot reaction mixture was filtered to remove the Sulphur catalyst. Then poured the mixture in to the crushed ice with constant stirring filtered and washed with distilled water, dried the crude product and recrystalised from ethyl alcohol.

The yield of the dried crude product was found to be 0.85 g (85%).

Melting Point: -218-219^{o}C

Colour of compound (5a) - Yellow Colour solid

IR (KBr, cm-1): 3548.38 cm^{-1}, 3471.24 cm^{-1}, 1330.54 cm^{-1}, 1222.65 cm^{-1}, 1673.91 cm^{-1}, 1010.52 cm^{-1}, 759.82 cm^{-1}, 3143.40 cm^{-1}, 1446.35 cm^{-1}

^{1}H NMR (500 MHz, CdCl3): δ 4.0 (s, 1H, OH), δ 4.6 (s, 1H, -C=C-H), δ4.47 (s, 2H, NH_2), δ 7.3 -8.5 (m, 5H,-C10H5)

Elemental Analysis of $C_{13}H_9BrN_2O_2$

%Found: C, 51.23 %; H, 2.68%; Br, 26.57%;N, 9.13%

%Calculated: C, 51.17%; H, 2.97%; Br, 26.19%; N, 9.18%

2.2 Synthesis of 4-amino-2-(2-amino-1, 3-oxazol-4-yl)naphthalen-1-ol (5b)

1-[2-(4-amino-1-hydroxynaphthalen-2-yl)-2-oxoethyl]thiocarbamide(4b) (1.0 mmol), Sulphur (50 % mmol) and PEG (25 mL) was Taken in a 100 ml Round bottom flask and refluxed the reaction mixture on oil bath for 5 hour between temperature 150^0 to 160^0C completion of the reaction was monitored by Thin Layer Chromatography (N-Hexane: Ethyl acetate 80:20). The hot reaction mixture was filtered to remove the Sulphur catalyst. Then poured the mixture in to the crushed ice with constant stirring filtered and washed with distilled water, dried the crude product and recrystalised from ethyl alcohol.

The yield of the dried crude product was found to be 0.90 g (90%).

Melting Point - 142-144^{o}C

Colour of compound (5b) –Light Brown colour solid

IR (KBr, cm^{-1}): 3513.67 cm^{-1}, 3421.10 cm^{-1}, 1276.65 cm^{-1}, 1187.94 cm^{-1}, 1670.05 cm^{-1}, 752.10 cm^{-1}, 3008.41 cm^{-1}, 1415.49 cm^{-1}

^{1}H NMR (500 MHz, CdCl3): δ 2.73 (s, 1H, OH), δ1.59 (s, 1H, -C=C-H), δ 1.25 (s, 2H, NH_2), δ7.54 -8.47 (m, 5H,-C10H5)

Elemental Analysis of $C_{13}H_{11}N_3O_2$

%Found: C, 64.80%; H, 4.67%; N, 17.20%

%Calculated: C, 64.72%; H, 4.60%;N, 17.42%

2.3 Synthesis of 2-(2-amino-1, 3-oxazol-4-yl)-4-nitronaphthalen-1-ol (5c)

1-[2-(1-hydroxy-4-nitronaphthalen-2-yl)-2-oxoethyl]thiocarbamide(4c) (1.0 mmol), Sulphur (50 % mmol) and PEG (25 mL) was Taken in a 100 ml Round bottom flask an d refluxed the reaction mixture on oil bath for 8 hour between temperature 150^{0} to 160^{0}C completion of the reaction was monitored by Thin Layer Chromatography (N-Hexane: Ethyl acetate 80:20). The hot reaction mixture was filtered to remove the Sulphur catalyst. Then poured the mixture in to the crushed ice with constant stirring filtered and washed with distilled water, dried the crude product and recrystalised from ethyl alcohol.

The yield of the dried crude product was found to be 0.80 g (80%).

Melting Point.- 262-264^{o}C

Colour of compound (5c) –Light Yellow colour solid

IR (KBr, cm^{-1}): 3532.95 cm^{-1}, 3363.25 cm^{-1}, 1315.21 cm^{-1}, 1619.91 cm^{-1}, 1234.22 cm^{-1}, 1500.34 cm^{-1},1407.78 cm^{-1}, 755.96 cm^{-1}, 3039.26 cm^{-1}, 1450.21 cm^{-1}

^{1}H NMR (500 MHz, CdCl3): δ 3.03 (s, 1H, OH), δ 2.95 (s, 1H, NH), δ 2.70 (s, 1H, -N-CH), δ 2.95 (s, 1H, Ar-NH), δ 2.03 (s, 1H, -C=C-H), δ 7.59 -8.50 (m, 5H,-C10H5)

Elemental Analysis of $C_{13}H_9N_3O_4$

%Found: C, 57.36%;H, 3.66%; N, 15.30%

%Calculated: C, 57.57%; H, 3.34 %; N, 15.49%

2.4 Procedure for Synthesis 1-[2-(4-bromo-1-hydroxynaphthalen-2-yl)-2-oxoethyl] Thiocarbamide (4a)

1-[2-(4-bromo-1-hydroxynaphthalen-2-yl)-2-oxoethyl]thiocarbamide (4a) is prepared by, a mixture of 2-bromo-1-(4-bromo-1-hydroxynaphthalen-2-yl)ethanone (2a) (1 gm, 3.6 mmol), thiourea (3a) (0.29 gm, 3.6 mmol) in 10 ml of PEG 400 was stirred at 0-5^{0}C temperature on Magnetic stirrer until 5-6 minutes. The time of the reaction was monitored by a stop watch. The progress of the reaction was monitored by thin layer chromatography. On completion of the reaction, the reaction mixture was poured into crushed ice. The product was precipitated by adding 2N Sodium hydroxide up to neutralization of reaction mixture. The precipitated product was filtered and dried. The product was pure enough (single spot on TLC) for all practical purposes. However, for characterization purposes, it was further purified by column chromatography.

The yield of the dried crude product was found to be 0.96 g (96%).

Melting Point - 119^{o}C

Colour of compound - Yellow Crystalline solid

IR (KBr, cm^{-1}): 3432.67cm^{-1}, 3232.11 cm^{-1}, 3351.68 cm^{-1}, 1604.48 cm^{-1}, 1569.77 cm^{-1},

1199.51 cm^{-1}, 1307.50 cm^{-1}, 1014.37 cm^{-1}, and 748.25 cm^{-1}

^{1}H NMR (500 MHz, CdCl3): δ 1.642 (s, 2H, -CH_2), δ 2.172 (s, 2H, -NH), δ 2.869 (s, 1H, OH), δ7.130-8.098(m, 5H,-$C_{10}H_5$)

Elemental Analysis of $C_{13}H_{11}BrN_2O_2S$

% Found: C, 45.98%; H, 3.33%; Br, 23.46%; N, 8.18%; S, 9.60%

% Calculated: C, 46.03%; H, 3.27%; Br, 23.56%; N, 8.26%; S, 9.45%

2.5 General Procedure for Synthesis 2-bromo-1-(4-bromo-1-hydroxynaphthalen-2-yl) Ethanone (2a)

Mix 1.2 gm(1.2mmol)of N-Bromosuccinamide 1gm(1mmol) of 1-acetyl-2-naphthol (1a) 100mg of benzoyl peroxide as a radical initiator and 20 ml of dry redistilled carbon tetrachloride in 100 ml round bottom flask reflux on a water bath for 15 to 20 minutes by this time all the solid should have risen to the surface of the liquid filter off the succinamide at the pump and wash with a little dry carbon tetrachloride remove the solvent on a water bath and distile the residue under reduced pressure through a short fractionating column collect the product (2a) yield is 75%.

2.6 Procedure for Synthesis Of Substituted 1-acetyl-2-naphthol (1a)

In hot glacial acetic acid (80ml), fused ZnCl2(50 gm) was added and refluxed till dissolved, then powdered 1-naphthol (30gm)was added and the mixture was refluxed for about 8 hours then cooled & poured in acidulated water. The solid obtained was filtered, washed, dried and recrystallized from rectified spirit to obtain 2-acetyl-1-naphthol (1a)

2.7 Preparation of Catalyst Benzoyl Peroxide

Immerse a 600 ml beaker containing 50 ml of 12 percent (40 Volume) hydrogen Peroxide and equipped with mechanical stirrer in an ice bath sited in a fume cupboard support two dropping funnel's containing respectively 30 ml of 4M sodium hydroxide solution and 30 gm (25 ml, 0.214 ml) of redistilled benzoyl chloride with their stem inside the beaker add two reagent alternatively a few drops at a time taking care that the temperature does not rise above 5-8 ^{0}C and that solution is maintain faintly alkaline throughout when all reagent is added stir the solution for further half an hour by this time the odor of the benzoyl chloride should have disappeared filter off the flocculants precipitates at the pump wash it with a little cold water and air dry upon filter paper the yield of benzoyl peroxide is 12 gm (46 %)

Like all organic peroxide benzoyl peroxide should handled with care behind Shatter (to break in small pieces suddenly forcefully) proof screens and horn moulded polyethylene (not Nickel) spatula should be used It is very shock sensitive.

3. RESULTS AND DISCUSSION

Synthesis of 2-(2-amino-1, 3-Oxazol-4-yl)-4-substitutednaphthalen-1-ol (5) from 1-[2-(4-substituted-1-hydroxynaphthalen-2-yl)-2-oxoethyl]thiocarbamide (2) and sulphur were carried out in different solvent medium the time required for completion of reactions is in between 8 to 24 hours. As well as the solvent medium is hazardous to environment and human health. Reduce time duration of reaction and for maintaining green chemistry parameters and to develop new reaction conditions, The reactions were carried out in various mediums and it was observed that the time required to the reaction in Polyethylene glycol 400 medium is reduced as compared to the other medium as well as yield also increased as shown in Table 1. From the table it is observed that the reaction product in the medium acetone, ethanol, DMF, ethanol-acetone mixture and Iso propyl alcohol reaction gave comparatively smaller conversions with low yield whereas in the medium PEG 400 the product yields in higher proportion and in smaller duration. Therefore PEG 400 was used as solvent to obtain Oxazole.

As shown in Table 3, a series of thiocarbamide bearing either electron-donating or electron withdrawing groups on the aromatic ring were investigated. The substituted groups on the phenyl ring did not make any difference on the yields. In all the cases, the products were afforded in reaction time of 5-13 hrs.

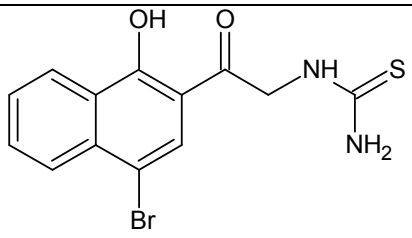
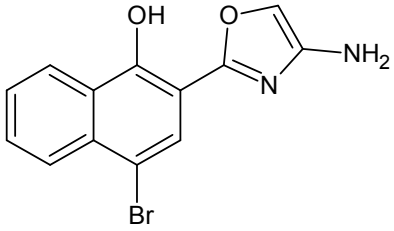
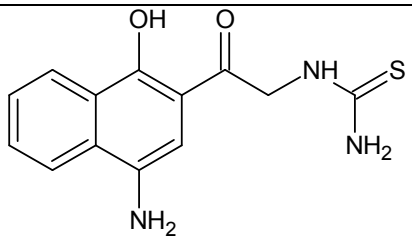
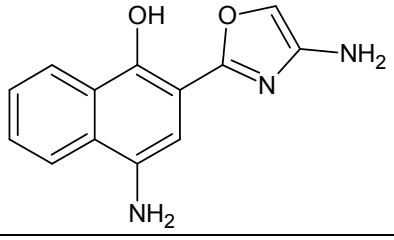
Table: 1 Synthesis of 2-(2-amino-1, 3-Oxazol-4-yl)-4-substitutednaphthalen-1-ol (5a) in different solvent medium.

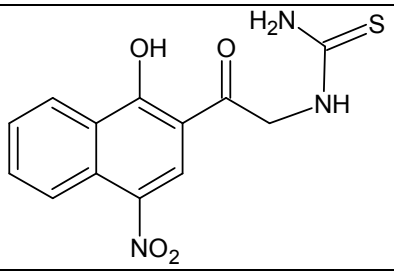
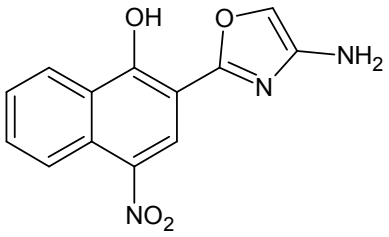
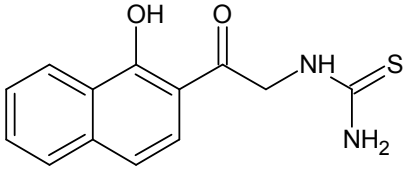
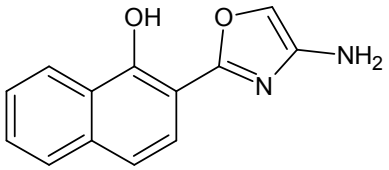
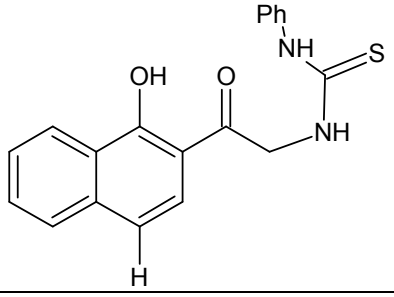
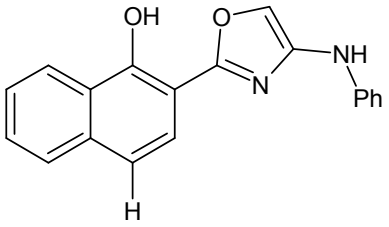
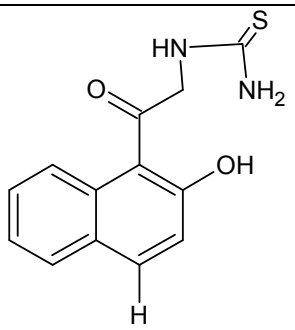
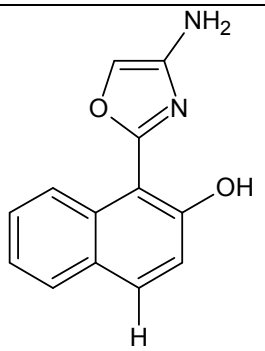
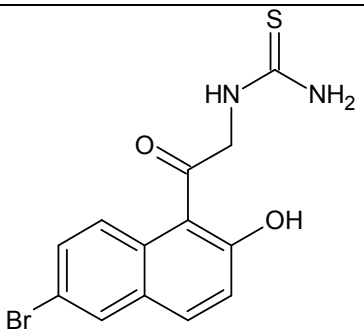
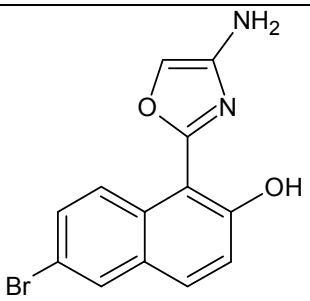
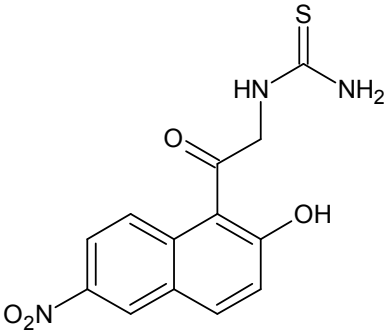
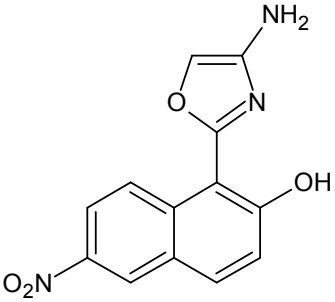
Sr. No.	Medium	Time Duration in hours.	Yield (%)
1.	Acetone	14	30
2.	Ethanol	9	45
3.	DMF	12	65
4.	PEG-400	06	85
5.	Acetic acid	15	60
6.	Iso propyl alcohol	16	55

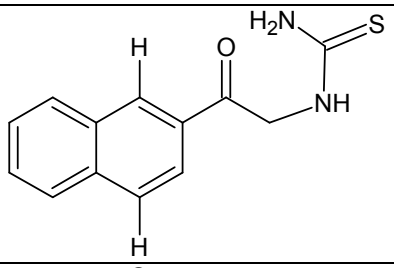
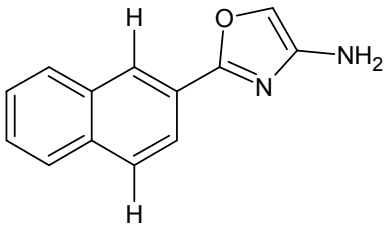
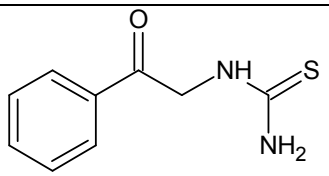
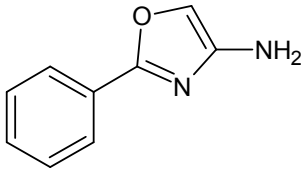
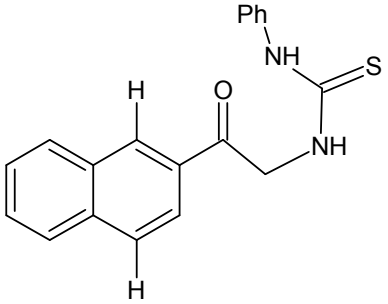
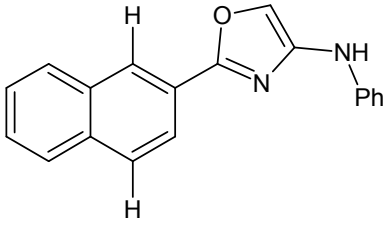
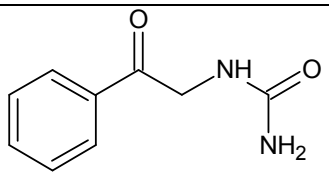
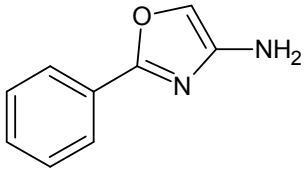
Table: 2 Effect of catalyst concentration on synthesis of 2-(2-amino-1, 3-Oxazol-4-yl)-4-substitutednaphthalen-1-ol (5a)

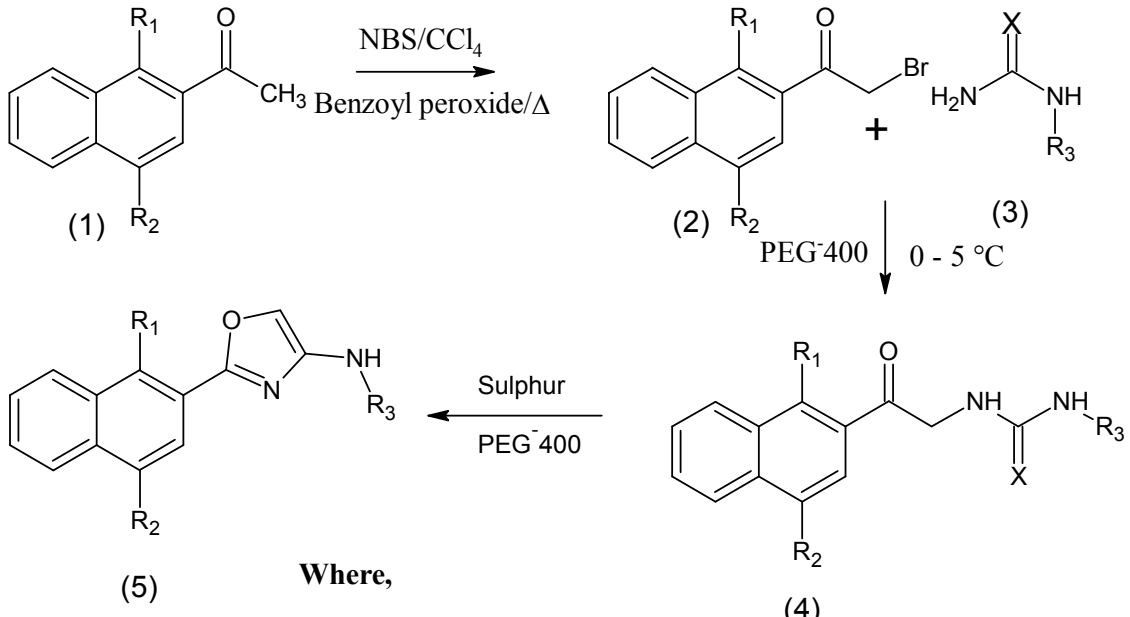
Sr. No.	Catalyst mol %	Time Duration in hours.	Yield (%)
1.	15	12	15
2.	25	10	40
3.	40	15	65
4.	50	8	85
5.	100	18	72

Table: 3 Synthesis of various substituted oxazole

Sr. No.	Entry	Reactant	Product	Time in Hrs.	% Yield
1	5a			8	85 %
2	5b			5	90 %

3	5c			7.50	82 %
4	5d			9	80%
5	5e			10	72 %
6	5f			7.5	82
7	5g			11	75
8	5h			8	70

9	5i			9	60
10	5j			9	75
11	5k			10	55
12	5l			7	80



Where,

X= S, O, R_1= H, OH

R_2= H, Br, NO_2, NH_2, R_3 = H, Ph

Figure: 1

4. CONCLUSION

We have developed an efficient PEG-promoted solvent and sulphur catalysed method for the synthesis of mono and di substituted oxazoles with good yield. These results further demonstrate the importance of PEG-promoted synthesis in avoiding hazardous organic solvents and toxic catalysts with comparatively less reaction time which is in the context green chemistry.

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