Indian Journal of Chemistry
Vol. 61, March 2022, pp. 325-327

Synthesis of substituted benzo[*e*][1,3]oxazino analogs

Ranade Prasanna B*[a], Navale Dinesh N[a], Zote Santosh W[b] & Patil Digambar K[c]

[a] Department of Chemistry, Vivekanand Education Society's College of Arts, Science and Commerce, Sindhi Society, Chembur, Mumbai 400 071, India

[b] Department of Chemistry, Sathaye College, Dixit Road, Vile Parle, Mumbai 400 057, India

[c] Department of Chemistry, Changu Kana Thakur Arts, Commerce and Science College, (Autonomous), New Panvel, Raigad 410 206, India

E-mail: prasannaranade@yahoo.com

Received 26 June 2020; accepted (revised) 8 November 2021

A synthesis of substituted benzo[*e*][1,3]oxazin-4-one analogs has been carried out by two methods. One of the common procedures involves refluxing *in situ* generated imine with salicylic acid while other method involves one-pot three component condensation reaction between aldehyde, amine and salicylic acid using DCC. The synthesized compounds have been characterized by IR, ^{1}H and ^{13}C NMR spectroscopy. Melting points reported are uncorrected.

Keywords: Cyclisation, Schiff base, salicylic acid, DCC, benzo[*e*][1,3] oxazines

Heterocyclic compounds[1-5] are very important as they exhibit potential biological activities including antiviral, anticancer, antimalarial, antihepatitis, antifungal and antibacterial[6-10].

Therefore, it is necessary to synthesize heterocyclic compounds. There are number of methods including conventional, one pot multi-component, microwave method etc. are available to synthesize different heterocycles efficiently[11-15]. Each of method has its own benefits and limitations. Oxazino derivatives are known to exhibit potential biological activites[16-20]. Hence in current work we have used conventional method and one pot multi-component method to synthesis substituted benzo[*e*][1,3]oxazino analogs.

In present work, *in situ* generated imine with salicylic acid[21,22]were refluxed to get substituted benzo[*e*][1,3]oxazino analog[23]. One pot three component reaction was subjected between benzaldehyde, 2-aminopyrimidine and Salicylic acid using DCC to afford substituted Benzo[*e*][1, 3] Oxazin-4-One derivative[24].

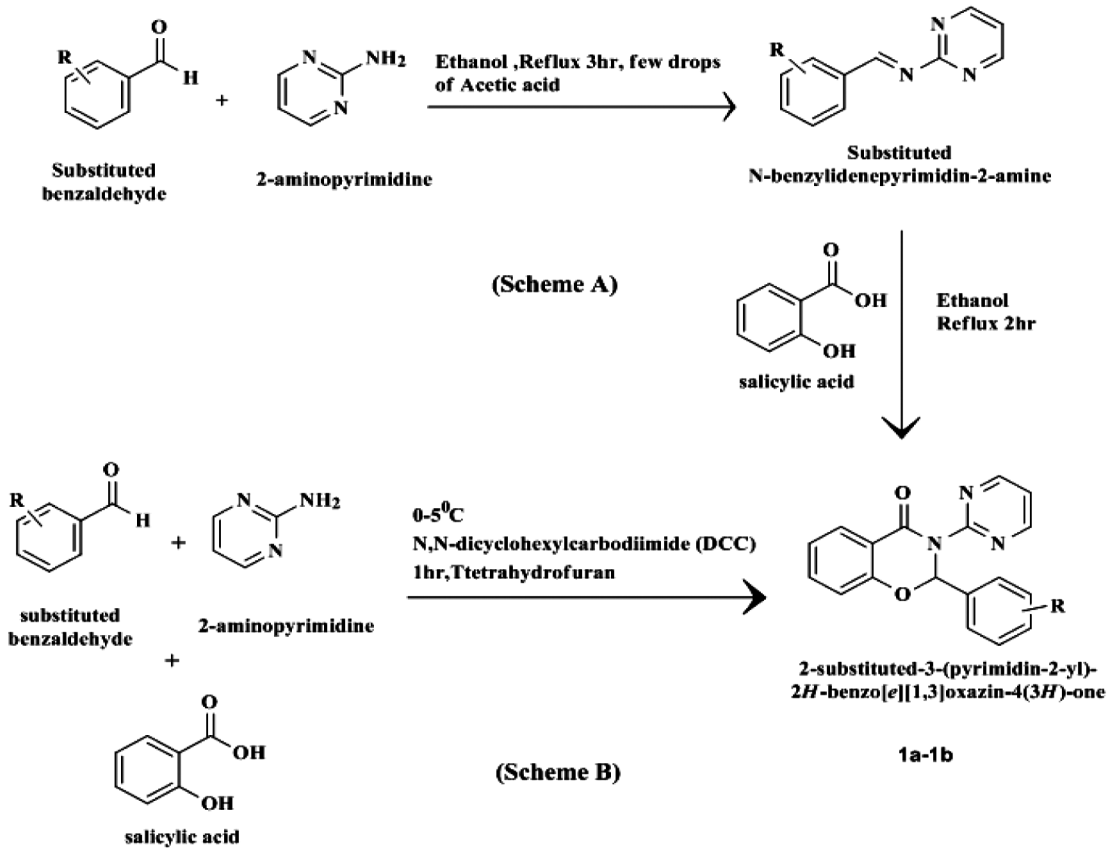
Experimental Section

The chemicals and solvents were purchased from Alfa Aesar, SD-Fine Chemicals (India), Sigma Aldrich and were used without further purification. 60-120 Silica mesh were used for column chromatography. Silica gel G was purchased from Fisher Scientific for TLC.^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on Bruker AVANCE spectrometer. An internal standard TMS is used as internal standard and $CDCl_3$ as solvent for NMR spectra. Perkin-Elmer Frontier IR spectrometers were used for IR spectra.

General procedure for the synthesis of 2-substituted-3-(pyrimidin-2-yl)-2*H*-benzo [*e*][1,3]oxazin-4(3*H*)-one

Scheme A

0.01 mol of substituted benzaldehyde and 0.01 mol of 2-aminopyrimidine were refluxed in10 mL ethanol containing few drops of acetic acid for 3 h to get substituted N-benzylidenepyrimidin-2-amine (Schiff base). After 3 h 0.01 mol salicylic acid was added to reaction mixture. The reaction mixture continued to reflux for additional 2 h. Progress of reaction was monitored on TLC. After the completion of reaction, ethanol was distilled out. Reaction mixture was taken up in ethyl acetate. The ethyl acetate layer was washed with water, (2×10 mL), aq. sodium hydrogen carbonate (2×15 mL) to remove any salicylic acid. The ethyl acetate layer was collected and solvent was removed under reduced pressure. The crude product obtained was purified by column chromatography on silica gel to afford yellow solid. (Yellow solid 65-70%) (**1a-1b**) (Scheme I, Table I).



Scheme I

Table I — Yield of synthesized compounds

Scheme A		
Compd	R	Yield in %
1a	H	68
1b	2-methoxy	67
Scheme B		
Compd	R	Yield in %
1a	H	84
1b	2-methoxy	85

Scheme B

One pot synthesis of 2-substituted-3-(pyrimidin-2-yl)-2*H*-benzo[*e*][1,3]oxazin-4(3*H*)-one

In tetrahydrofuran, the mixture of 0.01 mol of 2-aminopyrimidine, 0.01 mol of aldehyde and 0.01 mol salicylic acid were stirred for 10 min at 0-5°C. While stirring, after 5 min, 0.012 mol of *N*, *N*-dicyclohexylcarbodiimide[21,24] (DCC) was added slowly to the reaction mixture. The reaction mixture was allowed to stir for an additional 1 h till it attains RT. The completion of reaction was monitored on TLC. After the completion of reaction, DCU was removed by filtration. Filtrate was taken up in ethyl acetate. The ethyl acetate layer was washed with water, (2×10 mL) aq. sodium hydrogen carbonate (2×15 mL) to remove any salicylic acid. The ethyl acetate layer was collected and solvent was removed under reduced pressure. The crude product obtained was purified by column chromatography on silica gel to afford Yellow solid (Yield 80-85%) (**1a-1b**) (Scheme I, Table I).

Spectral Data

1a: m.p.88°C. IR: 1625 (Amide), 1190 (C-O), 1589 cm^{-1} (Aromatic =C-H); ^{1}H NMR: δ 8.43 (Singlet, CH, 1H), 7.19-7.22 (doublet, Aromatic hydrogens, 2H), 7.35-7.38 (Aromatic hydrogens 2H), 7.45-7.47 (Aromatic hydrogens, 2H triplet), 7.88-7.90 (Aromatic protons, Doublet, 2H); ^{13}C NMR: δ 29.61 (due to aliphatic carbon substituted by O and N and Aromatic ring), 115.06, 118.50, 120.85, 125.91, 128.74, 128.80, 128.97, 129.12, 129.25, 129.70, 131.34, 134.39, 136.25, 152.10, 160.31 (Amide Carbonyl Group peak), 192.26 (due to tri nitrogen substituted carbon of pyrimidine ring).

1b: m.p.86°C. IR: 1621 (Amide), 1247 (C-O), 1570 cm^{-1} (Aromatic=C-H); ^{1}H NMR: δ 3.8 (Singlet 3H, OCH_3), 6.96-6.99 (doublet, Aromatic hydrogens,

2H), 7.17-7.22 (Aromatic hydrogens 2H), 7.35-7.40 (Aromatic hydrogens, 2H triplet), 7.83-7.86 (Aromatic protons, Doublet, 2H), 8.37 (Singlet 1H Aliphatic); ^{13}C NMR: δ 55.41, 55.56 (aliphatic carbon substituted by O and N and Aromatic ring), 114.18, 114.30, 115.08, 120.86, 125.54, 129.09, 129.27, 130.50, 131.97, 152.36, 159.67, 162.25 (Amide Carbonyl Group peak), 190.77 (due to tri nitrogen substituted carbon).

Conclusion

By the use of readily available and inexpensive chemicals, substituted benzo[*e*][1,3] oxazino-4-one can be synthesized easily with good yield in one pot, three component reaction.

Supplementary Information

Supplementary information is available in the website http://nopr.niscair.res.in/handle/123456789/58776.

Acknowledgement

The authors Prasanna Ranade and Dinesh Navale gratefully acknowledge the use of central instrumentation facilities at V.E.S College of Arts Science and Commerce funded by FIST-DST (Ministry of Science and Technology, Department of Science and Technology) and DBT STAR College Scheme.

References

1 *Heterocyclic Chemistry*, Ahluwalia V K (Alpha Science International, ISBN 1842657097 9781842657096) (2012).
2 Shweta S, Saloni G & Abdul R, *Rasayan J Chem*, 1 (2008) 693.
3 Santosh L G, Vignesh U N & Swarnagowri N, *Mini Reviews in Org Chem*, 16 (2019) 43. https://doi.org/10.2174/1570193X15666180531092843
4 Dhafer S, Zinad A M, Ranjan K, Mohapatra A K & Sarangi M R F P, *Chem Biol Drug Des*, 95 (2020) 16. https://doi.org/10.1111/cbdd.13633
5 Mohammad A & Mohammad I, *Int J New Chem*, 7 (2020) 60. https://iranjournals.nlai.ir/2049/pdf_650040_3f8e2d4599f6bbcd15c9573410b09582.html
6 Cleiton M S, Daniel L S, Luzia V M, Rosemeire B A, Resende M A, Cleide V B & MartinsÂ F, *J Advanced Res*, 2 (2011) 1. https://doi.org/10.1016/j.jare.2010.05.004
7 Francesca A, Antonella B, Antonio G, Fedora G, Gaetano R, Raveendra D & Nouri N, *Bioorg Med Chem*, 12 (2004) 4459. https://doi:10.1016/j.bmc.2004.05.037
8 Guoqiang D, Shengzheng W, Zhenyuan M, Jianzhong Y, Yongqiang Z, Zizhao G, Wannian Z &Chunquan S, *J Med Chem*, 55 (2012) 7593. https://dx.doi.org/10.1021/jm300605m
9 March L C, Romanchick W A, Bajwa G S & Joulli M M, *J Med Chem*, 16 (1973) 337. DOI: 10.1021/jm00262a006
10 Xiaokai L, Nina L, Huaning Z, Susan E K, Richard A S & Peter J T, *Bioorg Med Chem Lett*, 20 (2010) 6306. https://doi:10.1016/j.bmcl.2010.08.076
11 Prasanna B R, Dinesh N N, Santosh W Z & Ramana M M V, *J Appl Chem*, 7 (2018) 1343.
12 Gupta R R, Kumar M & Gupta V (1998). https://www.springer.com/gp/book/9783540648406
13 Marcos A P, Martins C P, Frizzo D N, Moreira L B & Pablo M, *Chem Rev*, 109 (2009) 94140. https://doi.org/10.1021/cr9001098
14 Lokman H C & Tasneem P, *Tetrahedron*, 67 (2011) 8213. https://doi.org/10.1016/j.tet.2011.07.020
15 Aitken R A & Youcef B, *Advances in Heterocyclic Chemistry*, 115 (2015) 93. https://doi.org/10.1016/bs.aihch.2015.03.002
16 Muralidhar P D, Rama S R, Sreenivasa R, Naganjaneyulu B & Murthy Y L N, *Med Chem Res*, 24 (2015) 611. https://DOI 10.1007/s00044-014-1159-x
17 Maher A El-H, Amira T A, Rasha A H & Wael M El-S, *Anti-Cancer Agents in Medicinal Chemistry*, 19 (2019) 4538. https://doi.org/10.2174/1871520619666190201145221
18 Mona P, Robert J M J, Beverly C C, Ronald M, KlabeS E-V, George L T & Soo S K, *Bioorg Med Chem Lett*, 9 (1999) 3221. https://doi.org/10.1016/S0960-894X(99)00565-X
19 Andrea R, Gernot F, Lothar H, Ute M & Susanne H, *Antimicrob Agents Chemother*, 46 (2002) 2010. Doi: 10.1128/AAC.46.6.2010–2013.2002
20 Ramaiyan M & Shanmugam M, *Indian J Chem*, 49B (2010) 1083. http://nopr.niscair.res.in/bitstream/123456789/10079/1/IJCB%2049B(8)%201083-1087.pdf
21 Tumul S, Haq W & Katti S B, *Tetrahedron*, 58 (2002) 387619. https://doi.org/10.1016/S0040-4020(02)00866-9
22 Unsworth W P, Kitsiou C T & Richard J K, *Org Lett*, 15 (2013) 2258. DOI: 10.1021/ol303073b
23 Kametani T, Chu V L, Ihara M & Fukumoto K, *Heterocycles*, 9 (1978) 673. DOI: 10.3987/R-1978-05-0673
24 Ranade P B, Navale D N, Zote S W & Ramana M M V, *Indian J Chem*, 59A (2020) 569. http://nopr.niscair.res.in/bitstream/123456789/54454/1/IJCA%2059A%284%29%20569-573.pdf