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International Journal of Pharmaceutical and Phytopharmacological Research

ISSN (Online) 2249 – 6084

ISSN (Print) 2250 – 1029

Int.J.Pharm.Phytopharmacol.Res. 2012, 1(4): 156-160

(Research Article)

Synthesis of Di and Trisubstituted Oxazoles in Nonionic Liquid Under Catalyst Free Conditions

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Received on: 06/01/2012 ***Accepted on:*** 16/02/2012

ABSTRACT

Catalyst free synthetic method was developed for di and tri substituted oxazoles from α -haloketones and urea/phenyl urea in Nonionic liquid like PEG 400.The reaction was carried out at ambient temperature and the product were obtained in excellent isolated yields (80-90%). Additionally, PEG could be recovered easily and was reused without evident loss in activity.

Key Words: α -haloketone, PEG 400, Oxazoles, Urea, Phenyl urea.

INTRODUCTION

The derivatives of Oxazole have become increasingly important in the past few years because of their use in intermediates for the preparation of new biological materials. The oxazole ring is present in numerous pharmacologically important compounds, including those used as antibiotics [1] and antiproliferative[2]. The wide range of biological activities of oxazoles includes anti-inflammatory[3], analgesic [4], antibacterial, antifungal[5], hypoglycemic[6], antiproliferative[7], anti-tuberculosis[8], muscle relaxant[9] and HIV inhibitor activity[10]. In addition, oxazole derivatives are useful synthetic intermediates and can be used as diversity scaffolds in combinatorial chemistry[11] and also as peptidomimetics[12].

A number of synthetic methods to prepare oxazoles have been reported. The typical procedure for the synthesis of oxazoles involves the reaction of readily available substituted urea derivatives with halogenated alkenes or α-haloketones[13-16]. $Zn(OTf)_2$ catalyzed cyclization of propargyl alcohols with anilines and phenols in toluene at 100°C[17] and highly efficient copper-catalyzed tandem oxidative cyclization for synthesis of polysubstituted oxazoles have been reported[18]. Many of these procedures are associated with one or more disadvantages such as long reaction time, low yield, use of hazardous organic solvents, excess reagents or catalysts, and harsh reaction conditions, which leaves scope for further development of new environmentally clean syntheses.

Unique advantages of Polyethylene glycol (PEG) and its monomethyl ethers like high thermal stability, negligible vapor pressure, nontoxicity, and recyclability attracted the attention of organic chemists in recent years. They are also widely used as media for phase-transfer catalysts[19- 23]. Recently, PEG assisted solvent free reaction of α-haloketones and variety of thiamides/thioureas was reported for synthesis of substituted thiazoles[24].

In the present article we want to establish efficient solvent free, catalyst free methodology for substituted oxazoles using PEG 400 - a non ionic liquid. We started with cyclisation of 2-bromo-1-phenylethanone and urea using different organic solvents including PEG 400. (Table 1, Fig 1)The reaction was optimized to get good yield in lesser reaction time at ambient temperature. The reaction was monitored by TLC. Then we extended the same reaction for synthesis of substituted oxazoles with different electron withdrawing and donating substituents.

MATERIALS AND METHODS

Chemistry

Purity of the starting materials used in the reaction was confirmed by melting point, boiling point, TLC. The purity and structure of compounds synthesized were confirmed by melting point, boiling point, TLC, Infrared (IR) Spectroscopy and Nuclear Magnetic Resonance (NMR) Spectroscopy. The melting point and boiling point of the compounds reported were uncorrected and were recorded by open capillary method on THERMONIK-Campbell Melting Point apparatus and they were in good agreement with the literature reported values.

All the reactions were monitored by the TLC technique, using pre-coated Silica gel plates (Silica gel 60 F_{254}, Merck). TLC was generated by "Ascending Development of the Mobile Phase" method. Development of the Chromatogram was recorded on the "Perkin Elmer FTIR spectrometer-Spectrum RX1". Solids were recorded as KBr pallets and liquids as thin film or $CHCl_3$.

The proton magnetic spectra were recorded on "Jeol JNM MY60 FT-FTNMR System". Chemical shifts were reported in parts per million (δ ppm) downfield with respect to TMS (Trimethylsilane). All the solvents used in reactions were commercial grade and used as such without purification. All chemicals and reagents were obtained from S.D. Fine Chemicals, Mumbai and used without further purification.

Experimental

Geneal procedure for the Synthesis of 2-Amino-4-phenyloxazole

A mixture of 2-bromo-1-phenylethanone (1.0 mmol), urea (1.0 mmol) and PEG (0.5mL) was stirred at room temperature until completion of the reaction (monitored by thin layer chromatography). The mixture was washed with water (4mL) extracted with ethyl acetate (3 X 15 ml); the organic phase was separated, dried over anhydrous sodium Sulphate, and filtered. The solvent was removed under vacuum. The crude product was purified by silica gel column chromatography using ethyl acetate-petroleum ether (1:1).After extraction with ethyl acetate, the solution of H_2O and PEG 400 was concentrated.

B.P.: 113-115^{0}C

IR (KBr): cm^{-1} 3432, 2975, 1624, 1388.

^{1}H NMR: (300 MHz, $CDCl_3$): δ 7.52–7.47 (m, 2H, ArH), 7.33–7.28 (m, 2H, ArH), 7.09 (m, 1H, ArH), 6.74 (s, 1H,oxazole), 5.15 (br s, 2H, NH2)

RESULTS AND DISCUSSION

With the aim of developing green and efficient methodology for di and tri substituted oxazoles under catalyst and solvent free conditions, we first investigated the cyclisation reaction of 2-bromo-1-phenylethanone with urea at room temperature under different reaction conditions. (Fig.1, Table-1)

It was observed that solvents such as toluene, alcohol, acetone when used for reaction gave comparatively smaller conversions. Whereas in the presence of PEG 400: Toluene the yield is low because of reduced efficiency of PEG 400 as a result of dilution. (Table-1, entry 1). Therefore PEG 400 was used as solvent to obtain Oxazole from α -haloketone and urea without additional catalyst.

As shown in Table 2, a series of α-bromoacetophenones 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 3 hrs. To the best of our knowledge, it has not been reported that the reaction could be conducted without the use of any catalyst with short reaction times at room temperature.

Finally, we investigated the recycling of PEG-400 in a subsequent reaction, for example, the synthesis of 1. (Table-2) It was observed that for the reaction of 2-bromo-1-phenylethanone with urea, PEG-400 can be reused for subsequent five runs without any appreciable loss of activity (Fig.2).

CONCLUSION

We have developed an efficient PEG-promoted solvent and catalyst free method for the synthesis of di- and trisubstituted 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.

ACKNOWLEDGEMENT

Support of HSNC Board and Principal, Dr L. H. Hiranandani College of Pharmacy, Ulhasnagar is gratefully acknowledged.

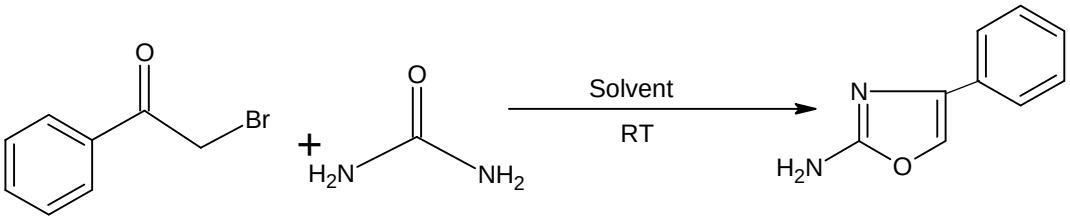


Fig. 1: Reaction scheme for substituted oxazole

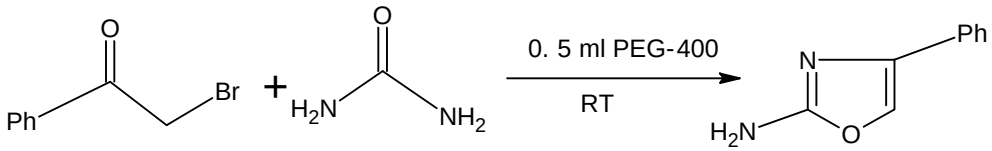
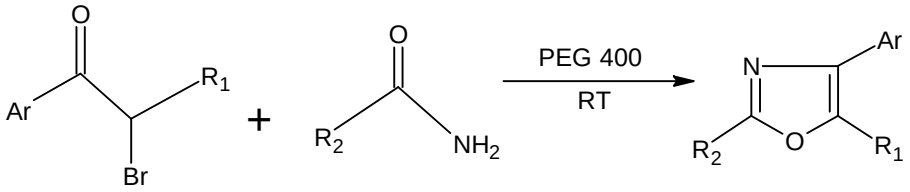


Fig. 2 : Reuse of PEG-400. Run 1, 82%; Run 2, 80%; Run 3, 78%; Run 4, 77%; Run 5, 77%

Entry	Solvent	Yield [b]
1	PEG-400/Toluene(1:1)	57%
2	Toluene	24%
3	Acetone	14%
4	Dichloromethane	34%
5	Ethanol	64%
6	PEG-400	82%

Table-1: Reaction of 2-bromo-1-phenylethanone with urea under different reaction conditions. [a]
[a]Reaction conditions: 2-bromo-1-phenylethanone (1.0mmol), urea (1.0mmol), and solvent (0.5ml) at room temperature for 3hrs. b. Isolated Yield



Sr.No.	Ar	R^1	R^2	Yield [b]
1	C_6H_5	H	NH_2	82 %
2	p-$NO_2C_6H_5$	H	NH_2	72%
3	p-$NO_2C_6H_5$	H	NHPh	76%
4	p-$OCH_3C_6H_5$	H	NH_2	92.%
5	C_6H_5	H	NHPh	79%
6	p-$OCH_3C_6H_5$	H	NHPh	90%

Table-2 : Catalyst-free synthesis of di- and tri-substituted oxazoles in PEG [a]
a. Reaction of substituted and unsubstituted α-bromoacetophenone (1mmol) with urea (1 mmol) and PEG 400 (0.5 ml) at room temperature for 3hrs. b. Isolated Yield.

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