An Eco-friendly Method for the Synthesis of Solvent-Free Reaction of Oxazine Derivatives

S.A. Shaikh[1,*], S.R. Labhade[2], R.R. Kale[2], C.K. Nerkar[3], S.B. Ghoderao[4], S. S. Chobe[5] and S.A. Ahire[5]

[1]Chemistry, KVN Naik Arts, Commerce and Science College (Affiliated to S.P. Pune University, Pune), Nashik, India
[2]Chemistry, K.R.T. Arts, B.H. Commerce & A.M. Science College (Affiliated to S.P. Pune University, Pune), Nashik, India
[3]MGV's Arts, Science and Commerce College (Affiliated to S.P. Pune University, Pune), Manmad, Nashik, India
[4]RNC Arts, JDB Commerce and NSC Science College (Affiliated to S.P. Pune University, Pune), Nashik Road, Nashik, India
[5]Chemistry, L.V.H. Arts, Science and Commerce College (Affiliated to S.P. Pune University, Pune), Nashik, India

ABSTRACT

A new solvent-free method is being developed for the environmentally friendly synthesis of the 2,3-dihydro-1,3-diphenyl derivative-1H-naphtho [1,2-e] [1,3] Oxazine, which is being developed due to the numerous advantages of solvent-free reactions. An oxazine derivative may have a single or dual affinity marker. In a preferred embodiment, the oxazine ring is linked to a linker compound to facilitate its adsorption on the target material. As oxazine molecule can be labelled with any measurable detection marker. In this case, the oxazine ring is preferably used as a fluorescence or trivalent labelled fraction. This three-component approach is efficient, clean, experimentally simple, convenient, safe, and environmentally sound. It is also simple to implement. The spectral analysis confirmed the structures of the synthesized compounds. Additionally, antimicrobial activity was determined Invitro for these newly synthesized products.

KEYWORDS: Green chemistry, Solvent-free, Oxazine derivative, In vitro activity.

INTRODUCTION

Green chemistry is the useful design of chemical products which reduces or eliminates the use of hazardous substances. Green chemistry is applied throughout the life cycle of a chemical product. All synthetic processes involve the use of various solvents. Green chemistry provides "Green" pathways for different synthetic routes using non-hazardous solvents, solvent-free reactions, and environmentally friendly chemicals. Solvent-free synthesis has several advantages over the classical synthesis method [1]. Green chemistry is useful in preventing molecular-level emission [2], a concept that refers to all fields of chemistry but not a particular discipline in chemistry [3]. It gives solutions to prevalent environmental problems throughout the world [4-6]. It decreases the risk of hazardous chemical substances generated during the process to yield the products. Green chemistry also helps in sustaining health and the environment [7]. Hence the invention of a new procedure is a necessity to reduce the intrinsic hazards of the products manufactured in the chemical industries [8].

In a classical approach, an oxazine derivative is added by a condensation reaction between the derivatives of aldehyde, beta naphthol, and ammonium acetate. Naphthol-oxazines are synthetically important compounds used to synthesize a number of compounds that act as drugs, dyes, polymers and are used as a feed in many reactions[9].

There are many benefits to solvent-free synthesis over the classical synthesis process. The following are some of the major advantages - a. Waste/by-products prevention. b. safer reactions. c. maximum penetration into the final products of the reactant (starting material & reagents). d. hazardous substance avoidance or minimization. e. the goods obtained are biodegradable for the most part. f. the requirement for energy for such synthesis is minimal. g. prevention of harsh conditions for reactions. h. elevated commodity yields. i. shorter time for reactions. j. in several of the reactions, strong selectivity. k. prevention of the use of solvents that are toxic [1-9]

Oxazines are heterocyclic compounds containing, in a doubly unsaturated six-membered ring, one oxygen, and one nitrogen atom. Depending on the relative location of the heteroatoms and the relative position of the double bonds, isomers exist (Figure. 1) [10].

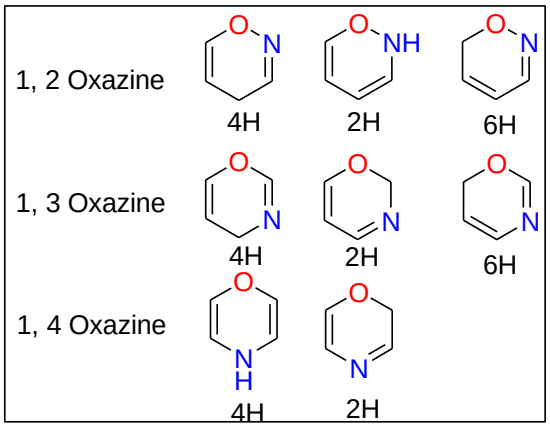


Figure 1 Structure of Oxazine compound's

Thorough literature survey, revealed that the compounds containing dihydro1,3-oxazine ring system exhibited a wide spectrum of pharmacological activities such as anti-tumor [11], anti- bacterial [12] anti-HIV [13,] and antimalarial agents[14].

EXPERIMENTAL

All chemicals, unless otherwise specified, were purchased from commercial sources and were used without further purification, with the exception of liquid aldehydes, which were distilled before use. All yields refer to isolated products after purification. All reactions were monitored by thin-layer chromatography (TLC) on an alumina plate coated with silica gel and spot visualized under UV light. Melting points were determined in open capillaries with a Buchi 510 melting-point apparatus. Products were characterized by the comparison of physical data with those of authentic samples and the use of spectroscopic data (FT-IR, ^{1}H NMR, and ^{13}C NMR). The NMR spectra were recorded on a Bruker Avance DPX 500 MHz instrument. The spectra were measured in $CDCl_3$ relative to tetramethylsilane (0.00 ppm). All chemical shifts were recorded in delta (ppm) and the following abbreviations are used: s-singlet; d-doublet; t-triplet; q-quartet & m-multiplet

General procedure for the synthesis of 2, 3-dihydro-1,3-diphenyl- 1H- naphthol[1,2-e][1,3] oxazine (4a-e): Beta naphthol (1 g, 6.93 mmol) were added with benzaldehyde 1a (1.47 g, 13.86 mmol) and ammonium acetate (0.8019 g, 10.40 mmol). The reaction mixture was stirred for 2-3 minutes and kept some time in an oven at 45 ^{0}C and then again stirred. The reaction was completed within 50 minutes. The reaction mixture was poured into crushed ice. The product was filtered and washed with water and ethanol. The product was recrystallized by using ethanol as solvent. Mobile phase: n- Hexane: Ethyl acetate = 7:3

Detection Methods

2,3-dihydro-1,3-diphenyl- 1H- naphtho[1,2-e][1,3] oxazine: Mobile phase: n- Hexane: Ethyl acetate = 7:3, Yield 97.51 %, White, M.P. 158-162 ^{0}C. ***H^{1} NMR:*** δ_H 7.70(dd,1H), 7.61(dd,1H), 7.44(d,1H), 7.31(dt,1H), 7.18(dt,1H), 6.91(d,1H), 6.11(d,1H), 5.19(d,1H), 2.0(bs,1H), 7.06(dd,2H), 7.14(t,2H), 7.07(tt,1H), 7.19(dd,2H), 7.19(m,3H). ***C^{13} NMR:*** δ_C 152.6, 111.8, 133.6, 129.2, 128.0, 120.1, 123.0, 126.3, 123.4, 128.3, 89.5, 48.8, 142.8, 128.3, 129.3, 126.3, 135.2, 128.0, 128.6, 127.1, 127.2, 135.4, 129.2, 138.1.

1,3–bis(2-chlorophenyl)-2,3–dihydro-1H-naphtho[1,2-e][1,3]oxazine: Mobile phase: n- Hexane: Ethyl acetate = 7:3, Yield 70.46 %, White, M.P. 168-172 ^{0}C. ***H^{1} NMR :*** δ_H 7.70(dd,1H), 7.61(dd,1H), 7.44(d,1H), 7.31(dt,1H), 7.18(dt,1H), 6.91(d,1H), 6.11(d,1H), 5.19(d,1H), 2.0(bs,1H), 7.15(dd,1H), 7.01(dt,1H), 7.02(dt,1H), 7.0(dd,1H), 7.13(dd,1H), 7.07(dt,1H), 7.13(dt,1H), 7.20(dd,1H). ***C^{13} NMR :*** δ_C 111.8, 133.6, 129.2, 128.0, 120.1, 123.0, 126.3, 123.4, 128.3, 80.4, 39.7, 143.4, 133.6, 129.4, 127.7, 127.4, 129.7, 137.6, 133.3, 128.7, 128.5, 126.7, 129.4.

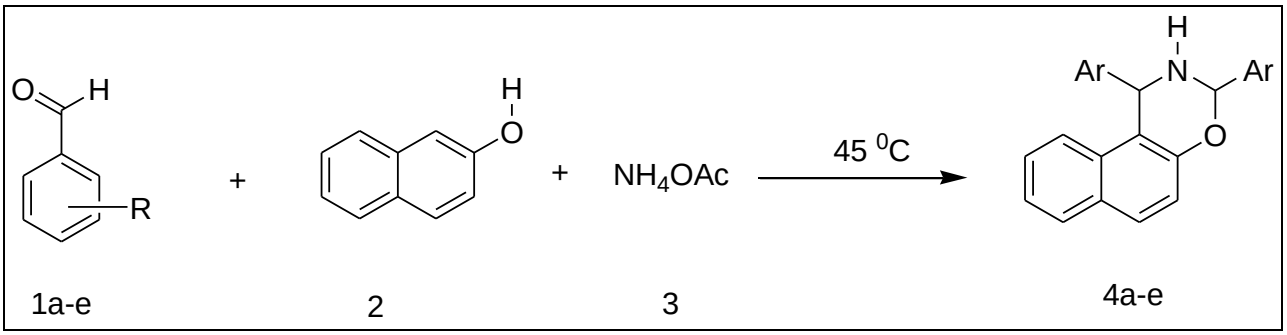
1,3-bis(3-chlorophenyl)-2,3-dihydro-1H-naphtho[1,2-e][1,3] oxazine: Mobile phase: n- Hexane: Ethyl acetate = 7:3, Yield 67.61 %, Pink, M.P. 124-128 ^{0}C. ***H^{1} NMR :*** δ_H 7.70(dd,1H), 7.61(dd,1H), 7.44(d, 1H), 7.31(dt, 1H), 7.18(dt,1H), 6.91(d,1H), 6.11(d,1H), 5.19(d,1H), 2.0(bs,1H), 7.07(t,1H), 7.08(m ,2H), 6.96(dt,1H), 7.20(m,2H), 7.13(t,1H) 7.07 (dt, 1H). ***C^{13} NMR :*** δ_C 152.6, 111.8, 133.6, 129.2, 128.0, 120.1, 123.0, 126.3, 123.4, 128.3, 89.0, 48.3, 144.2, 128.1, 134.8, 126.4, 130.7, 126.0, 136.6, 127.8, 134.1, 127.2, 130.0, 126.1.

1,3-bis(2-bromophenyl)-2,3-dihydro-1H-naphtho[1,2-e][1,3]oxazine: Mobile phase: n- Hexane: Ethyl acetate = 7:3, Yield 58.47 %, Brown, M.P. 148-152 ^{0}C. ***H^1 NMR :*** δ_H 7.70(dd,1H), 7.61(dd,1H), 7.44(d, 1H), 7.31(dt, 1H), 7.18(dt,1H), 6.91(d,1H), 6.11(d,1H), 5.19(d,1H), 2.0(bs,1H), 7.31(dd,1H), 6.96(m,2H), 7.08(dt,1H), 7.08(m,2H), 7.13(dt,1H) 7.36(dd, 1H). ***C^{13} NMR :*** δ_C 111.8, 133.6, 129.2, 128.0, 120.1, 123.0, 126.3, 123.4, 128.3, 71.7, 41.0, 146.3, 123.2, 132.2, 128.5, 128.3, 129.5, 140.5, 130.2, 127.6, 129.3, 131.5, and 122.9

1,3-bis(3-bromophenyl)-2,3-dihydro-1H-naphtho[1,2-e] [1,3] oxazine: Mobile phase: n- Hexane: Ethyl acetate = 7:3, Yield 85.67 %, Brown, M.P. 130-134 ^{0}C. ***H^1 NMR (500 MHz, CDCl$_3$) :*** δ_H 7.06(t,1H), 7.15(m,3H), 7.25(m,3H), 7.33(d,1H), 7.41(m,2H), 7.73 (m,4H), 5.50(d,1H), 5.36 (d,1H). ***C^{13} NMR (500 MHz, CDCl3) :*** δ_C 112.57, 119.41, 122.55, 122.77,123.02, 123.15, 123.58, 123.78, 125.10, 127.01, 129.40, 129.78, 129.98, 130.02, 130.09, 130.80, 131.42, 131.75, 132.32, 140.80, 145.0, 152.22, 81.41 and 56.87.

RESULT AND DISCUSSION:

To prepare 2, 3-dihydro-1, 3-diphenyl derivative-1H-naphtho [1, 2-e] [1, 3] oxazine more efficiently by minimizing reaction time and temperature, the non-catalytic reaction of beta-naphthol (1 equiv), benzaldehyde / benzaldehyde derivative (2 equiv) and ammonium acetate (1.5 equiv) was selected as a model system under solvent-free conditions in one step (Scheme 1). Within 50 – 150 min, the expected products (4a –e) were obtained. (Table 1).



Scheme 3.1. For the synthesis of 2,3-dihydro-1,3-diphenyl derivative-1H-naphthol [1, 2-e][1, 3] oxazine.

Solvent-free reactions have benefits including cost savings, energy reduction consumption, short reaction times and significantly reduced reactor size. These characteristics inspired a considerable amount of research work aimed at solvent-free reaction growth.

Table 3.1. Synthesis of 2, 3-dihydro-1, 3-diphenyl derivative-1H-naphtho [1, 2-e] [1, 3] oxazine

R	2, 3-dihydro-1, 3-diphenyl derivative-1H-naphtho [1, 2-e] [1, 3] oxazine	Color	M.P (^{0}C)	Reaction Time (min)	Yield (gm)	% Yield
H	4a	White	160	50	2.4	97.51
2-Cl	4b	White	170	150	1.98	70.46
3-Cl	4c	White	126	90	1.9	67.61
2-Br	4d	Brown	150	100	2.0	58.47
3-Br	4e	Brown	132	75	2.3	85.67

In all cases, aromatic ortho-substituted benzaldehyde slowly reacted than benzaldehyde and meta substituted benzaldehyde due to steric effect. In the case of benzaldehyde and meta substituted benzaldehyde, a high yield was observed than ortho-substituted benzaldehyde (Table 1).

CONCLUSIONS

Most attention has been achieved by the solvent-free synthesis of organic compounds. It is one of the best green chemistry techniques that can synthesize several significant oxazine derivatives in an effective and environmentally friendly manner. The tremendous benefits of solvent-free reactions are to be found in modern solvent-free methods for environmentally safe oxazine derivatives synthesis.

ACKNOWLEDGEMENT

I am very thankful to Principal Dr. V. B. Gaikwad, K.T.H.M College, ex-principal Dr. S. P. Badgujar K.V.N.Naik College, and Principal Dr. V.G Wagh K. V. N. Naik College for making available the necessary facilities for this work in the chemistry department. I also extend my sincere thanks to Mr. Akshay Patil, Mr. Nitin Jadhav, Smt. S.C. Deokar, Smt. V.S.Raut, Mr. S.G. Shinde, Smt. Lata Avhad, Smt. Chaya Pekhale, Ms. Sumaiya Sayyed, Mr. V.D. Pardeshi, Mr. Kapil Randhir, Ms. Sonali Mahajan, and Ms. Nikita Wagh all the teachers of K.V.N.Naik College and K.T.H.M College for their valuable guidance and continuous inspiration during the course of this project work. I am also thankful to lab-assistants Mr. S. G. Sanap, Mr. Dyaneshwar Sangale, Mr. Kailas Landage, and all non-teaching staff of the K.V.N.Naik College, who sincerely made available all the necessary apparatus and chemicals during the project work. I am also thankful to my parents, family members, and the students like Mr. Prashant Jangam, Mr. Ganesh Patil, Ms. Mohini Katkade, Ms.Ashvini Nagpure, Ms.Mamata Purohit Ms. Dipali Bodake, Mr..Akshay Manvatkar, Ms.Shashikala Vishvkarma, & Mr.Satyam Sangale, directly co-operated during the course of the synthesis of products.

REFERENCES:

1. K.V. Girijesh, R. Keshav, K.V.Rajiv, D. Pratibha, M.S. Singh, *Tetrahedron.,* **67,** 3698-3706 **(**2011).
2. R. A. Sheldon, I. Arends, U. Hanefeld, John Wiley & Sons., *Green chemistry and catalysis*., (2007).
3. J.H, Clark, R, Luque, A.S, Matharu, *Rev. Chem. Biomol. Eng.*, **3,** 183-207(2012).
4. Cernansky, R. Chemistry, *Nature.*, **519(7543),** 379-380 (2015).
5. Sanderson K, *Nature.*, **469(7328),** 18-20 (2011).
6. M, Poliakoff, P, Licence, *Nature.*, **450(7171),** 810-812 (2007).
7. J.H.Clark, *Green Chem.,* **1,** 1-8. (1999).
8. 12 Principles of Green Chemistry, *American Chemical Society*, (2018).
9. A.K . Koch, S.K.Klod, I.S. Szatmari, F.H. €op, E.K, Kleinpeter, *Tetrahedron,*. **62,** 11081-11089 (2006).
10. T.W. Stone, N, Stoy, L.G.Darlington, *Trends Pharmacol. Sci.*, **34(2),** 136-143 (2013).
11. (a) M.E.Kuehne, E.A.Konopka, *J. med. pharm. chem.*, **5,** 257-280 (1962). (b) J.B. Chylinska, T.Urbanski, *J. Med. Chem.*, **6,** 484-487 (1963). (c) L-Y.Hsu, C.-H. Lin, *Heterocycles*, **43,** 2687-2699 (1996).
12. N.Latif, N. Mishriky, F. Massad, *Aust. J. Chem.*, **35,** 1037-1043 (1982).
13. (a) O.S. Pedersen, E.B. Pedersen, *Synthesis*, 479-495(2000). (b) A.J. Cocuzza, D.R.Chidester, B.C.Chidester, S.Jeffrey R.L.Parsons, *Bioorg. Med. Chem. Lett.*, **11,** 1177-1179(2001).
14. W.M.Duffin, I. M. Rollo, *J. Pharmacol. Chemother.,* **12(2),** 171-175(1957).