1,3-OXAZINES: A REVIEW ON SYNTHESIS AND BIOLOGICAL APPLICATIONS

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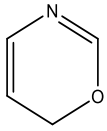
Abstract
1,3-Oxazines are six-membered heterocyclic compounds characterized by the presence of an oxygen atom at position 1 and a nitrogen atom at position 3. These heterocycles have attracted significant attention due to their broad spectrum of biological activities and diverse synthetic routes. This review summarizes the structural features, biological relevance, and various environmentally benign synthetic methodologies reported for 1,3-oxazine and its derivatives in recent literature.
Keywords: *1,3-Oxazine, Heterocyclic compounds, Oxazine derivatives, biological activity, Synthetic methodologies*

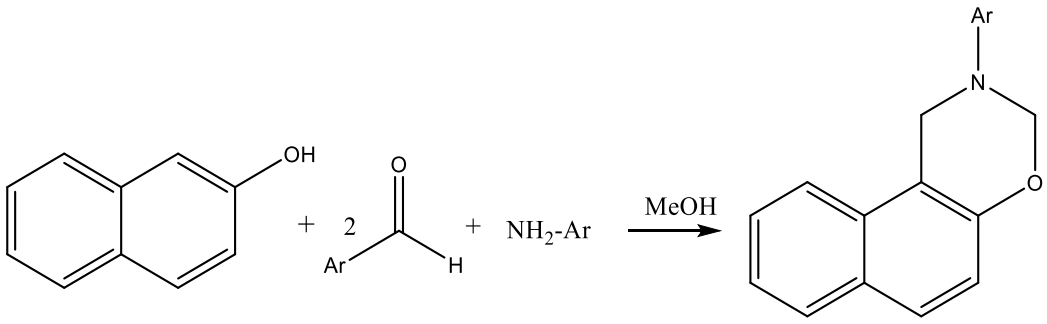
Introduction

Heterocyclic compounds play a pivotal role in organic and medicinal chemistry due to their structural diversity and bioactivity. Among them, 1,3-oxazines, which are six-membered rings containing an oxygen atom at position 1 and a nitrogen atom at position 3, are of considerable interest resect to biologically active compounds[1]. It can be represented as follow.

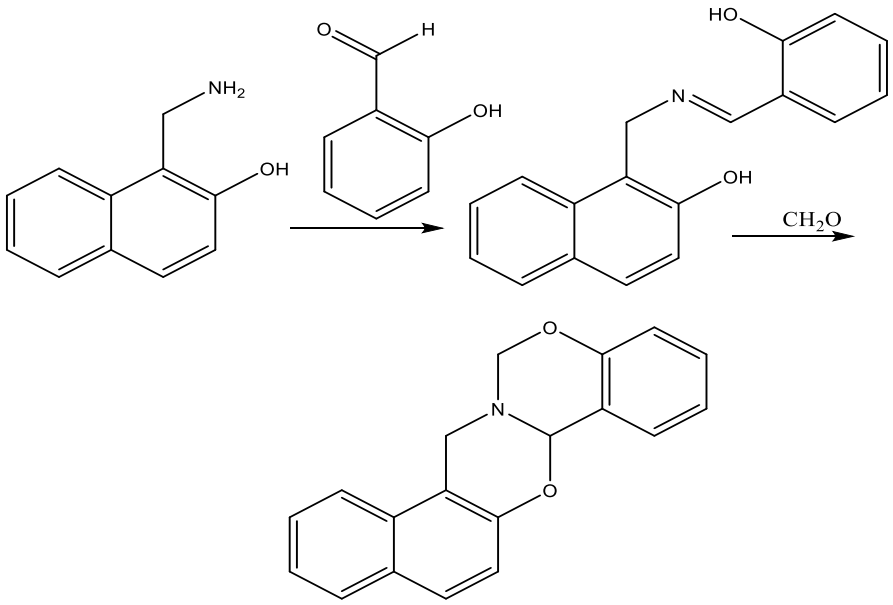


1,3-Oxazine derivative has been found to be potential scaffold in many drugs chemistry applications[2]. Versatile properties of 1,3- Oxazine derivative keep these compounds as a promising source of bioactive compounds. Compounds containing the 1,3-oxazine moiety shows the various biological properties it includes anticancer, antimicrobial, anti-inflammatory, antiplatelet, antitubercular, alpha-glucosidase inhibition, cytotoxic, analgesic, antipyretic, anticonvulsant, and anti-tumor activities[3-4]. Its derivative dihydro-1,3-oxazine perform the active reagent in the Meyers synthesis of aldehydes.

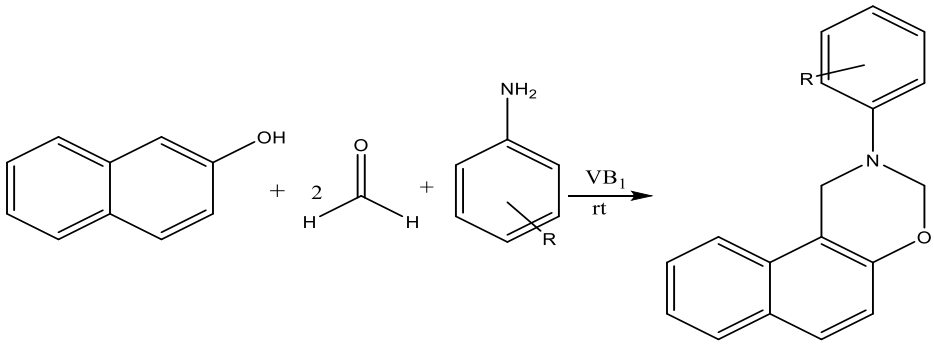
1,3-Oxazine derivatives are synthesized through the condensation reaction of primary aliphatic or alicyclic amines with formaldehyde and either substituted phenols or naphthol.[5]



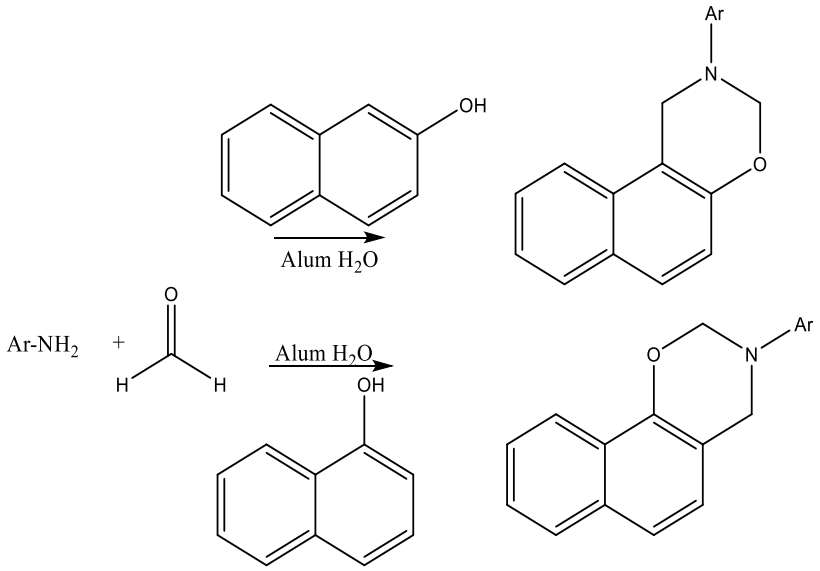
M. Heydenreich and co-workers described a method for introducing a hydroxy group into a Betti base by reacting it with salicylaldehyde. The resulting naphthoxazine intermediates were subsequently subjected to ring-closure reactions using various reagents, including formaldehyde, acetaldehyde, propionaldehyde, or phosgene, to produce the corresponding naphtha[1',2':5,6][1,3]oxazino[3,2-c][1,3]benzoxazine derivatives.[6].



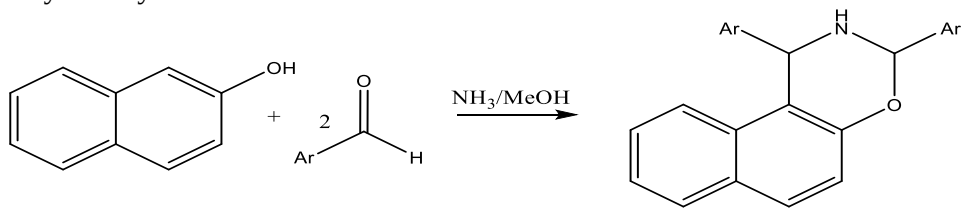
Subsequently, Walmik D. Dhakane and his team synthesized [1,3] oxazine derivatives using thiamine hydrochloride (vitamin B1) as a catalyst in water, offering an environmentally friendly and efficient synthetic approach.[7]



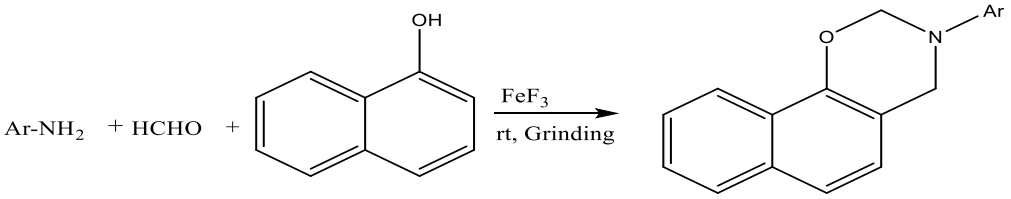
S.A. Sadaphal and co-workers introduced a simple, effective, and practical method for synthesizing a range of substituted 2,3-dihydro-2-phenyl-1H-naphtho[1,2-e][1,3]oxazines and 3,4-dihydro-3-phenyl-2H-naphtho[2,1-e][1,3]oxazines. In this technique, potassium alum [$KAl(SO_4)_2 \cdot 12H_2O$] is employed as a non-toxic, inexpensive, reusable, and easily accessible catalyst, with water used as an environmentally friendly reaction medium.[8]



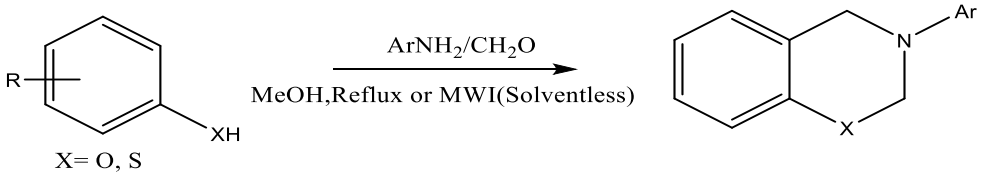
Zuhal Turgut and colleagues[9] synthesized 1,3-disubstituted-2,3-dihydro-1H-naphtho[1,2-e][1,3]oxazine derivatives by carrying out ring-closure reactions between aminobenzylnaphthols and various substituted aryl and heteroaryl aldehydes.



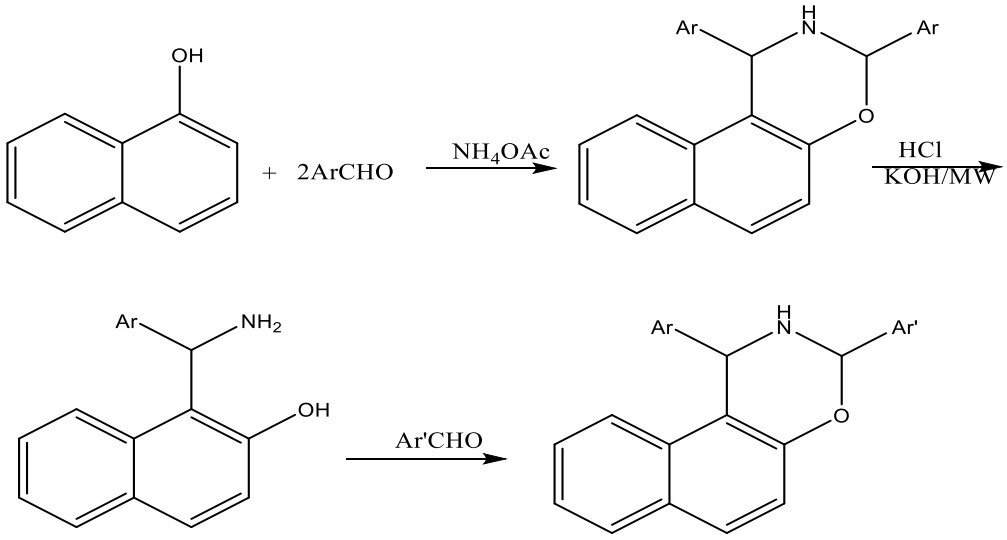
S. K. Parveena et al. synthesized the Biologically active 3,4-dihydro-3-substituted-2H-naphtho [2,1-e][1,3]oxazine derivatives[10] using environmentally benign and economically feasible Lewis acid FeF3.



S. Tumtin[11] and co-workers reported an environmentally friendly, solvent-free method for synthesizing substituted benzo[1,3]oxazine and benzo[1,3]thiazine derivatives using both conventional heating and microwave irradiation. This process involves the reaction of electron-rich phenols, formaldehyde, and aromatic amines in methanol.



S.B. Sapkal and colleagues reported that ammonium acetate serves a dual function in the solvent-free synthesis[12] of 1,3-oxazine, both under neat heating at 60°C and using microwave irradiation, delivering excellent product yields.



Biological Activities of 1,3-Oxazines

The biological potential of 1,3-oxazine derivatives is well-documented. Their activities span across various therapeutic areas:

- **Anticancer and Cytotoxic Agents**: Several derivatives show potent cytotoxicity against cancer cell lines.
- **Antimicrobial and Antitubercular Agents**: Exhibiting activity against bacterial and mycobacterial strains.

- **Anti-inflammatory and Analgesic Properties**: Potential in managing chronic inflammation and pain.
- **Anticonvulsant and CNS Activity**: Useful in treating neurological disorders.
- **Enzyme Inhibition**: Such as **alpha-glucosidase**, relevant in managing diabetes.

Conclusion

1,3-Oxazines represent a highly versatile class of heterocycles with broad pharmaceutical and synthetic relevance. Continued efforts in green chemistry, microwave-assisted techniques, and bioactive compound screening are expected to yield novel therapeutic agents. Environmentally sustainable methods are playing a crucial role in modern synthetic chemistry, and the progress in 1,3-oxazine synthesis reflects this paradigm shift.

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