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SYNTHESIS OF SOME DIAZINE AND TRIAAZOLE DERIVATIVES FROM FURFURAL

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Abstract

The synthesis of heterocyclic compounds especially when their structure containing nitrogen ,oxygen and sulfur atoms are growing up due to their wide spread in nature ,many mechanistic pathways to reach the target with nearly negligible loss of their dose and there are numerous me thods to derivatives their structures There for the development in hetero cyclic synthesis will provide new metabolic pathways when these compounds have succeeded to be used as drug ,Moreover it was known for long time that about 95 % of cancer drugs are heterocyclic compounds .There are also many methods found in the literature for the synthesis of both triazoles and trdiazines from different routes In this investigation furfural was used as precursor for the synthesis of some new diazine and triazole derivatives (3-11).The synthesized compounds were characterized by IR ,and 1HNMR and are discussed.

Keywords: Diazine; Triazine Derivatives; Synthesis; Furfural.

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1. Introduction

Heterocyclic compound are important class of organic chemistry due to their wide spread in nature and there is versatile ways to synthesize them and also many site are available of functionalization for a given structure. Different metabolic pathways of heterocyclic compounds associated with living organism encouraged researchers to introduce different ways for synthesizing these types of compounds ,These researchers spent much efforts to design these types of compounds as drugs[1-4].Since drugs needs to reach the target at certain time to penetrate through body tissue without interference with other cells and maintain it's does through this pathway. Accordingly, heterocyclic compounds were found to be used for many biological, clinical and pharmaceutical applications [5-7]. Furfural for example 2-(2-furyl) [1,3] dioxane,5-nito(1,3-imidazolyl-2,5-dion)-3-yl furfurlidine was found to be used for treatment of urinary tract [8-10] also furfural derivatives were used for different biological applications[11,12] It was also known that many triazoles and diazines compounds were synthesized from different routes[13-16] . Some heterocyclic

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compound derived from furfural were prepared previously [17] and here we are going to complete this work by using furfural as precursor for other new heterocyclic compounds which might find an applications as drugs ,since Triazoles such as fluconazole, Isavuconazole, Hexaconazole, epoxiconazole, difenoconazole, tebuconazole etc.,) were commercially used as a fungicidal drugs[18]. In this investigation we use furfural molecule as a core compound for heterocyclic synthesis including diazoles ,triazoles so that to increase their activity through introducing furfural moiety toward their synthesis in a way that will make them suitable for this type of studies which will be investigated in our next work .The synthesized compounds were studied by IR and one of them by ^{1}HNMR and used for elucidating their structures..

2. Experimental

Melting point were measured using electrothermal melting point apparatus type IR spectra were measured using Infra-red spectrophoto meter model Tensor 27 Bruker 1HNMR spectra were performed using Bruke 400 MHz. All chemical compound were supplied by Aldrich, Fluka,BDH chemical companies . Compound 1 was prepared using the published procedure [19], compounds 2 was prepared following the else were published procedure [20], Their mp. and IR ,^{1}HNMR spectra were the same of the published one.

2.1. Synthesis of 5-Bromo-6-phenyl-2-benzoyl pyridine-3(1H) one (3)

This compound was prepared following similar procedure [21], A mixture of 0.02 mal ,5.02g of compound (2) and (0.02 mal ,3.739g) of benzoyl chloride in 100 ml of dry benzene was refluxed with continuous stirring for 24 hour under dry condition. The solvent was evaporated under reduced pressure. The residue was dried and crystallized from ethanol to afford brown powder mp. 194-196°C ,65% yield.IR :1697 cm^{-1}, 1658 cm^{-1} ,1496-1621 $cm^{-1}$and 870 cm^{-1}.

2.2. Synthesis of 5-Bromo-2-(chloro methyl)-6-phenyl pyradazin-3-(2H)-one (4)

A mixture of (0.01 mol. ,2.5 g.) of compound (3) and paraform aldehyde 1.5 g. And 3ml of thionyl chloride in 50 ml of dry benzene was refluxed for one hour, cooled and filtered, the filterate was then evaporated under reduced pressure. The white solid residue with mp. 273-275°C, 60%yield was used without further purification .IR:1655 cm^{-1} ,1444-1635 cm^{-1},702 cm^{-1}

2.3. Synthesis of 3-(substituted phenyl) -(1H)-1,2,4-triazole-5-thiol (5)

Benzoyl chloride or 4-nitrobenzoyl chloride (0.02 mol) was gradually added to a mixture of 0.02 mol. ,1.8g.) of thiosenicarbazide in 25ml of dry benzene after complete addition ,the reaction mixture was left at room temperature for 4 hours .sodium carbonate 1 mole was then added .the final mixture was refluxed at 100°C for 16 hours ,cooled and water was then added ,the p.pt was filtered and dried ,recrystallized from water ,mp. for 5a 255-265°C, 63% yield as white solid, 5b 2mp=205-207°C also as white sold 56% yield. IR :3205, 1666 cm^{-1}, 1460-1625 cm^{-1}, 1288 cm^{-1}, 1307 cm^{-1} and 154 cm^{-1}.

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2.4. Synthesis of 5-Bromo-6-phenyl-2- [5-substituted phenyl] -(1H)-1,2,4-triazol-2-yl thio methyl pyradazin-3(2H)-one (6)

Compound 5a or 5b (0.002 mol.) in 30 of acetone was mixed with compound (4),(0.002 moh) and 0.5g. of potassium carbonate ,after complete addition the reaction was refluxed for 2 hours ,filtered the filterate was evaporated under reduced pressure .the solid residue was then crystallized from petholeum ether/ ethylacetate mixture, mp. of compound a 116-118°C, yield 55 while for compound b,mp. =109-11°C, yield 52% as yellow crystals. IR: 3361-3070 cm^{-1}, 1699-1698 cm^{-1}, 1647-1641 cm^{-1}, 1685-1633 cm^{-1}, 617-573 cm^{-1}, and 1514, 1321 cm^{-1}.

2.5. Synthesis of 4-Bromo-6-phenyl pyradazin-3-(2H)-one (7)

Compound (3),(0.02ml ,5.02g.) and 0.02mol.,2.73g. of benzoyl chloride in 100ml of dry benzene ,the reaction mixture was stirred for 12 hour under dry conditions ,the solvent was evaporated under reduced pressure, the residue was dried and recrystallized from ethanol, the brown crystal has mp of 196-199°C and 65% yield. IR:1697 cm^{-1}, 1658 cm^{-1}, 1496-1621 cm^{-1} and 870 cm^{-1} .

2.6. Synthesis of 5-Azido-6-phenyl-2-benzoyl pyridazin-3(2H)-one (8)

A mixture of (0.005 mol.,1.8g.) of compound(7) and 0.01 mol. 0.65g. of sodium azide in 10ml of acetonitrite, the mixture was left at r.t for 24 hour.,25 ml of water was then added after this period .the final mixture was extracted with ether, the ether layer was then washed with 5% solution of sodium thio sulfate then with water . the solvent was evaporated under reduced pressure resulting in the formation of with solid which was recrystallized from methanol to give white powder mp 137-139°C, yield 62%, IR: 2154 cm^{-1}, 1655 cm^{-1} and 1456-161 cm^{-1}.

2.7. Synthesis of 2-Benzoyl-3-phenyl-5-N (substituted triazoyl) pyridazin-3(2H)-one (9-11)

Alkyne or alkene compound (0.01 mol) was added to a mixture of (0.005ml., 1.6g.) of compound(8) dissolved in 30ml. of dry acetone .the mixture was refluxed for 12 hour under dry condition cooled ,evaporation of the solvent under reduced pressure affords solid product which was recrystallized from ethanol, the product and yields are as follows; for compound 9,,mp 187-189°C ,60% yield ,compound 10 mp. 276-278°Cyield 70% while compound 11, showed a mp of 211-213 °C, 57% yield as brown and yellow crystals respectively IR :1661-1640 cm^{-1}, 1439-1601 cm^{-1}, 1352-1437 cm^{-1}.

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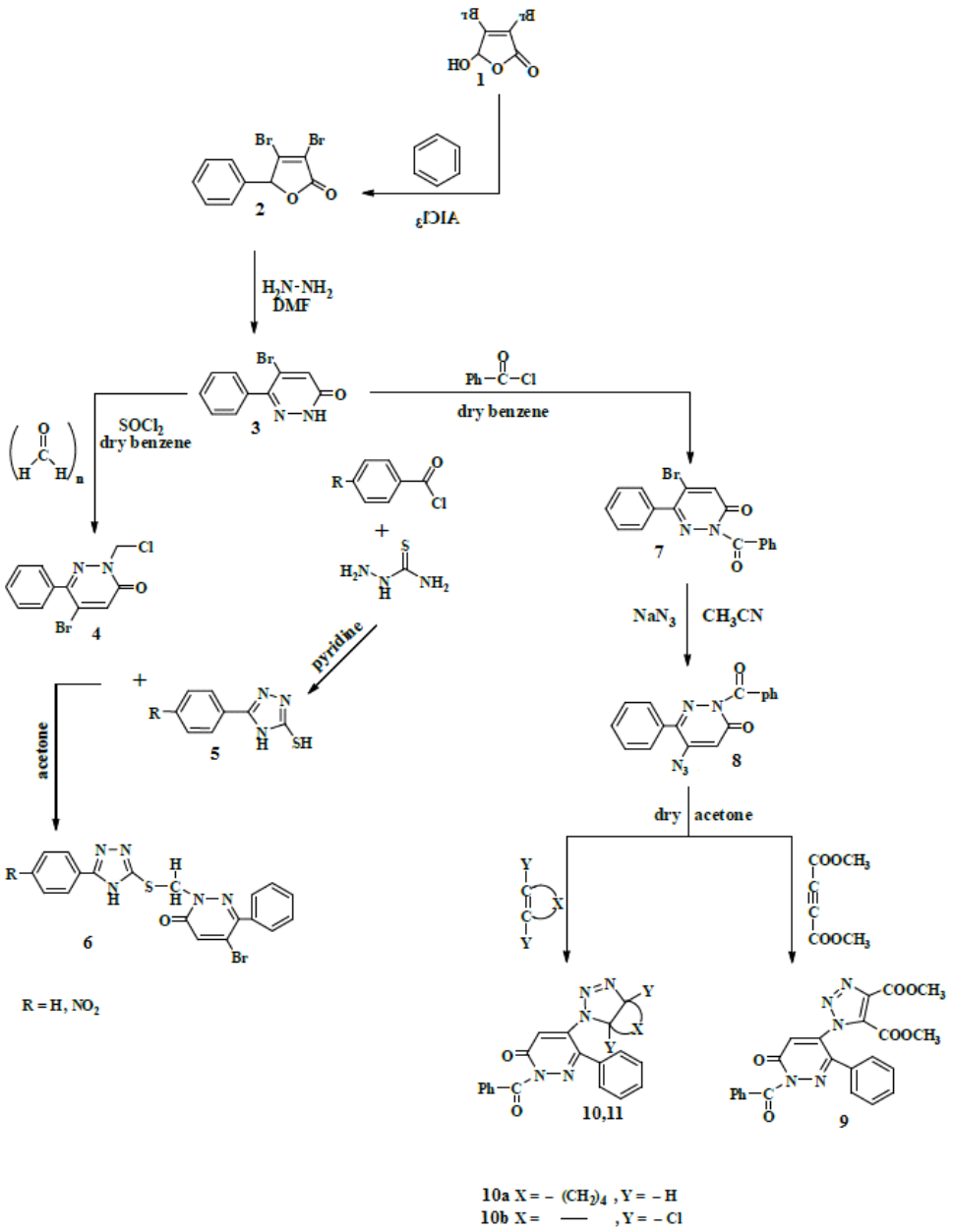

Scheme 1

3. Results and Discussion

3.1. 5-Bromo-6-phenyl pyridin-3(2H)-one (3)

This compound was prepared from treatment of compound (2) with bydrazin in DMF as shown in scheme (1). It is characterized by the following IR absorbation bands 32975 cm^{-1} for NH,1695 cm^{-1} for C=O,1456-1601 cm^{-1} for C=C aromatic, C=N while C-Br streching vibration observed at 870 cm^{-1}. ^{1}HNMR spectrum showed the following signals 12.4 ppm for NH proton as singlet, 7.41-

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7.54 ppm. for benzene ring(5H), 5.94ppm for pyridazine ring proton as singlet signal., 3.57 and 2.51ppm belongs to OH proton (enolic proton).

3.2. 5-Bromo-2-(chloro methyl)-6-phenyl pyradazine-3-(2H)-one (4)

The above compound was prepared from the treatment of compound (3) with thionyl chloride and with paraformaldehyde as it was stated in the experimental part. This compound was characterized by IR cm^{-1} 1655,1444-1635,702 for C=O, C=C aromatic, C–Cl respectively.

3.3. 5-Bromo-2-(chloro methyl)-6-phenylm pyradazine-3(2H)-one (5a, b)

IR characterization of these compounds were as follows:
3205 cm^{-1} for NH ,1666 cm^{-1} for C=N while the aromatic protons absorbed between 1460-1625 cm^{-1} and C=S at 1288 cm^{-1}, NO_2 absorbation bands for sym. And a ssym. Appeared at 1307,1514 cm^{-1} respectively.

3.4. 5-Bromo-6-phenyl-2- [(5-substituted phenyl-(1H)-1,2,4-triazol-2yl thiomethyl pyradazine-3-(2H)-one (Ga,b)]

IR characterization of this compound showed the following absorption bands:; 3070-3361 cm^{-1} for NH ,1698-1699 cm^{-1} related to C=O while the C=N appeared at 1641-1647 cm^{-1} , the aromatic absorption bands appeared between 1485-1633 cm^{-1},C–S at 573-617 cm^{-1} and finally the NO_2 streching sym and assym . at 1321-1514 cm^{-1} respectively.

3.5. 5-Bromo-6-phenyl pyradazine-3-(2H)-one (7)

This compound was prepared from the reaction of compound (3) with benzoyl chloride as shown in scheme (1). It is characterized by the following IR absorption bands : 1697 cm^{-1} for C=O of pyradazine ring ,1658 cm^{-1} for C=O benzoyl amide group and 1496-1621 cm^{-1} for aromatic and C=N which appeared within the same region and finally C–Br absorption at 870 cm^{-1}.

3.6. 5-Azido-6-phenyl-2-benzoyl pyradazine-3(2H)-one (8)

The above compound was prepared from sodium azide and compound (7) as listed in the experimental part of this work.

IR characterization of this compound showed the following absorbation bands cm^{-1},2154,1697,1655,1456-1601, for N_3, C=O of pyradazine ring, C=O of benzamide group while C=N, C=C for aromatic appeared within the same region.

3.7. 2-Benzoyl-6-phenyl-5-N (substituted triazoyl) pyradazine-3(2H)-one-(9-11)

The above compounds were prepared from the treatment of compound (8) with Dimethyl cyclohexene, acetylene dicarboxylate (DMAD) and dichloro ethylene as it was stated in the experimental part the reaction involve 1,3-diplor addition between (DMAD) and the azido group resulted into the formation of the corresponding triazoles. compound (9) as shown in scheme (1)

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Compound (9) was afforded by treatment of cap (8) with DMAD while compounds 10 and 11 were obtained by treatment of compound (8) with cyclohexene and dichloro ethylene respectively. All compounds were characterized by the following IR main absorption bands :
cm^{-1}: 1640-1661 for C=N and C=O of amide group while the aromatic C=C absorbed within the same of C=N region the ester stretching bands appeared at 1739 and finally the C-Cl stretching band absorbed at 721 Cm^{-1} .

4. Conclusion and Recommendations

We conclude from the above study that triazole ,compound(5)when allowed to react with furfural derivative compound (4) resulted into the formation of new type of triazoles (6a and 6b) while compound(7) which is derived from furfural when allowed to react with sodium azide it forms azidido derivative which intern allowed to react with alkenes or alkyne they cyclized into new triazole derivatives(10a,b and 11) These compounds are new nitrogen based heterocyclic compounds. We knew as stated before that nearly 65% of anti - cancer drugs granted market approved by FDA between 210-1015 are heterocyclic compounds and about 95% of heterocyclic compounds are drugs so this type of compounds drew attention of researchers to synthesize this valueable compounds. In our work we have synthesized the above heterocyclic compounds having new nitrogen-based heterocycles which need further studies.

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