

An Efficient One-Pot Synthesis of 2, 3-Dihydro-2-Phenyl-1H-Naphtho [1, 2-e] [1, 3] Oxazine Derivatives using L-Cysteine as Catalyst

Bhaskar Ankush

Department of Chemistry. Kai. Rasika Mahavidyalaya, Deoni, Dist. Latur (M.S.), India

Email: bhaskarankush2@gmail.com

Abstract: L-Cysteine acts as a mild and efficient reaction promoter for the cyclocondensation of β -naphthol, formalin, and aromatic amines, affording the corresponding 2,3-dihydro-2-phenyl-1H-naphtho-[1,2-e][1,3]oxazine derivatives. The significant advantages offered by this method are inexpensive and readily available catalyst, simple procedure, faster reactions, involved the nonchromatographic moderate to high yield of products and offers an attractive alternative to conventional metal-based or hazardous catalysts.

Keywords: L-Cysteine, [1,3] Oxazine derivatives, Mild reaction conditions, Hazardous catalyst alternatives,, Cyclocondensation.

Introduction

Nitrogen heterocycles are of special interest because they constitute an important class of natural and non natural products, many of which exhibit useful biological activities.¹ Oxazine derivatives are played important role in biological and pharamacological field. According to literature survey, Variety of substituted 1, 3 oxazine derivatives have been reported claiming diversified biological activities, such as antimicrobial²⁻³ anti-tumor⁴, anti-bacterial,⁵ anti-HIV⁶ and antimalarial⁷ agents. In addition, 6-arylbenzoxazines are reported as potent non-steroidal progesterone receptor agonists.⁸ Realizing the importance of 1,3-oxazine derivatives as an intermediates as well as in the synthesis of various drug sources, reported in a few classical methods using basic condition⁹ Cu(OAc)₂/ZnCl₂,¹⁰ dry methanolic ammonia,¹¹ 2-azadienes with alkynes,¹² Bu₄NF/EtI,¹³ Au(I) complex,¹⁴ and ammonium acetate.¹⁵ But, there have only been a few reports for the synthesis of 2, 3-dihydro-2-phenyl-1H-naphtho-[1,2-e] [1,3] oxazine derivatives from formalin, 2-naphthol and aromatic amines.¹⁶

However, these methods have its own merit while some of these are plagued by the limitation of prolonged reaction time, exotic reaction conditions and lower yields. Hence, the development of a new method for the synthesis of [1, 3] oxazine derivatives would be highly desirable.

Recently, the commercially available and inexpensive amino acid L-cysteine has been elegantly used to catalyze many reaction such as the Mannich reaction and the direct asymmetric Aldol reaction.¹⁷ The cysteine function has been proposed to act like a 'microaldolase' that facilitates each step of the mechanism including the formation of the intermediate imine and the carbon-carbon bond. Very recently, L-cysteine has also been effectively used as a versatile organo catalyst in various organic transformations.¹⁸ L-cysteine exploited as an efficient organo catalyst in the organic synthetic routes for carbon-carbon, carbon heteroatom bonds and heterocycles.¹⁹ In the present study, we extend the scope of the L-cysteine catalyzed synthesis of 2, 3-dihydro-2-phenyl-1H-naphtho-[1, 2-e] [1,3]oxazine derivatives and the results from our study are presented herein.

Experimental

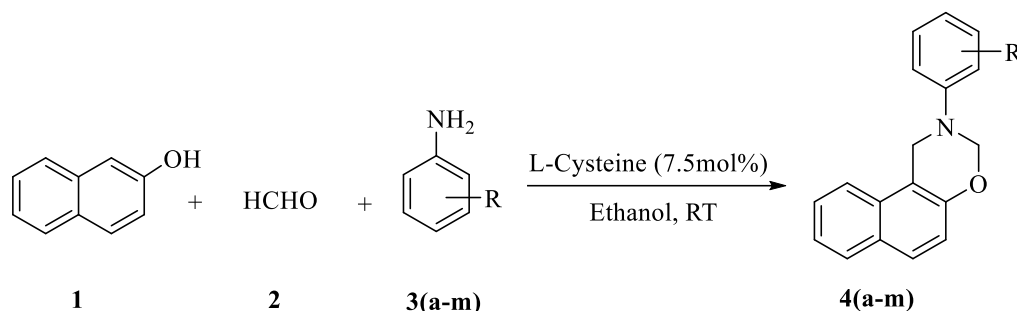
a) Material and methods

All aldehydes were obtained from freshly opened container and used without further purification with the exception of benzaldehyde and 2-furaldehyde which were distilled prior to use melting point was determined in open capillary tubes and is uncorrected. IR spectra were recorded on Perkin Elmer FTIR spectrophotometer in KBr disc, ¹H NMR spectra were recorded on variant 500 MHz spectrophotometer in CDCl₃ using TMS as internal standard. The chemical shifts

have been expressed in δ -ppm scale the melting points and other data were recorded in Table-2 General procedure for Synthesis of 2, 3-dihydro-2-phenyl-1H-naphtho-[1, 2-e] [1,3]oxazine derivative

b) General procedure for the synthesis 2, 3-dihydro-2-phenyl-1H-naphtho-[1, 2-e] [1, 3]oxazines derivatives

A mixture of 2-naphthol (1 mmol) formalin (2 mmol), aromatic amine (1 mmol), and L-cysteine (7.5mol%) as catalyst in ethanol at room temperature was stirred for specified time period as shown in Table 3. The progress of reaction was monitored on TLC. After completion of the reaction, mixture was cooled to room temperature and poured on crushed ice. Thus, solid obtained was filtered, dried and Purified by crystallization in ethanol.



Spectral analysis of principle compound

2,3-dihydro-2-(4-methoxyphenyl)-1H-naphtho[1,2-e][1,3]oxazine (4K): ^1H NMR (DMSO) δ = 3.5 (s, 3H, Ar-OCH₃), 4.7 (s, 2H, N-CH₂), 5.6 (s, 2H, O-CH₂-N), 6.6-7.8 (m, 10H, Ar-H). MS (m/z)= 292 (m⁺).

Result and Discussion

In continuation of our research work on the development of novel synthetic methodologies, herein, we would like to report a highly efficient route for the synthesis of 2, 3-dihydro-2-phenyl-1H-naphtho-[1, 2-e] [1, 3]oxazine derivatives catalyzed by an commercially available, inexpensive, mild organocatalyst L-cysteine. This protocol is a one-pot three component coupling of 2-naphthol, formalin and aromatic amine, in ethanol in room temperature (Scheme 1).

In our search for the better solvent and the best experimental reaction conditions in the preparation of 2, 3-dihydro-2-phenyl-1H-naphtho-[1, 2-e] [1,3]oxazine derivatives, we have determined that the reaction of, 2-naphthol, formalin and aniline in ethanol at room temperature is the standard model reaction. We have determined that the reaction of, 2-naphthol, formalin and aniline (3a) in ethanol at room temperature is the standard model reaction. To evaluate the effect of solvent, we have screened different solvents such as water, methanol, 2-propanol, dichloromethane, tetrahydrofuran, dioxane, ethanol:water(1:1) and ethanol at room temperature. Ethanol stand out as the solvent of choice among the solvents tested because of the rapid conversion and excellent yield (93%) of desired product, whereas the product formed in lower yields (30~76%) by using other solvents (Table 1, Entry 1~7).

To determine the optimum concentration of catalyst, we have investigated the model reaction at 2.5, 5, 7.5 and 10 mol% of L-cysteine in ethanol at room temperature. The product was obtained in 68, 84, 93 and 93% yield, respectively. This indicates that the use of 7.5 mol% of L-cysteine is sufficient to promote the reaction forward (Table 2).

To study the generality of this process, variety of examples were illustrated for the synthesis of 2, 3-dihydro-2-phenyl-1H-naphtho-[1, 2-e] [1, 3] oxazine and results are summarized in Table 3. The reaction is compatible for various substituents such as -CH₃, -OCH₃, -OH, -N(CH₃)₂, -Cl and -F.

Table 1: Screening of solvents for the synthesis of 4a^a

Entry	Solvent	Yield (%) ^b
1	Water	30
2	Methanol	67
3	2-Propanol	72

4	Dichloromethane	34
5	Tetrahydrofuran	32
6	Dioxane	31
7	Ethanol:Water (1:1)	76

^aReaction condition: **1** (1 mmol), **2** (2 mmol), **3a** (1 mmol), L-Cysteine (7.5mol%) at room temperature. ^bIsolated yield.

Table 2: Effect of concentration of L-cysteine

Entry	Concentration (mol %)	Yield (%) ^b
1	2.5	71
2	5	85
3	7.5	92
4	10	92

^aReaction condition: **1** (1 mmol), **2** (2 mmol), **3a** (1 mmol) in ethanol at room temperature.

^bIsolated yield.

Table 3: L-cysteine catalyzed synthesis of 2, 3-dihydro-2-phenyl-1H-naphtho-[1, 2-e] [1,3]oxazines ^a

Entry	Compound	Ar-NH ₂	Time (min)	Yield (%) ^b	M. P. (°C)
1	4a	C ₆ H ₅ -	8	92	50-52
2	4b	3-OMe-C ₆ H ₄	7	92	67-69
3	4c	4-OMe-C ₆ H ₄	6	88	78-80
4	4d	2-NO ₂ -C ₆ H ₄	9	90	110-112
5	4e	4-F-C ₆ H ₄	6	93	135-137
6	4f	4-Br-C ₆ H ₄	6	89	114-116
7	4g	2-Me-C ₆ H ₄	7	91	56-58
8	4h	3-NO ₂ -C ₆ H ₄	7	91	128-130
9	4i	3-Me-C ₆ H ₄	6	87	70-72
10	4j	4-NO ₂ -C ₆ H ₄	6	89	166-168
11	4k	4-Me-C ₆ H ₄	7	89	89-91
12	4l	4-OEt-C ₆ H ₄	7	91	69-71
13	4m	2,4,6-triBr-C ₆ H ₂	9	89	97-99

^aReaction condition: **1** (1 mmol), **2** (2 mmol), **3** (1 mmol) in ethanol at room temperature.; ^bIsolated yield.

Conclusion

In conclusion, we have developed efficient and environmentally benign methodology for the synthesis of 2, 3-dihydro-2-phenyl-1H-naphtho-[1, 2-e] [1,3]oxazines derivatives by a one-pot, Multicomponent reaction from cyclocondensation of 2-naphthol, formalin and aromatic amines and under stirring in ethanol at room temperature in the presence of L-cysteine. The advantages of this method over other existing methods are reduced reaction times, higher yields, mild reaction condition, easy purification, non-hazardous and economic viability of the catalyst. We feel that this economically viable procedure will find practical utility for the one pot synthesis of novel [1,3]oxazines derivatives.

References

- [1] Zhichao, J.; Feng Y.; Xiao, W.; Huicai, H.; Xiaoyan, L.; Xinmiao, L.; Jinxing, Y. *Org. Biomol. Chem.* **2011**, *9*, 1809.
- [2] Mathew, B. P.; Kumar, A.; Sharma, S.; Shukla, P. K.; Nath, M. *Eur. J. Med. Chem.*, **2010**, *45*, 1502.
- [3] Fringuelli, R.; Pietrella, D.; Schiaffella, F.; Guarraci, A.; Perito, S.; Bistoni, F.; Vecchiarilli, A. *Bioorg. Med. Chem.* **2002**, *10*, 1681.
- [4] (a) Kuehne, M. E.; Konopke, E. A. *J. Med. Chem.* **1962**, *5*, 257; (b) Chylinska, J. B.; Urbanski, T. *J. Med. Chem.* **1963**, *6*, 484; (c) Hsu, L. Y.; Lin, C. H. *Heterocycles*, **1996**, *43*, 2687.
- [5] (a) Chylinska, J. B.; Janowiec, M.; Urbanski, T. B. *J. Pharmacol.* **1971**, *43*, 649; (b) Latif, N.; Mishriky, N.; Massad, F. *Aust. J. Chem.* **1982**, *35*, 1037.
- [6] (a) Pedersen, O. S.; Pedersen, E. B. *Synthesis*, **2000**, 479; (b) Cocuzza, A. J.; Chidester, D. R.; Cordova, B. C.; Jeffrey, S.; Parsons, R. L.; Bacheler, L. T.; Erickson, V. S.; Trainor, G. L.; Ko, S. S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1177.
- [7] Duffin, W. M.; Rollo, I. M. *J. Pharmacol.* **1957**, *12*, 171.
- [8] Zhang, P.; Terefenko, E. A.; Fensome, A.; Zhang, Z. Y.; Zhu, J.; Cohen, R.; Winneker, J.; Wrobel, J.; Yardley, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 787.
- [9] Tovar, F.; Ochoa, G. *Org. Lett.* **2000**, *2*, 965.
- [10] Lee, J.; Lee, K.; Kim, H. *Bull. Korean Chem. Soc.* **1996**, *17*, 115.
- [11] Szatmari, I.; Martinek, T. A.; Lazar, L.; Fulop, F. *Eur. J. Org. Chem.* **2004**, 2231.
- [12] Palacios, F.; Herran, E.; Rubiales, G.; Ezpeleta, M. J. *J. Org. Chem.* **2002**, *67*, 2131.
- [13] Murai, T.; Sano, H.; Kawai, H.; Aso, H.; Shibahara, F. *J. Org. Chem.* **2005**, *70*, 8148.
- [14] Kang, J. E.; Kim, H. B.; Lee, J. W.; Shin, S. *Org. Lett.* **2006**, *8*, 3537.
- [15] Sapkal, S. B.; Shelke, K. F.; Kategaonkar, A. H.; Shingate, B. B.; Shingare, M. S. *Green Chem. Lett. Rev.* **2009**, *2*, 57.
- [16] (a) Burke, W. J.; Murdoc, K. C.; Ec, G. *J. Am. Chem. Soc.* **1954**, *76*, 1677.
- [17] (a) Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580; (b) Dalko, P. I.; Moisan, L. *Angew. Chem, Int. Ed.* **2004**, *43*, 5138; (c) Lacoste, E. *Synlett.* **2006**, *12*, 1973.
- [18] (a) Wang, Y.; Shang, Z. C.; Wu, T. X.; Fan, J. C.; Chen, X. *J. Mol. Catal. A: Chem.* **2006**, *253*, 212; (b) Srinivasan, M.; Perumal, S.; Selvaraj, S. *Arkivoc* **2005**, *xi*, 201; (c) Sabitha, G.; Fatima, N.; Reddy, E. V.; Yadav, J. S. *Adv. Synth. Catal.* **2005**, *347*, 1353; (d) Dodda, R.; Zhao, C. G. *Synthesis*, **2006**, *19*, 3238.
- [19] (a) Varala, R.; Ramu, E.; Sreelatha, N.; Adapa, S. R. *Tetrahedron Lett.* **2006**, *476*, 877; (b) Varala, R.; Adapa, S. R. *Org. Proc. Res. Dev.* **2005**, *9*, 853; (b) An, Z.; Zhang, W.; Shi, H.; He, J. *Journal of Catalysis* **2006**, *241*, 319-327; (c) Karade, N. N.; Budhewar, V. H.; Shinde, S. V.; Jadhav, W. N. *Lett. in Org. Chem.* **2007**, *4*.