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# New Approach for the Synthesis of Aryloxy 1,3-Oxazines

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**ABSTRACT**

Oxazinne compounds have drew the attention of many researchers to find different approaches to the synthesis of this type of compounds according to the success of their use in a wide range of pharmaceutical application during the last decades .It is also for the difference reactivity of these analogues is exhaustively depicted and illustrates the rich versatility of this class of starting material. They proved to have most of actions of a combination of other drugs. We are herein investigate the synthesis of ethyl aryloxy acetate(S1-6) from the reaction of the corresponding ethyl bromo acetate with aryl phenols .These intermediates were cyclized with antharanilic acid affording the titled compounds.

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## Introduction

The chemistry of Oxazine becomes an important branch of heterocyclic compounds not just as synthetic intermediates but also due to the wide spectrum application of this type of compounds in medicine. There are many routes for their preparation were employed some of them from malonyl chloride, Ethyl salicylate other methods of synthesis such as the work of N.R Taati et al., from the condensation of 3-amino propanol with carboxylic acids under solvent free condition. Nadeem Siddiquia and his co-workers have reviewed the synthesis of some 1,3- oxazines from the condensation of different types of phenols such as hydroquinone, sulfone scaffold, Chavicol, Eugino l, Cardanol as well as ,salicylic acid with different amines in presence of formaldehyde and studied the biological activity of the synthesized compounds. Ahmed El-Mekabaty in 2013 have reviewed versatile methods for oxazine synthesis from antharanilic acid and its derivatives. Sayaji and Pravina B. Piste have reported the preparation of some 1,3-oxazine compounds from phenols and aromatic aldehydes in methanolic ammonia and have studied their anti-microbial activity against two gram positive and two gram negative bacteria .Antifungal activity was screened against Candidaalbicans, Aspergillus niger. Some other researchers have cyclized chalcones into 1,3-oxazines using fly-ash and other catalysts . They also studied their antimicrobial activities. Against gram negative bacteria. Chaitra G and Rohini RM have also synthesized 1,3-oxazine compounds from pyridyl chalcones and studied their Anti-Oxidant and Anti-Inflammatory activity [1-10]. Among the other medical application of the oxazine compounds is the work of Vashundhra Sharma and his coworkers in synthesis and anticancer study of 2-oxo-benzo oxazines [1,4,11]. JC Wouter, de Bruijna and his coworkers have studied the drug designing of 1,4- oxazines and found that their possible multitarget mechanism of the studied compounds as anti-inflammatory drug through quantitative structure-activity relationships (QSAR) [12]. Dadmohammad and his coworker have reported a green and efficient method for the synthesis of 1,3 oxazine compounds from aroyl chlorides and hydroxyl naphthaqunone in presence of ammonium thiocyanate at ambient temperature, In 1919-2020 researchers studied the synthesis of 1,3-oxazines and their human DNA topoisomerase I inhibitory potentials [13,14]. Recently Seyed Gholamhossein Mansouri et-al have synthesized naphtho[1,2-e][1,3]oxazines and studied their anticancer and antifungal activity [15]. According to the above utility and applications of this type of heterocyclic compounds and in continuing of our current drug discovery program we have synthesize new 1,3- oxazine derivatives using new route of condensation protocol [16-18].

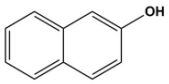
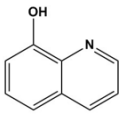
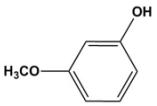
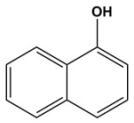
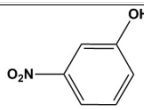
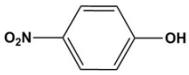
## Experimental

All melting points were uncorrected using thermal SMP30 UK melting point apparatus. IR spectra were recorded using Alpha (ATR) instrument .$^{1}$HNMR spectra were recorded using Varian Agilent 499.53MHZ instrument, DMSO as internal solvent. All chemical were supplied by sigma –Aldrich, BHD and Fluka companies.

### Synthesis of Ethyl Substituted Aryloxy Acetate($S_{1-6}$)

Using an elsewhere similar procedure of preparation of1, 3, 4-oxadiazole Derivatives, A mixture of any indicated phenols (1mmol), ethyl bromoacetate (0.122g, 1mmol) and anhydrous potassium carbonate (0.55g,4mmol) in 30 ml of dry acetone was refluxed for 20 h. the reaction mixture was evaporated under reduced pressure, The residue was dissolved in water. The final solution was extracted with ether, The ether extract was then dried over sodium sulphate anhydrous and filtered off [19]. Evaporation of the solvent afforded the crude product which was crystallized from ethanol. Table(1) below shows the physical properties of the titled compounds.

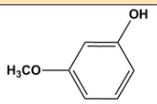
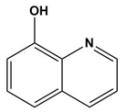
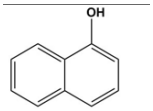
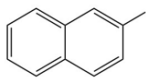
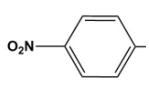
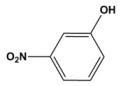
**Table 1: The Physical Properties of Compounds ($S_{1-6}$)**

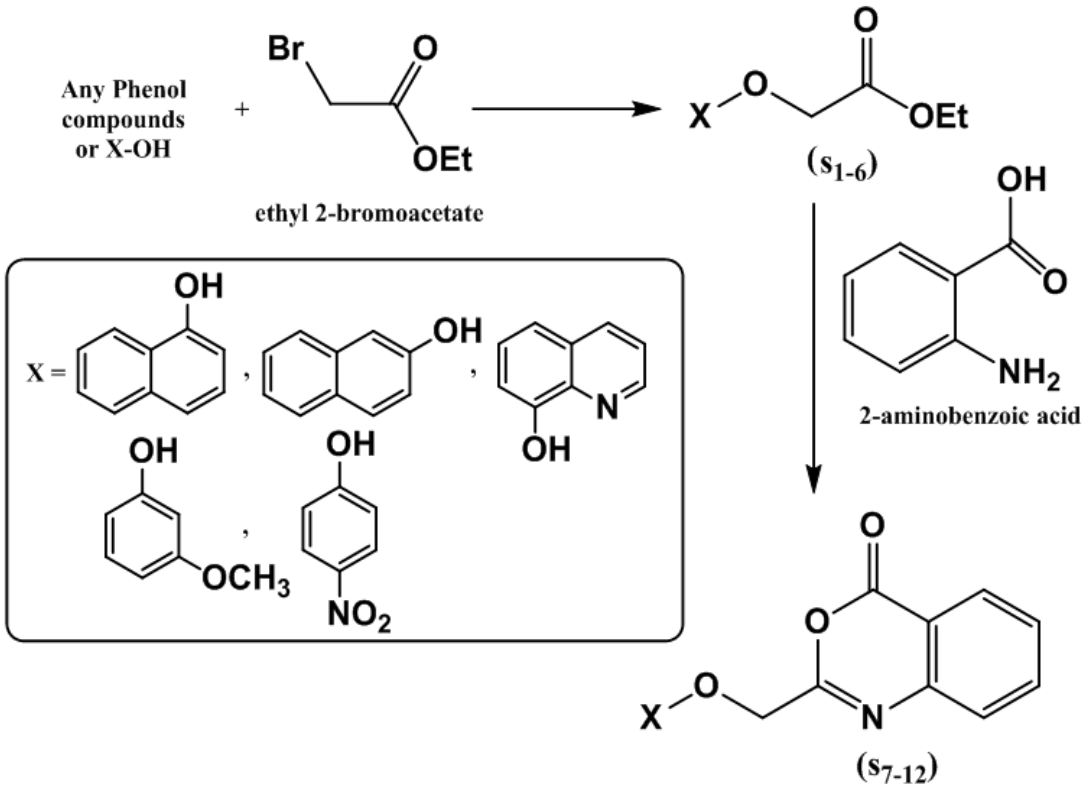
| Comp. No. | X = Phenol | Molecular Formula | M.Wt gm/mol | M.P. (°C) | Yield % | Colour |
|---|---|---|---|---|---|---|
| $S_1$ |  | $C_{14}H_{14}O_3$ | 230 | 64-65 | 75 | white |
| $S_2$ |  | $C_{13}H_{13}NO_3$ | 231 | 50-52 | 60 | orange |
| $S_3$ |  | $C_{11}H_{14}O_4$ | 210 | Colorless oil | 56 | Brown |
| $S_4$ |  | $C_{14}H_{14}O_3$ | 230 | Colorless oil | 52 | yellow |
| $S_5$ |  | $C_{10}H_{11}NO_5$ | 225 | Colorless oil | 56 | brown |
| $S_6$ |  | $C_{10}H_{11}NO_5$ | 225 | Colorless oil | 60 | brown |

**Synthesis of 2-Aryloxy Methyl -3,1-Benzoxazine-4-One :(S7-12)**

Similar published procedure was used for the synthesis of the above compounds [20]. So a quimolar amounts of anthranilic acid (0.13g,1mmol) and ($s_{1-6}$),(1mmol) were heated at (110 °C) on sand bath for 5 hs. The reaction mixture was then treated by addition of 20 ml. ethanol ,The crude precipitated product was filtered off and was then crystallized from petroleum ether (60-80) Table(2) below shows the physical properties of the synthesized compounds.

Table. 2 Physical Properties of Compounds ($S_{7-12}$)

| Comp. No. | PHENOLS | Molecular Formula | M.Wt gm/mol | M.P. (°C) | Yield % | Colour |
|---|---|---|---|---|---|---|
| $S_7$ |  | $C_{16}H_{13}NO_4$ | 283 | 127-128 | 61 | Brown |
| $S_8$ |  | $C_{18}H_{12}N_2O_3$ | 304 | 68-69 | 50 | yellow |
| $S_9$ |  | $C_{19}H_{13}NO_3$ | 303 | 127 | 66 | brown |
| $S_{10}$ |  | $C_{19}H_{13}NO_3$ | 303 | 84-86 | 56 | brown |
| $S_{11}$ |  | $C_{15}H_{10}N_2O_5$ | 298 | 123-124 | 61 | purple |
| $S_{12}$ |  | $C_{15}H_{10}N_2O_5$ | 298 | 110-111 | 57 | brown |



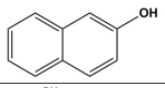
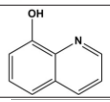
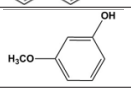
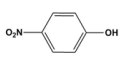

Scheme(1)

**Results and Discussion**

Ethyl Subistituded Aryloxy Acetate($S_{1-6}$)

These compounds(Scheme1) were synthesized using similar reported procedure[102] , and were characterized by the following main absorption bands ($\upsilon_{max}cm^{-1}$) at(3003-3198)for C-H aromatic,(2835-2971) for C-H aliphatic,(1628-1687)for C=O,(1048-1166) for C-O-C .The other absorption bands were shown in Table (3)

**Table 3: IR Spectral Data for Compounds ($S_{1-6}$)**

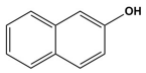
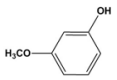
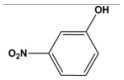
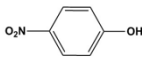
| Comp. No. | X = Phenol | C-H Ar | C-H aliph. | C=O | C-O-C | others |
|---|---|---|---|---|---|---|
| S1 |  | 3198 | 2952,2867 | 1678 | 1050,1144 | …… |
| S2 |  | 3013 | 2957,2871 | 1687 | 1077,1166 | C=N 1603 |
| S3 |  | 3100 | 2954,2849 | 1628 | 1056,1154 | …… |
| S4 |  | 3064 | 2953,2835 | 1655 | 1048,1150 | ….. |
| S5 |  | 3003 | 2971,2837 | 1672 | 1103,1158 | N-O Sym 1259 Asym 1410 |
| S6 |  | 3064 | 2922,2849 | 1638 | 1084,1105 | N-O Sym 1233 Asym 1387 |

$^1$HNMR for ($s_2$) compound as a representative of this series of intermediates showed triplet signal at (2.46 ppm) for $CH_3$,q. signal at (3.34 ppm) for $CH_2$ near Oxygen atom, doublet signal (with and opposite side of ring plane) resonated at (6.72-6.74 ppm) for $CH_2$ between carbonyl group and Oxygen atom while quinolone ring protons appeared at (7.05 ,7.13,8.22, 8.91 ppm)

**2-Aryloxy Methyl-3,1-Benzoxazine-4-One :($S_{7-12}$)**

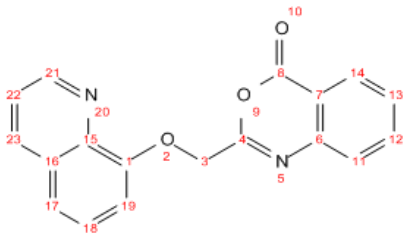
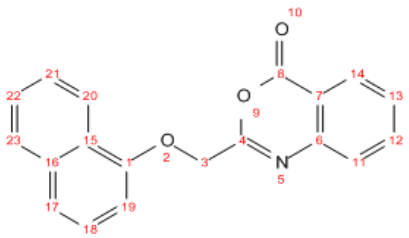
These compounds (Scheme1) were synthesized using similar reported procedure as it was mentioned in the experimental part. They are characterized by the following main absorption bands ($\upsilon_{max}cm^{-1}$) at (1045-1145) for C-O-C, (1452-1650) for C=C aromatic, (1650-1684) for C=N, (1684-1711) for C=O Table. 4 showed the details of all compounds spectral data below:

**Table 4: IR Spectral Data for Compounds ($S_{7-12}$)**

| Comp. No. | X = Phenols compounds | IR ν $cm^{-1}$ | | | |
|---|---|---|---|---|---|
| | | C-O | C=N | C=C Ar. | C=O |
| $S_7$ |  | 1045,1144 | 1670 | 1455,1606 | 1684 |
| $S_8$ |  | 1045,1145 | 1684 | 1455,1558 | 1697 |
| $S_9$ |  | 1078,1118 | 1663 | 1465,1599 | 1705 |
| $S_{10}$ |  | 1040,1146 | 1679 | 1468,1586 | 1696 |
| $S_{11}$ |  | 1071,1145 | 1650 | 1451,1650 | 1711 |
| |  | 1050,1127 | 1687 | 1453,1590 | 1684 |

Some selected compounds ($S_8$and$S_{10}$) as representative of this series were studied and revealed the following NMR results. Their proton assignment were referred to the carbon number of the aromatic rings as shown below:

**$^1$HNMR for Individual Compounds were As Follow:**

| Como.no. | Structure compounds | $^1$HNMR (PPM) DMSO-d6 |
|---|---|---|
| $S_8$ |  | 5.18 (s,2H)$CH_2$-O ;(7.04-7.05) (d,2H,$C_{12}$,$C_{13}$-H); (7.34-7.53)(t,2H,$C_{17}$,$C_{18}$-H) ; (7.60-7.78) (m,2H,$C_{22}$,$C_{23}$-H) ;(7.87-7.89) (m,1H,$C_{14}$-H) ;(8.04-8.05) (m,1H,$C_{11}$-H) ;8.65 (m,1H,$C_{21}$ –H) |
| $S_{10}$ |  | 5.23 (S,2H) $CH_2$-O ;(7.0 -7.02) (d,2H,$C_{21}$,$C_{22}$-H) ; (7.31-7.53) (m,1H,$C_{23}$-H) ; (7.64-7.68)(m,3H,$C_{11}$,$C_{12}$,$C_{13}$-H) (7.73-7.69) (m,2H,$C_{17}$,$C_{18}$) ; (7.74-7.75) (m, 1H,$C_{19}$,-H) |

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