Synthesis of New Oxazin Compounds Derived from Furfural, Chalcones and Schiff Bases

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Abstract

Oxazine compounds have been succeeded to be used for versatile applications in various area of pharmacy, medicine and other biological uses such as Antiplatet aggregation activity, antidiabetic, antidepressant activity. In the investigation some new oxazine compounds have been synthesized using different routes [1]. The oxazine (A2-6) were prepared from the corresponding chalcone compounds (A1-6) by treatment of ethyl urea with these chalcones. Oxazine (A5-8) were prepared from the cyclization of the corresponding compounds (A4-7) by formaldehyde compounds (A4-8) themselves were prepared by reduction of Schiff bases (A3-7) using NaBH₄. The third series of oxazines (A6-9) were synthesized by the reaction of furfural with hydroxyl Aromatic Compounds in methanolic ammonia. The synthesized compounds were studied by IR spectroscopy and are discussed [2].

Keywords: Oxazines; Furfural; Chalcones; Schiff bases

Introduction

Oxazine compounds were first synthesized from malonyl chloride and some aliphatic and aromatic ketones. These oxazine compounds were also synthesized by self-condensation of malonyl chloride with nitrile compounds. But, Elivdge and foster found that condensation of malonyl chloride with isocyanates results into the formation of the corresponding pyrano oxazine derivatives. Ried, Ninninger and Bats have prepared pyrano oxazines from the condensations of malonyl chloride with thiocyanates. Some of the synthesized compounds showed anticancer activities. There are a lot of methods in the literature for the preparation of benzoxazin compounds including, ring expansion methods, oxidation of 2-isopropyl indole with monoperphthalic acid, Intramolecular rearrangement, isocyanate precursors, antranilic acid precursor, N-acetylthranilic acid[11], from chalcones precursors[12-14] and recently pd-catalyzed carbonylation of 1-azido-2-iodobenzene has proved to have significant effect as thrombin inhibitor, 16 potassium modulator[17], antiplatelet[18], inhibitory activity toward human leukocyte elastase[19] and many other biological and medical uses. In our investigation and according to the above importance of this type of compounds we choose antranilic acid, chalcon and Schiff bases as precursors for the synthesis of new series of oxazine compounds, in an attempt to study their possibility to be used as drugs which is our next work [4-8].

Experimental

All melting point were uncorrected using electro thermal melting point apparatus type SMP30 U. K, IR spectra were recorded using FTIR spectrophotometer type Bruker Alpha (ATR). All chemical were supplied by Fluke, Sigma-Aldrich companies.

2-Acetylbenzimidazole was prepared according to the published procedure [9-12].

Synthesis of Benzimidazoyl Chalcones (A1-6)

2-Acetyl-benzimidazole compound was prepared by chromic acid oxidation of the corresponding alcohol following the same publisher procedure. Its structure was checked by IR and melting point in comparison with the published one. This compound was allowed to react with equimolar amount of some aromatic aldehyde following similar procedure [13-18].
General Procedure

2- Acetyl-benzimidazole (0.01mol.) was dissolved in (30ml) from Ethanol and (30 ml) of water then10% sodium hydroxide solution (3ml) was added drop-wise to the reaction mixture, the mixture stirred for( 1h. ) then [0.01mol] of aldehyde was added to the mixture with continuous stirring for (3-5h). the solid was filtered off and recrystallized from ethanol/water [19-24].

Synthesis of 4-Benzimidazoyl-6H-2-Ethylamino 1,3-Oxazines(A2-6)

General Procedure

A mixture of chalcone (0.02mol),urea(0.02mol.) were dissolved in ethanolic solution of sodium hydroxide(30ml).The reaction mixture was stirred for( 3-4h) with magnetic stirre, it was then poured on 20ml of cold water with stirring for 1h.then kept in refrigerator for 24h. the ppt was filtered off and recrystallized from ethanol [25,26].

Synthesis of Schiff bases(A3-6)

General Procedure

Substituted Benzaldehyde (0.01 mol.) and substituted aniline (0.01 mol.) was dissolved in methanol (15ml) and two drops of acetic acid and refluxed for (3 h.). The resulting solution was cooled and poured in cold water. The separated solid was filtered, washed with water and crystallized from ethanol.

General Procedure for the Hydrogenation of Schiff bases(A4-7)

Each Compound of (A4-7) (0.01mol) was dissolved in methanol (15ml) and sodium borohydride(0.015mol) was added in small portions with stirring within 10 minutes. The reactions mixture was kept at room temperature for (1 h.). The solid separated on evaporation of most of the solvent was filtered off, washed with water and crystallized from ethanol.

Synthesis of 3,4-Dihydro-3-Aryl-2H-Naph[2,1-e] [1,3] Oxazines:(A5-8)

General Procedure

Any compound of(A3-7), (0.01mol) and formaldehyde (0.015mol) was dissolved in ethanol and refluxed in a water bath for 3 hours. The solid separated on cooling was filtered and crystallized from ethanol.

Synthesis of 1,6-Bis Furyl -3,2-and4,3--Aryl-1,3-Oxazines(A6-9)

General Procedure

Aromatic hydroxy compound (0.01 mol) in methanol (10ml) was added to Furfural and 10ml of 30% methanolic ammonia .the final mixture was left to stand at room temperature for 3-4 days during which the crystalline product was separated out. The crude product was filtered off, washed with cold methanol and was recrystallized from minimum amount of methanol (Figures 1-3).

Figure 1: Scheme 1.
Results and Discussion

Chalcone compounds (A1-7) were synthesized from the corresponding 2-acetyl benzimidazole and some aromatic aldehydes as shown in scheme 1.

1-(benzimidazoyl-2-yl)-3-phenyl-2-propene-1-one

Yellowish-white, mp. 142-145°C, yield 83.58%, IR (neat sample cm⁻¹): 1653 for C=O, 1501, 1507, 1584 for C=C Ar., 1653 for C=C, 1706 for –C=O, 3241 for –NH.

1-(benzimidazoyl-2-yl)-3-(4-hydroxy phenyl)-2-propene-1-one

Black Crystals, mp. 265°C, yield 79.55%, IR (neat sample cm⁻¹): 1366 C-O, 1552 for C=C Ar., 1643 for C=N, 3188 for NH.

1-(benzimidazoyl-2-yl)-3-(2-bromophenyl)-2-propene-1-one

Yellow mp. 216-218°C, yield 86.3%, IR (neat. cm⁻¹): 1326.19 for C=N, 1475, 1514, 1587 for C=N, C=C Ar., 1655 for C=O, 3259 for NH.
1-(benzimidazoyl-2-yl)-3-(4-dimethylamino)-2-propene-1-one

Orange Crystals. mp.125-127°C, yield: 90.33%, IR (neet. Cm⁻¹): 1341.28 for C-N, 1519, 1589 for C=C Ar, C=N, 1665 for C=O, 2971.35 for CH, 3281 for NH.

1-(benzimidazol-2-yl)-3-(2-methoxy phenyl)-2-propene-1-one

Yellowish-Green mp.196-198°C, yield: 54.33%, IR (neet. Cm⁻¹): 1206, 1236 for C-O, 1470, 1513, 1574 for C=C Ar., 1647 for C=N, 1699 for C=O, 0.1322 for -NH.

1-(benzimidazol-2-yl)-3-(4-nitrophenyl)-2-propene-1-one

Yellow Crystals. Mp. 101-103°C, yield: 78.3%, IR (neet. Cm⁻¹): 1333 for C=N, 1209, 1512 for NO2 sym and asym., 1590 for C=C Ar., C=N, 1654 for C=N, 1698 for C=O, 0.3113 for -NH.

1-(benzimidazol-2-yl)-3-(2-chlorophenyl)-2-propene-1-one


Oxazines from Chalcones

The above compounds were synthesized from the corresponding chalcones with ethyl urea as stated above the IR data were in agreement with similar published one.

6-(Benzimidazol-2-y1)-2-Ethylamino-4-Phenyl-4H-1,3-Oxazine-4H-1,3-Oxazine


6-(benzimidazol-2-yl)-2-ethylamino-4-(4-hydroxy phenyl)-4H-1,3-Oxazine

Brownish Crystals. mp 36-38°C, yield: 85% IR (neet. Cm⁻¹).

6-(benzimidazol-2-yl)-2-ethylamino-4-(2-bromo phenyl)-4H-1,3-Oxazine


6-(benzimidazol-2-yl)-2-ethylamino-4-(4-dimethylamino phenyl)-4H-1,3-Oxazine

Orange Crystals. mp.178-180°C, yield: 90%, IR (neet. Cm⁻¹): 1216, 1333 for C-O, 1512, 1576 Ar C=C, 1341 for C=N, 1638 for C=N, 3257 for NH.

6-(benzimidazol-2-yl)-2-ethylamino-4-(2-methoxy phenyl)-4H-1,3-Oxazine

Yellowish-white crystals. mp 188-191°C, yield: 87%, IR (neet. Cm⁻¹): 1236.22, 1322.36 for C-O sym and asym., 1322.36 for C-N, 1513, 1574 for C=C Ar., 1647 for C=N, 3247.72 for NH.

6-(benzimidazol-2-yl)-2-ethylamino-4-(4-nitrophenyl)-4H-1,3-Oxazine


6-(benzimidazol-2-yl)-2-ethylamino-4-(2-chlorophenyl)-4H-1,3-Oxazine

Yellowish-white crystals. mp 201-203°C, yield: 87%, IR (neet. Cm⁻¹): 1273, 1325 for C-O, 1325.90 for C-N, 1476, 1504, 1585 for C=C Ar. 1652 for C=N, 3257 for NH.

Schiff Bases (A3-6)

The above Schiff bases were synthesized by treatment of 2-hydroxy naphthaldehyde with some amines see scheme 2. These compounds were characterized by the Main IR bands as below:

2-Hydroxy Naphylidine-1- Naphthyl Amine

Deep brown crystals. mp.182-185°C, IR (neet. Cm⁻¹): 1605 For C=C Ar., and C=N, 1330 for C-O, 3440 for OH.

2-hydroxy naphylidine-2-thiozolyl amine

Yellow Crystals. mp.158-160°C, yield: 88% IR (neet. Cm⁻¹): 740.37 For C-S, 1458.98, 1468.96 For C=C Ar., 1128, 1219 For C-O, 1604 for C=N, 3009, 3273.59 For C-H, 3558 for OH.

2-hydroxy naphylidine-2-benzothiazol-2-yl amine

Orange crystals. mp.196-199°C, yield: 68.9%, IR (neet. Cm⁻¹): 73.7.98 For C-S, 1139, 1306 For C-O, 1139, 1306.3 For C=O, 1514.68, 1463.89 For C=C Ar., 1596 For C=N, 3410 for OH.

2-hydroxy naphylidine-2-(4-methyl pyridine-2-yl) amine

Yellow Crystals. mp.177-179°C, yield: 69%, IR (neet. Cm⁻¹): 1126, 1276 For C-O, 1599, 1528, 1480.5 For C=C Ar., 3026 for C-H, 3363 for OH.

Schiff Bases Reduction, The Synthesis of Arylamino Naphthos (A4-7)

Schiff bases reduction was accomplished by NaBH₄ at room temperature as stated in the experimental part see scheme 2. The reaction with this reagent cause to color change of the colored Schiff bases into white or faint colored products.

1-Naphtyl amino methyl 2- napthol

Brownish yellow crystals. mp.86-92°C, yield: 83.4%, IR (neet. Cm⁻¹): 759.99 For NH def., 1257, 1357 C=O, 1466, 1516, 1580 For C=C Ar., 3042.7 For C-H, 3367.0 For NH, 3542 for OH.

2-Thiazol-2-yl amino methyl-2-napthol

White crystals. mp.193-196°C, yield: 89.3%, IR (neet. Cm⁻¹): 744.3, 812.36 For NH def., 1215, 1270, 1393.94 C=O, 1443, 1540, 1597.8 For C=C Ar., 3009, 3272 For C-N, 3488 for OH.

2-Benzothiazol-2-yl Amino methyl -2-napthol

for OH.

(2-Amino-4-methyl pyridyl) methyl -2- naphthol

White crystals, mp. 154-157°C, yield 90.98%, IR (neet. Cm raining 1): 731.07, 793.85, 1507.8 C=Ar, 3045 for CH, 3355.1 for OH.

Aryl Oxazine from Reduced Schiff Bases (A5-8)

3-(1-Naphthyl)-3H-2,4-Dihydro[2,1-e] [1,3] Naphthoaxazine

Red –Orange crystals, m.p 159-162°C, yield 64.1%, IR (neet. Cm raining 1): 1152 for C=O, 1024, 1226, C=O-C, 1462, 1510, 1584 for C=Ar, 3060 C-H

3-(2-aminothiazol-2-yl)-3H -2,4-dihydro[2,1-e] [1,3] naphthoaxazine

Brownish yellow crystals, mp. 191-193°C yield 79.87%, IR (neet. Cm raining 1): 808 for C-S, 1122.46, 1538, 1586.6, 1607 for C=Ar, 2998, 3133 for C-H.

3-(2-amino-4-methyl pyridine-2-yl)-3H-2,4-dihydro[2,1-e] [1,3] naphthoaxazine

White crystals, m.p 103-106°C yield 95.6%, IR (neet. Cm raining 1): 729.4 for C-O-C, 1156.3, 1213 for C =O-C, 1445, 1519.79, 1588.72 for C=Ar, 3060 for C-H.

2,4 Bis furyl naphth oxazines(A6-9)

These compounds were synthesized by treatment of furfural with some hydroxyl aromatic aldehydes as shown in scheme 3

2,4-Bis furyl-2,4-dihydro-2H[3,2-e] [1,3] naphthoaxazine(A6)

Brown crystals, m.p 103-105°C yield 86.35%, IR (neet. Cm raining 1): 1083, 1265.43 for sym. and asym.C=O, 1323.12 for C=O-C, 1445, 1538, 1586.6, 1607 for C=Ar, 2998, 3133 for C-H.

2,4-Bis furyl-2,4-dihydro-2H[4,3-e] [1,3] naphthoaxazine(A7)

Bronch-yellow crystals, Mp. 97-100°C yield 82.8%, IR (neet. Cm raining 1): 1072.32, 1223.47 for C=O-C, 1381.92 for C=O-C, 1596.39, 1461.18 for C=Ar, 3062.83 C-H, 3362.7 for -NH.

2,4,6-Bis furyl-2,4-dihydro-2H[7,6-e] [1,3] quinoloxazine(A8)


2,4,6-Bis furyl-2,4-dihydro-3H[10,9-e] -7,8-dihydroxy [1,3] benzoxazine(A9)

Brown crystals, m.p. 330°C, yield 92% IR (neet. Cm raining 1): 1461.081, 1229.26 for C=O-C, 1381.92 C-N, 1416.11, 1569.36 for C=Ar, 3273 for C=H, 3362.7 for -NH.

Conclusion

It is clear from the above results that all furfural, Schiff base and chalcone precursors formed 1,3- oxazine compound this finding is in agreement with similar published compounds24-26 for chalcones and as it was mentioned in the introduction for Schiff bases and furfural precursors.

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References


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