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Synthesis of Some Heterocyclic Compounds Derived from Furfural Using Ultrasonic Waves

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ABSTRACT

Heterocyclic compounds especially those with Oxygen and Nitrogen atoms have shown many applications in chemotherapy as anti-cancer drug, anti-depression, anti-viral, anti-microbial as well as many other medical applications. In our investigation we use ultrasonic technique for preparing heterocyclic compounds mainly compounds E_4, E_{5-7}, E_{8-14}, E_{15-18} and E_{19-22}. Compounds E_4 was prepared by condensation of meta toluidine with diabromo acrylyl chloride and cyclization with thiouria while compounds E_{5-7} were derived from either furfural as dibromo furfural on condensation with dimedon , compounds E_{8-14} were synthesized by condensation of dibromo furfural with acetone , urea , thiouria and sulfuric acid while compounds E_{15-18} and E_{19-22} were prepared from condensation of, α, β- Naphthol and urea using zarconyl chloride. The synthesized compound were identified by IR, NMR and were discussed.

Introduction

Furfural was first time produced industrially from rice huks in1840 after drying mixing with sodium chloride and addition of 10% H_2SO_4 and distilled water [1], Other researchers have synthesized it from rice straw in 2007 [2]. Punsuvon and his co-workers have synthesized furfural from sugar cane stalks and sulfuric acid [3] with an overall yield of 71%. In 2010 researchers have succeeded to synthesize furfural from xylose sugar [4]. In 2012 other researchers have prepared furfural from epic rap of wild mango [5]. In 2016 researchers have prepared furfural from bagasse [6] According to the above works it was known that furfural is cheap precursor and was used for the synthesis of variety of heterocyclic compounds. Furfural itself and its derivatives MCA, MBA for example 4,5-Dibromofurfuraldehydle, 2-(2-furyl) [1,3] dioxane,5-nito(1,3-imidazolyl-2,5-dion)-3-yl furfuraldine was used as drag in treatment of urinary tract [7,8]. Among the reactions of furfural are the synthesis of tetrazine derivatives [9], furyl methylene diacetate [10] and 4-methyl furfural [11]. Among the known reactions of furfural which leads to the formation of heterocyclic compounds are the synthesis of 1,3-imidizolyl-2,5- furfuryl amine-2,s5- dione which is used for treatment of urinary tract infections [12]. Furoin compound on oxidation forms furil which is known as insect side [13]. flavon compound contains furfural ring, furfuraldehyde exhibited ICso values of 75.9,51.0 and 59.3 M for HT29, MCF7 and A498 respectively as anti-cancer cell lines [14]. It was also known that bromo derivative of furfural (MBA) reacts with boronyl indole to form indolyl derivatives of furfural, which is known for treatment of prostate, stomach, pancreatic, kolon cancer types [15]. In our investigation, We started from furfural as precursor for the synthesis of some heterocyclic compounds in continuing of our previous study [16-18] for the preparing of new derivatives of this type of furyl compounds in drug discovery program.

Experimental

All melting points were uncorrected and measured using Electro thermal melting point apparatus, All chemical were supplied by Aldrich and fluka and BDH companies. Bruker Avance 111 400 MHz was used for 1HNMR measurements. Infrared spectrophotometer model FT (600) CO. LTD (UK) and FT (8400 s) shimadzo were used for IR measurements. power sonic 405 micro process-controlled bench –top ultra-sonic cleaner was used for Ultrasound chemical

condensation. Dibromo acrylic acid and its chloride derivative E_1, E_2 were prepared according to the published procedure [19]. Dibromo furfural and mucobromic acid were prepared following the published procedure [20,21].

Synthesis of 2-Bromo –N- (3-ethyl phenyl)-3, 3-dimethyl propion amide (E_3)

A mixture of 1.87 g. of $KHCO_3$ in 10 ml of water was mixed with (1.18 g., 0.01 mol.) of meta toludine in 5 ml of THF. And stirred at r.t for 1 hr. at 60-65ºC, after that 4.22 g. of 75% solution of compound E_2 in THF was added gradually within 2hr. while the mixture was then stirring. after complete addition 10 ml of THF was then added and the stirring was continued for further 2 hr. at the same temperature after that the solvent was evaporated and to the residue was added 1.98 g of 30% methanolic sodium methoxide within a period of 1 hr. stirring was continued for further 3hr. evaporation of methanol gave an oil product 57% which was used in next step.

Synthesis of 2-Amino thiazole -5- (3-methyl phenyl) Carboxy Amide(E_4)

Compound E_3 (1.5 g ,.0048 mol.), 3.5 ml of acetic acid and 1.09 g. of HCL were mixed together and stirred at 60-65ºC , then 0.92 g. of thiouria was added , the stirring was continued for 11 hr. at the same temperature. The reaction was subject for distillation to distill the excess acetic acid methanol 8.47 ml was then added together with 1.35 g. of 30% methanolic sodium methoxide until pH of the mixture becomes 8-9. The reaction mixture was filtered off, to the filtrate was added 2g. of activated charcoal and stirred at 60 ºC for 1 hr., filtered evaporation of the solvent, 20ml of cold water was then added to the residue. The final mixture was cooled to 0ºC. the yellow oil was extracted with ether, the extract was evaporated to give oil product 55%.

Synthesis of Some Furyl Substituents of polyhydroquinoline (E_{5-7})

A mixture of (0.96 g., 0.01 mol.) of furfural, (1.4, 0.01 mol.) of dimedon, (0.015 mol.) of ammonium carbonate and (0.013 mol.) of either methyl acetoacetate or ethyl acetoacetate or acetyl acetone in 30 ml of water. The final mixture was sonicated at 60ºC for 1 hr. After complete reaction (TCL) the reaction was cooled and filtered, washed with water and with 25ml of 50% Ethanol. The p.pt was re-crystallized from ethanol. physical data were presented in Table 1.

Table 1: Physical data of compounds(E_{5-7}).

Comp. No.	R	m.p. (˚C)	Molecular Formula	Yield (%)	Color
E5	$-OCH_3$	178-180	$C_{18}H_{21}NO_4$	88	Yello
E6	$-OCH_2CH_3$	167-169	$C_{19}H_{23}NO_4$	90	Yello
E7	$-CH_3$	207-208	$C_{18}H_{21}NO_3$	75	Brown

Synthesis of Some Furyl Substituents of 3,4 dihydropyrimidine -2-one(E_{8-14})

Urea or thiouria and dibromo furfural (0.015 mol.) were mixed together. To the mixture was added methyl or ethyl acetoacetate or acetyl acetone or benzoyl acetone, 50ml of ethanol and 0.08 mol. Of sulfuric acid. The final mixture was irradiated with ultrasound at 25-30ºC for 45 min. the reaction was monitored by TLC. After completion of the reaction the mixture was filtered off. The residue was washed with water then with ethanol, dried and recrystallized from 95% ethanol physical and data are illusterated in Table 2.

Table 2: Physical data of compounds (E_{8-14}).

Comp. No.	R	X	Y	m.p. (oC)	Molecular Formula	Yield %	Color
E8	$-OCH_3$	O	-Br	240-242	$C_{11}H_{10}Br_2N_2O_4$	70	Brown
E9	$-OC_2H_5$	S	-H	219-221	$C_{12}H_{14}N_2O_3S$	65	Yellow
E10	$-OC_2H_5$	O	-Br	231-233	$C_{12}H_{12}Br_2N_2O_4$	64	Yellow
E11	$-CH_3$	O	-H	218-220	$C_{11}H_{12}N_2O_3$	48	Yellow
E12	$-CH_3$	O	-Br	232-234	$C_{11}H_{10}Br_2N_2O_3$	55	Yellow
E13	$-CH_3$	S	-H	246-238	$C_{11}H_{12}N_2O_2S$	50	Yellow
E14	-ph	O	-H	254-256	$C_{16}H_{14}N_2O_3$	60	Yellow

Synthesis of some furan substituents of amino alkyl naphthol (E_{15-18})

Furfural (0.69 g., 0.01 mol.), 0.01 β-naphthol, 0.01mol. of acetamide or urea or methyl urea and (0.01 mol.) of $ZrOCl_2$. $8H_2O$ in 50 ml of 1,2 – dichloro ethane. The final solution was sonicated at r.t for 40 min. after complete reaction (TLC monitoring), The mixture was filtered off, washed with ether then with water, dried and recrystallized from methanol. physical and spectral data are illustrated in Table 3. The same above procedure was used for synthesizing of compound E20-23 at 60ºC and sonication for 30 min. The crude product was recrystallized from methanol and the physical properties are shown in Table 4.

Table 3: Physical data of compounds (E_{15-18}).

Comp. No.	R	m.p. (˚C)	Molecular Formula	Yield (%)	Color
E15	$-CH_3$	216-217	$C_{17}H_{15}NO_3$	62	Brown
E16	$-NH_2$	220-222	$C_{16}H_{14}N_2O_3$	65	Brown
E17	$-NHCH_3$	178-180	$C_{17}H_{16}N_2O_3$	60	Brown
E18	$-NHCH_2CH_3$	205-207	$C_{18}H_{18}N_2O_3$	62	Brown

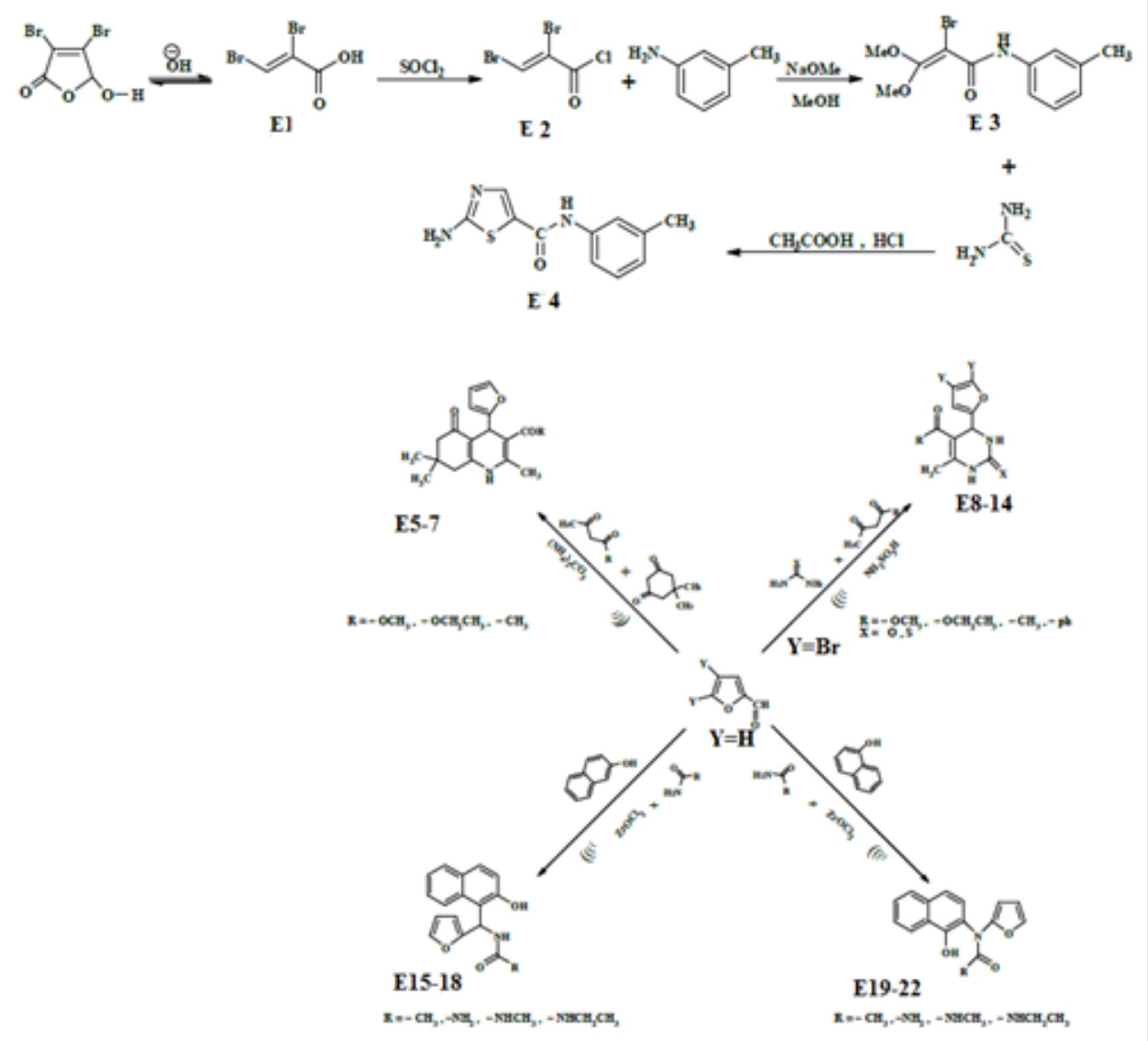
Table 4: Physical data of compounds(E_{19-22}).

Comp. No.	R	m.p. (°C)	Molecular Formula	Yield (%)	Color
E19	-CH	219-220	$C_{17}H_{15}NO_3$	62	Brown
E20	$-NH_2$	250-252	$C_{16}H_{14}N_2O_3$	66	Brown
E21	$-NHCH_3$	190-192	$C_{17}H_{16}N_2O_3$	64	Brown
E22	$-NHCH_2CH_3$	161-163	$C_{18}H_{18}N_2O_3$	57	Brown

Result and Discussion

Synthesis of 2-aminothiazole -5-(3-methyl phenyl) carboxy amide (E_4)

The first step of this route was the preparation of 2,3-dibromo acrylic acid from the reaction of Mucobromic acid with sodium hydroxide as shown in Scheme 1, the synthesized compound E_1 was characterized by the following IR cm^{-1} 3344 for OH , stretching band at 1765 for C=O while C=C appeared at 1624 ,C-O at 1394 ,C-Br at 850 .This compound was allowed to react with $SOCl_2$ forming compound E_2 which is characterized by the following IR bands cm^{-1} :C=O at 1786 ,C=C at 1659 ,C-Br at 850 and disappearance of the OH band . Compound E_2 was allowed to react with meto toludine forming 2,3-dibromo-N-meta tolyl acryl amide which intern reacts with sodium methoxide result into the formation of E_3. This compound was characterized by the following IR cm-1 3378 for NH, 1677 for C=O, Aromatic C=C absorbed between 1457-1605 while C-O appeared at 1312, C-Br at 832. The final steps of this route include the reaction of E_3 with thiouria forming E_4 which is characterized by the following IR stretching bands cm^{-1} : 3355 for NH , 1668 for C=O , 1590 for C=N , C=C Aromatic appeared within 1445-1612 , C-S sym. and asym. At 766, 1093 respectively. The amide group test showed positive result.



Scheme 1.

Synthesis of Some Furyl Substituent of Poly Hydro Quinolone (E_{5-7})

The reaction of furfural, dimedon and one of (methyl, Ethyl acetoacetate, acetyl acetone) in water afforded the title compounds. These compounds were characterized by IR as shown in Table 5 in which NH appeared between 3286-3348 cm^{-1}, C=O at 1656-1666 cm^{-1}, C=C Ar. Appeared at 1605-1626 cm^{-1} , C-O stretching both sym. and asym. At 1095-1238 cm^{-1}. This finding was in agreement with previously published similar compounds [22].

Table 5: IR spectral data of compounds(E_{5-7}).

Comp. No.	R	IR V(cm^{-1}), 1219, KBr				
		NH	C=Ocy	C=C	C-C-Cassym,Sym	Other
E5	$-OCH_3$	3286	1666	1605	1219 , 1143	1710(C=O)
E6	$-OC_2H_5$	3313	1664	1626	1238 , 1095	1697(C=O)
E7	$-CH_3$	3346	1655	1608	1219 , 1147	1676(C=O)

Synthesis of Some Furyl Substituent of 3,4 –dihydro pyrimidine 2-one, 2-thio (E_{8-14})

This series of compounds were prepared by ultrasonic irradiation of 4,5-dibromo furfural with uria or thiouria and one of compounds (Methyl, Ethyl acetoacetate, acetyl acetone and benzoyl acetone) see Scheme 1. The synthesized compounds were characterized by the following absorption bands cm^{-1}: 3248-5317 for NH stretching, 1624-1712 for C=O, C=C Aromatic appeared at 1450-1647 while C-N absorbed at 1145-12l40 see Table 6. Compound 9 as representative of the series was characterized by the following resonating signals in ppm. singlet signal at 10.38ppm., 9.62 ppm. for NH protons, doublet signal at 7.58ppm. for proton at 5 position of furan ring equivalent to 1H, Triplet signal at 6.15ppm. for proton at 3 position of the furan ring equivalent to 1H. Doublet signal at 5.24ppm. for pyridine ring equivalent to 1H, quartet signal of 4.07 ppm. belongs to CH_2 equivalent 2H, singlet signal at 3.43ppm. belongs to SH equivalent to 1H, Singlet signal at 2.33ppm. belongs to CH_3 proton of Ethyl Ester substituent of pyridine ring equivalent to 3H triplet signal at substituent 1.12 for CH_3 of ester moiety equivelent. to 3H.

Table 6: IR spectral data of compounds (E_{8-14}).

Comp. No.	R	X	Y	IR V(cm^{-1}) , KBr				
				NH	C=O	C=X	C=C	C-N
E8	$-OCH_3$	O	-Br	3290	1624	1608	1450	1175
E9	$-OC_2H_5$	S	-H	3315	1661	1191	1575	1235
E10	$-OC_2H_5$	O	-Br	3232	1712	1655	1512	1228
E11	$-CH_3$	O	-H	3317	1708	1676	1647	1240
E12	$-CH_3$	O	-Br	3307	1698	1634	1578	1223
E13	$-CH_3$	S	-H	3288	1630	1176	1573	1145
E14	-Ph	O	-H	3248	1645	1608	1572	1213

Synthesis of Furyl Substituent for Naphthol Compounds (E_{15-19})

This series of compounds were prepared by irradiation of a mixture of β- Naphthol and one of compounds (Acet amide, urea or methyl urea and ethyl urea) in presence of Zarconyl chloride using 1,2-dichloro ethane as a solvent under Ultrasonic waves at r.t. The synthesized compounds were characterized by IR cm^{-1} Absorption bands: 3435-3462 related to OH stretching, 3317-3397 for NH, 1708-1747 for C=O while the aromatic C=C stretching bands appeared within range (1433-1676). The C-O-C sym. and asym. stretching bands appeared at 1020-1279 as shown in Table 7.

Table 7: IR spectral data for compounds (E_{15-18}).

Comp. No.	R	IR V(cm^{-1}) , KBr				
		OH	NH	C=O	C=C C C	C-O-CAssym, Sym
E15	$_2CH$-	3441	3397	1735	1436-1647	1020 , 1220
E16	$_2NH$-	3462	3369	1747	1463-1631	1020 , 1279
E17	NH_3CH-	3435	3336	1735	1463-1632	1076 , 1261
E18	NHC_2H_5-	3446	3317	1708	1433-1676	1089 , 1240

Furyl Substituent of α-Naphthol Compounds (E_{19-22})

The synthesized compounds of this series were also characterized by the following absorption bands IR cm^{-1} :3402-3485 for OH stretching , 3234-3356 for NH , the carbonyl group was absorbed at 1698-1739 while the aromatic C=C appeared within the range (1458-1670) and finally C-O-C for both sym. and asym at 1009-1244 respectively as illustrated in Table 8.

Table 8: IR spectral data for compounds (E_{19-22}).

Comp. No.	R	IR V(cm^{-1}) , KBr				
		OH	NH	C=O	C=C, C C	C-O-CAssym, Sym
E19	$-CH_3$	3465	3356	1698	1670-1481	1138 , 1045
E20	$-NH_2$	3402	3249	1703	1635-1458	1198 , 1009
E21	$-NHCH_3$	3433	3300	1739	1655-1508	1244 , 1022
E22	$-NHC_2H_5$	3485	3234	1701	1612-1473	1142 , 1080

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Conclusion

We have demonstrated a simple and green method for efficient synthesis of some heterocyclic compounds containing furyl derivatives within short reaction time and a moderate yield.

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