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Research Article

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Synthesis of Some Heterocyclic Compounds Derived from Furfural

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Abstract

We know that most heterocyclic compounds are drugs or co- drugs. In our investigation furfural was used as a precursor for heterocyclic synthesis, either by ring opening of furfural going to pyrimidine derivative E3 then functionalizing this pyrimidine into its derivatives E8, E10 and cyclization into oxadiazole and thiadiazoles E8, 11. Or the reaction of pyrimidine with dimedon derivatives to afford dimedino pyrimidine derivatives. The second pathway involve the synthesis of oxamyl derivative of pyrmidine E21-25 these compounds were cyclized into new oxadiazoles E24-26. The third pathway involve the synthesis of mucobromic esters E27-29 from MBA acid then these esters were converted into the correspondig lactones E30-32 and E32-36 while reacting MBA with amines affording N-alkyland N-amidolactams. The last pathway was the reaction MBA with methanol, sodium azide to give azidointermeddiate which was cyclized with alkene or alkynes into triazole derivatives E42-49. The synthesized compounds were characterized by IR and some ^{1}HNMR measurements.

Keywords: Synthesis, Furfural, Heterocyclic Compounds

Introduction

Background

Furfural first time known in 1840 when Scottish scientist J.Stenhouse found that corn ash and wood treated with dilute sulfuric acid yield furfural compound Furfural was also extracted from rice straw and from palm fiber using hydrochloric acid, Quaker oat company was then succeeded in producing furfural industrially in large scale production [1-4]. After that time china and South Africa became the most countries in production of furfural. In the same year Binder et al.were also synthesized furfural from xylose and xylan [5]. In 2012 Ambalkar and Talib have succeeded in synthesizing furfural from lignocelluloses biomass as agricultural residues [6]. Warkasi and Naidoo in the same year succeeded in production of furfural from epic rap of wild mango [7].

The biological application of furfural compounds

Furfural was used as starting material for synthesizing many intermediate chemical including MCA, MBA ,4,5-Dibromo furfuraldehydle, 2-(2-furyl) [1,3] dioxane,5-nito(1,3-imidazolyl-2,5-dion)-3-yl furfuraldine which was used as drag in treatment of urnary tract [8-10]. The other application of furfural derivatives is the enzymatic inhibition of brostaclanidine by benzimidiazolyl derivative [11,12]. While S-Alkyl-3-Aryldihydro-2-(3H) one derived from (MBA) was used as anti fungal agent [13]. Thiazolyl furylhydazones were prepared from alkyl furyl ketones and thiosimicarbazide using ethyl bromopyrovate. These compounds showed significant biological application [14]. Thiazole, Thiadiazole, oxadiazole and triazole compounds themselves have been found to have many biological applications and as drugs pyridine, pyrimidine and pyradizine compounds were also found to have certain biological activities as well as drags [15-23]. As it was investigated above through this introduction, furyl derivatives are biologically active compounds and so as 5, 6-membered rings had biological applications and as drugs, so in our present work we use furfural in synthesizing new derivatives of this nucleus including diazoyl, triazoyl. Thiadiazolyl, oxadiazoyl, thiazoyl and pyridine derivatives. These new compounds might have important applications as drugs. In our next work we will investigate their antibacterial screening activates as a reliminary step for drug discovery regarding these types of compounds.

Experimental

All melting points were measured using Electrothormal9300 melting point apparatus. The chemicals were supplied by Aldrich, Fluka and BDH companies' .IR spectra were measured using infrared spectrophotometer model FT (8400s) Shimadzo company.1HNMR spectra were recorded using Bruker400MHz Tocat/gaziosmanpasa University (Turkey). Mucobromic acid (MBA) was prepared according to the published paper, S-methyl isothiourinum sulfate and 5-bromo-2-methyl thio pyrimidine-4-carboxylicacid were prepared according to else were published procedures [24-26]. The acid chloride and its ester derivative were prepared following the same published procedure while compounds E4,E5 and E6 were prepared following the same or similar published procedures [27,28]. Compounds E7-E9 were prepared using similar procedures [29-31]. The above prepared (E4-E9) compounds were found to have the following melting points, 125-124°C, yield of 80%, 235°C, yield of 75%,176-178°C, yield of 30%, oil, yield 60%, 63-65°C, yield

53%, 105-107°C, yield 60%, oil, yield 65%, 119-121°C, yield 60% and 150-152°C, yield 50% respectively Compounds E37a was prepared following the same published procedure, E_{37b} was prepared according to a similar published procedure with mp of 70-72°C , yield 80%. These intermediate compounds were checked by IR after purification [32,33].

Synthesis of 2-Methyl sulfonyl-4-(N-formylcarbohydrazido)-5-bromo pyrimidine (E_{10}) [34].

E7 compound (0.01md.3gm) was dissolved in 20 ml. of formic acid. The mixture was then refluxed for 30 min; evaporation of the solvent, the solid product was collected and recrystallized from ethanol giving wellow crystals, mp 160-162°C, yield 70%.

Synthesis of 2-Methyl sulfonyl-5-bromo-6-(1,3,4-thiuzol-5-yl)-1,3-pyrimidine (E_{11}) [34].

Compound E10 (0.01mol, 3.2g.) was dissolved in 5 ml. Xylene. To this mixture (0, 01mol. 2.2g) phosphorouspenta sulfide was added .The mixture was stirred and refluxed for 60 min. evaporation of the solvent and addition of 10 mil of water and extracting the product with chloroform. The chloroform was then evaporated giving brown precipitate. Recrystallization from ethanol affording pale-brown crystals, mp. 140-142°C, yield 53%.

Synthesis of 3-(4-Aryl amino) 5,5-dimethyl cyelonex-2-enone (E_{12-14}) [35].

Substituted aniline (0.05 mol.) and dimedon (0.05 mol) were dissolved in dry benzene. The mixture was refluxed for 3h. The progress of the reaction was monitored by TLC.Aftercompletion; the reaction mixture was left to cool to r.t, mixed with ether and stirred for 15-20 min, filtered and washed with ether and dried then crystallized from it. The melting point were found 207-208°C , 75% yield ; 160-162°C, yield 75 and 200-202°C, yield 73% as yellowish to white ,Brown and yellow products respectively.

Synthesis of 5-Bromo-N-(4-aryl)-N-(5,5-dimethyl-3-oxo cyclo hex-1-enyl)-2-(methyl thio) pyrimidine-4-carboxamide(E_{15-17}) [36].

Compounds (E_{12-14}), 0.01 mol. were dissolved in 25 ml. of dry benzene. To this mixture was then added (0.01 mol.,1g.) of TEA. The find mixture was then added to mixture of compound E4 in 25 ml of dry benzene gradually with continuous stirring under dry condition at r.t. The mixture was then refluxed for 24h. And left to cool, filtered and washed with 50 ml. of water. The organic layer was extracted and dried using an hydrous Na2SO4. The solvent was evaporated, the residue was crystallized from ethanol. Melting points of the above compounds 264-266°C yield 60%, 217-218°C, yield 64% with Brown, Brown and red respectively.

Synthesis of substituted amidoxime (E_{18-20}) [34].

Nitrile compound (acetonitrile or valeronitrile or benzyl nitrile) (0.1 mol.) was dissolved in 100 mil of 50% ethanol. To this solution 21.2g.of sodium carbonate was added then 27.8g. of hydroxyl amine hydrochloride. The final mixture was refluxed on water bath for 90 min , evaporation of the solvent and the residue was collected and re crystallized from ethanol affording the find crystals as white , coreless oil and yellow having mp 132-134°C , yield 72% , oily and 65-67°C yield 75% respectively .

Synthesis of 2-methyl thio-5-bromo-6-(substituted amino oxamyl)-1,3-Pyrimidine-4-carboxylate (E_{21-23})

Amidoxime compound (E_{18-20}), 0.002 mol. In 10 mil of chloroform was mixed with compound E3 (0.0022 mol. , 0.5g.) of Dcc. The mixture was stirred for 60 min at r.t. The final mixture was then filtered and the residue was re crystallized from benzene / petroleum ether (80-60°C). Affording white crystal of the above compounds with m.p 185-187°C, yield 65%, 190-192°C, yield 70% and 194-196°C, yield 73% respectively.

Synthesis of 2-methyl thio-5-bromo-6-(3-substituted 1,2,4) oxa diazole)-5-yl-1,3- pyrimidine(E_{24-26})

Compound (E21-23), 0.1 mol. was mixed with 25 ml. of dry DMSO. The mixture was there refluxed for 5h, cool and filtered. The residue was re crystallized from water affording Brown crystals of the above compounds having mp 140-142°C, yield 60%, 100-102°C, yield 65% and 180-182°C, yield 68% respectively.

Synthesis of 5-substituded -3,4-dibromo crotono lactone carboxyl ate(E_{27-29}).

Compound (E0.02 mol.) was dissolved in 100 ml of dry benzene was added (0.02 mol.) of compound (acetyl chloride or 4-nitrobenzoyl chloride or benzoyl chloride). The final mixture was refluxed with continuous stirring for 24h. Under dry condition, cooled and the solvent was evaporated under reduced pressure, giving the final product as oil for E_{27} and white solid for E_{28} mp. of 118-120°C, yield 72% while yellow for E_{29}m.p, 152-154°C, yield 74%.

Synthesis of (5-substituded amino) -3,4-dibromo crotono lactone (E_{30-32})

Compound (E_{27} 0.01 mol.) dissolved in 50 ml of toluene was mired with (Ethyl amine or isopropyl amine orcyclohexyl amine) the mixture was stirred for 20 h. at r.t. evaporation of the solvent afford the titled compounds in which E_{30} was oily while E_{31} and E_{32} were yellow solid products after recrystallitation from ethanol. mp of E_{31} was 96-98 °C, yield 65% while for compound E_{32} 102-104 0C yield 62%.

Synthesis of 2-methoxy-3-N-substituded triazolyl-4-bromo crotono lactone (E_{33-36}) [37].

Compound (E_{46} 0.005 mol.) was dissolved in 30 ml of dry acetone this solution was then added to a solution of DMAD or cyclohexene or Trans 1,2-dichloro ethylene 0.01 mol. The final mixture was refluxed for 12 h. under dry condition. Evaporation of the solvent, removed of the solvent afford a solid product which was recrystallized from ethanol. mp 102-104 °C, yield 65% as brown crystals, 140-142 °C, yield 66% as gray crystals ,110-112 °C yield 60% gray crystals respectively.

Synthesis of 3,4-dibromo-5-hydroxy-1-substituted -3-pyroline-2-one (E_{37-40})

Compound E_{37a} (0.003 mol., 0.8 g) dissolved in 25 ml of dioxane was gradually added to a cold solution of 0.006 mol. of amine dissolved in 10 ml of dioxane .The mixture was stirred for 15h at r.t. After the completion of the reaction (monitored by TlC) 25 ml of water was then added and extracted by 100 ml of CH_2Cl_2 .The organic layer washed with (^{1}NHCl) then with saturated NaCl solution, charcool. And filtered. Evaporation of the solvent to minimum amount and addition of n-hexane resulted in to the precipitation of the product which was then recrystallized from chloroform affording the final product for E_{38} mp. of 102-103°C as white crystals 72% yield while for E_{39} mp 118-120°C as yellowish white crystals, 55% yield and E_{40} mp 177-179°C, 63% yield as yellowish white product.

Synthesis of -1- substituted amindo-3,4- dibrome-5-hydroxy-3-pyroline-2-one (E_{41-44})

Compound E_1 (0.003 mol., 0.77g) was dissolved in 20 ml of ethanol, to this solution was added (0.03 mol) of methyl urea or ethyl urea or thiouria or phenyl urea. The final mixture was refluxed for 3hr in a water bath. Evaporation of the solvent under reduced pressure to a minimum amount and addition of 50 ml of water then extraction with 100 ml CH_2Cl_2 ,dried on Na_2So_4 anhydrous and evaporation of the solvent resulted into the formation of the precipitate which was recrystallized from chloroform forming E_{41} as white crystal, mp 241-243°C, 70% yield, E_{42}, white crystal mp 181-183°C, 75% yield while E_{43} formed as yellow crystal m.p 159-161°C, 55% yield and E_{44} as red crystal mp 145-148°C,63% yield .

Synthesis of 3,4-dibromo-5-methoxy crotono lactone (E_{45})

Conc. sulfuric acid (0.1 ml) was added to a solution of (0.025mol, 6.5g) E_1 dissolved in 10 ml methanol. The final mixture was refluxed for 24hr. After completion 30 ml of water was added the compound was extracted with benzene, washed with saturated soln. of sodium carbonate, dried on anhydrous Na_2SO_4, Evaporation of the solvent under reduced pressure resulted into the formation of an oily yellow compound which was used in next step.

Synthesis of -4-azido-3-bromo-5-methoxy crotono lactone E_{46}

Compound E_{45} (0.0413 mol. 11.23g) dissolved in 75 ml methanol .To this solution (0.0413mol.,2.7g) of sodium a zide was added. The mixture was stirred at r.t. for 60 min, addition of water cause to the formation of white precipitate, washed several times with cold water, mp 70-72°C, 80% yield.

Synthesisof-2-methoxy-3-N-substituted triazolyl -4-bromocrotono lactone (E_{47-49})

A mixture of compound E_{46} (0.005 mol,1.17g) dissolved in 30 ml of dry acetone and 0.01 mol of alkyne or alkene compound were refluxed for 12hr under dry conditions. The mixture was cooled ,Evaporation of the solvent affording final crude precipitate which was recrystallized from ethanol . the following physical properties was obtained :E_{47} as brown crystals mp 102-105°C, yield 65, E_{48} gray crystals mp 140-143°C, 66%yield and E_{49} as gray crystasmp 110-113°C, 60% yield .

Results and Discussion

Hydrazide comp (E_7) was prepared from its ester (E_6). This compound was checked by IR which showed the following absorption bands 1651cm^{-1} for C=O, 3188-3340 cm^{-1} for NH, 1632 cm^{-1} for C=N and the aromatic C…C absorbed at 1550 cm^{-1}, S=O at 118,1323. Compound E8 IR data are 3310,3165 cm^{-1} for stretching vibration of NH,1637 cm^{-1} for C=N,1526 cm^{-1} for AromaticC…C,1286 cm-1 for C=S, 1193,1343 for S=O group.

Compound E_9 was prepared from the cyclization of the corresponding thiosimicarbazide using AgO reagent. The compound showed the following absration bands, 3234 cm^{-1} for NH, 1178-1254 cm^{-1} for C-O-C, 1601 the carbonyl group and thion belongs to thiosimicarbazide.

2-methy sulfonyl-5-bromo-6-(2-1,3,4-thiadiazole)-5-yl-1,3-pyrimidine(E_{11}) was prepared from the reaction of E_7 with formic acid to afford compound E_{10} which was cyclized into the titled compound. Compound E_{10} was characterized by the following IR absorption bands 1689 cm^{-1} for C=O of formaide and 3200 cm^{-1} for NH. While the final compound E11was characterized by IR absorption band at 1623 for C=N stretching vibration and 863,1153 cm^{-1} for C-S-C symmetric and asymmetric types.

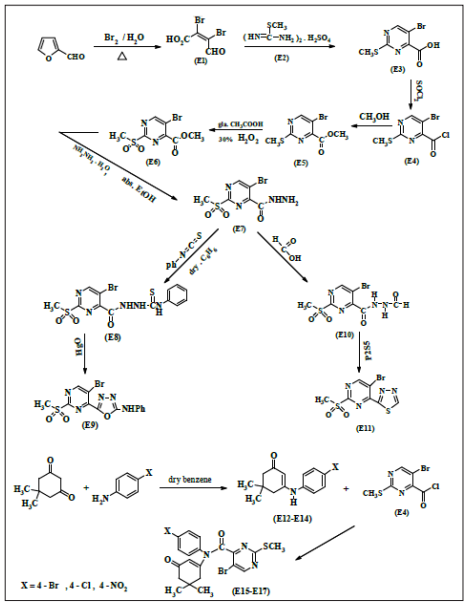
5-bromo-N-(4-Aryl)-N-(S,5, dimethyl-3-oxo-1-cyclohexenyl-2-methyl thio pyrimidine-4-carboxanide (E_{15-17})

The first step of preparing of these compounds was the formation of E_{12-14} through the reaction of substituted aniline with dime done. These compounds were characterized by IR spectra. The main characteristic bands were 3061-3241 cm^{-1} belongs to NH, 1609-1618cm^{-1} belongs to C=O stretching and C…C aromatic apparel at 1459-1593 cm^{-1}.

The second step involves the reaction of E_{12-14} with compound E_4 as shown in schem1. The final compounds were characterized by the following IR absorption bands 2950, 2960 cm^{-1} belongs to aliphatic C-H stretching, 1665 cm^{-1} and 1735 cm^{-1} belong to C=O while amide C=O appeared at 1651,1671 cm^{-1}. The aromatic C...C and C=N appeared within the range of 1601-1627 cm^{-1} which were undistinguishable from the conjugated C=C and the kenotic band.

2-methyl thio-5-Bromo-6-(3-Substituted-1, 2, 4-Oxadiazole-5-yl 1, 3-pyrimidine (E_{24-26})

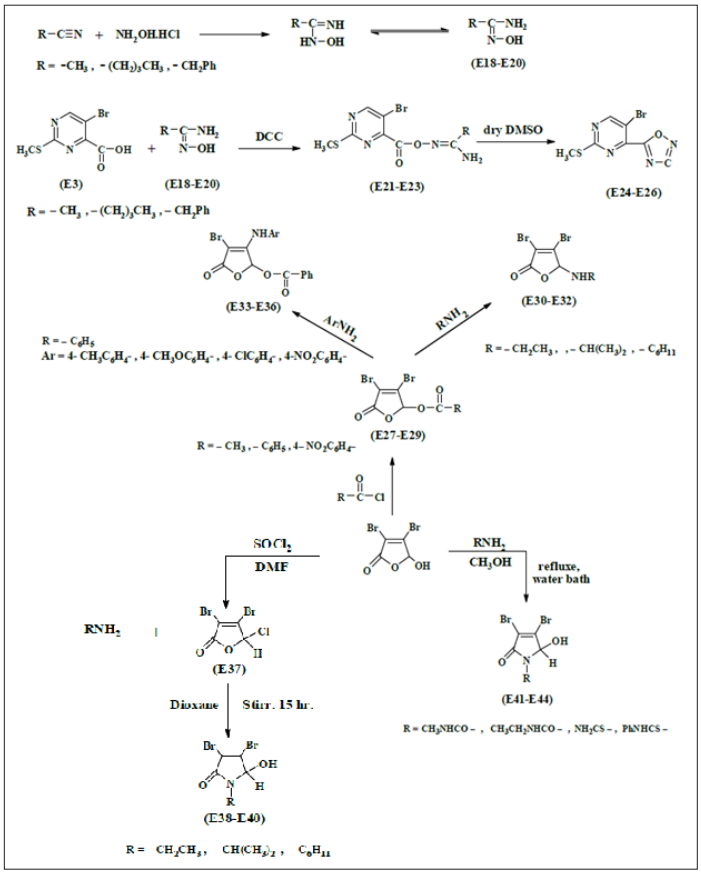
The compounds were also prepared by three steps. Step one is the preparation of amidoxirne compounds E_{18-20} from the reaction of some nitrile compounds with hydroxyl amino hydrochloride. Comps. E_{18-20} were confirmed by IR spectra and the melting points in comparison with that published [28-38]. The second step is the reaction of these amidoxime compounds with E_3 compound in presence of DCC as shown in scheme 1. The IR spectra of these compounds characterized by the following absorption bands 3244-3327 cm^{-1} for NH,1710-1718 cm^{-1} for C=O ester with C=N appeared at 1658-1670 cm^{-1} and the aromatic appeared at 1425-1602 cm^{-1}while C-O appeared at 1018-1140 cm^{-1}. The third step in synthesizing the above compounds (E_{24-26}) was the cyclization into the corresponding final products. These final compounds were characterized by IR and the main absorption bands were as following : 1616-1653 cm^{-1} for C=N, C…_C aromatic at 1432-1596 cm^{-1} while N-O at 1250-1311 cm^{-1} and C-O at 1087-1045 cm^{-1}.



Scheme 1

5-subsituted amino 3, 4-dibromo crotono lactone (E_{30-32})

These compounds were synthesized from the reaction of compound E1 with each of (acetyl chloride, benzyl chloride and 4-nitro benzyl chloride) as mentioned in the experimental part of this work and as shown in scheme 2. The products were characterized by the following IR absorption bands: 1764-1798 cm^{-1} for lactone C=O and at 1682-1750 cm^{-1} belongs to C=O stretching of ester. The aromatic C…C was appeared within the range of 1450-1588 cm^{-1} while C-O stretch appeared within 1120-1144 cm^{-1}. These products E_{27-29} were allowed to react with ethyl amine, isopropyl amine and cyclohexyl amine affording the titled compounds. These final compounds were characterized by the following absorption bands;3310-3368cm^{-1}related to NH stretch , 1765-1775 cm^{-1} to C=O lactone while C=C appeared at 1615-1621 cm^{-1}, C-O at 1119-1125 cm^{-1} and C-N at 1049-1090 cm^{-1}.



Scheme 2

4-Aromatic amino-3-bromo-5-benzeyl oxy crotono lactone (E_{33-36})

These compounds were synthesized by the nucleophilic displacement of-5-bromo substituted of the lactone ring with the aromatic amino group. The compounds were characterized by the following IR absorption bands : 3132-3394 cm^{-1} belongs to NH stretch , 1743-1779 cm^{-1} for C=O lactone ,1738-1685 cm^{-1} for C=O ester, C=C non aromatic appeared of 1610-1618 cm^{-1} while the aromatic C=C of 1426-1611 cm^{-1} and C-O at 1180-1192 cm^{-1} .

^{1}HNMRspectrumof compound E_{33} showed the following δ signals: 8.58-9.71ppm 5H aromatic protons of the benzyl group,7.45-7.47ppm AB quartet for p-methyl aromatic ring Protons , 6.8 pp(s) 1H of lactonic protons , 3.57 ppm 1H for NH proton and singlet 3H at 2.5 ppm assigned for CH_3 of the phenyl ring which is coinside with the DMSO(solvent) signal.

1HNMR spectrum of compound E36 showed the following resonating signals:
Atδ 8.26 ppm 4H (q) assigned for aromatic ring at position 4 of lactone ring appeared as AB quartet, δ 6.6, 6.94 ppm 6H (m) for the aromatic benzoyl group. and at δ 5.14 1H(s) for NH.

3, 4-Dibromo-5-hydroxy-1-1substitued -3-pyroline-2-one (E_{37-40})

These compounds were synthesized in two steps. Step one include the preparation of 3,4-Dibromo-5-chloro crotono lactone (E_{37b}) from the reaction of compound (E1) with thionyl chloride , this compound was characterized using IR spectral data and its melting point which was the same as the published one32 .In step two compound E37a was allowed to react with either ethyl or cyclohexyl or isoproxyl amine . The reaction involve ring opening and closer forming the above titled compounds see scheme 2 .These final compounds were characterized by IR spectroscopy which showed the following absorption bands : 3257-3356 cm^{-1} for OH ,1720-1741 cm^{-1} for C=O ,C=C at 1631-1641 cm^{-1} while C-O at 1219-1240 cm^{-1} and C-N at 1093-1111 cm^{-1}, ^{1}HNMR for compound E_{38} showed the following δ signals:1.10 ppm 3H(t) for $-CH_3$ group, 2.51 ppm 2H for CH_2 protons, 3.48 ppm (s) 1H for OH proton, 5.44 pp(s) 1H for ring proton.

1-Substituted amido -3, 4-dibromo-5-hydroxy-3-pyroline-2-one (E_{41-44})

These compounds were prepared by reacting mucobromic acid E1 with methyl urea, ethyl urea and phenyl urea see scheme 2. The final compounds were characterized by IR,1HNMR spectroscopy.

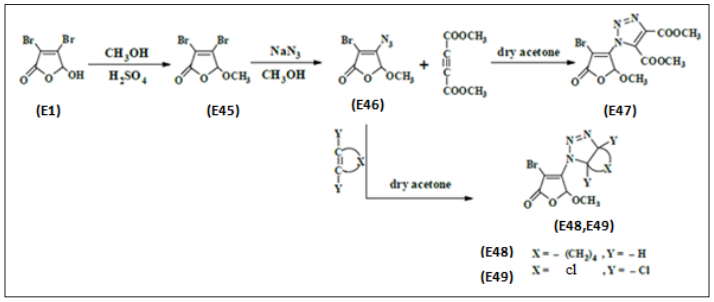
IR spectral data showed the following absorption bands:
3350-3423 cm^{-1} for OH, 3161-3282 cm^{-1} for NH, 1710-1710 cm^{-1} for C=O lactam , C=C appeared of 1610-1615 cm^{-1} and C-O at 1230-1259 cm^{-1} while C-N at 1060-1191 cm^{-1}.

1HNMR for compound E_{42} showed the following resonating signals : δ value 1.15 ppm (t) 3H for CH3 protons, 2.51 ppm (s) for (OH), 2.8 ppm (s) 1H for lactons proton, 3.35 ppm (q) 2H for CH2,8.94 ppm (s) 1H for NH. while ^{1}HMR for compound E_{44} showed the following signals in δ value :2.51 ppm (s) 1H for OH coinside with the DMSO signal, 3.32 ppm (s) 1H for lactono rig proton, 7.3-7.4 ppm (m) 5H for benzene ring protons, 9.66 ppm (s) 1H for NH proton [38].

2-methoxy-3-substuted triazolyl-4-Bromo crotono lactone (E_{45-49})

These compounds were synthesized by two steps, see scheme 3, the first one involves the preparation of 3, 4-dibromo-5-methoxy crotono lactone E_{45} by methylation of E_1 with methanol in sulfuric acid while compound E_{46} was obtained from the reaction of E_{45} with sodium azide. This intermediate was characterized by IR through the following absorption bands: 1237 cm^{-1} for azide group, 1772 cm^{-1} lactone C=O, 1639 cm^{-1} for C=C and 1304 cm^{-1} for C-O.

In step 2 compound E_{46} was allowed to react with dimethyl acetylene carboxylate ,cyclohexene and trans 1,2-dichloro ethylene respectively affording the final compounds E_{47-49}.These compounds were characterized by the following IR spectral data: 1734-1776 cm^{-1} for C=O lacton, 1608-1629 cm^{-1} for C=C, 1377-1438 cm^{-1} for N=N while N-N appeared at 1204-1253 cm^{-1}.



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