Synthesis of some azetidonone and 1, 3-oxazepine deritives from thymol

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الملخص

في هذا البحث تم تحضير بعض مركبات أزتدين−2−اون (11-16) من تفاعل مشتقات الهيدرازون (3-10) مع كلورو استيل الكلورايد بوجود ثلاثي اثيل أمين، حيث الهيدرازونات تم تحضيرها من تفاعل الدرازيد (2) مع مختلف معوضات البنزالدهيد. مركبات الاوكسابيين 4،7− ثنائي اون (17−22) حضرت من تفاعل الهيدرازونات (3-10) مع انهدريد ألماليك. شخصت المركبات الناتجة بالطرق الطيفية والفيزياويه المتاحة.

Abstract

A series of some azetidines -2-one derivative (11-16) have been synthesized by cyclocondensation of various hydrazones derivatives (3-10) with chloroacetyl chloride in the presence of triethylamine. Hydrazones (3-10) were synthesized from the reaction of hydrazide (2) with various substituted benzaldehyde. Oxazepain 4,7-dion derivatives (17-22) were synthesized from the reaction of hydrazones derivatives (3-10) with maleic anhydride

INTRODUCTION

Azetidine-2-one and 4, 7-oxazepaine derivatives were reported to posse's antibacterial, antifungal[1-3], antianflammatory and antitubercular activities[4] also oxazepine derivatives used as neuroleptic and as antidepressant [5, 6]

Azetidine-2-one can be prepared from ketene-imines cycloaddition[7] reaction, although many synthetic methods have been developed, Bhat and etal.[8] synthesized Schiff's bases from condensation of acid hydrazine of p-anisidine with aromatic aldehydes, which on treatment with chloroacetylchloride in the presences of triethylamine afforded 2-azetidiones.1, 4-benzoxazepine-2, 5-(1H, 3H)-dione was

prepared from the reaction of o.aminobenzoic acid with choroacetyl chloride. Alkyl substituted derivatives were prepared from the reaction of the corresponding alkyl halide with benzoxazepinedione in the presence of a suspension of sodium hydride in dimethylforamide.[9]

In this paper we report the synthesis of some azetidinone and oxazepine derived from ethyl thymoxy acetate

EXPERIMENTAL

Melting points were measured on akofler hot stage. The IR spectra were recorded by using infra red spectrophotometer model Tensor 27 Bruker co. Germany. The ^{1}HNMR were recorded by Bruker ultra shield Dp″400 MHz Avancell (2008), Ortaduteknek university using $CDCL_3$ as solvent with tetra methylsaline as references.

Ethyl thymoxy acetate (1)

This compound was prepared from the reaction of (0.06 mole, 9.0g) thymol, (0.06mole, 8.28g) anhydrous potassium carbonate and (0.06mole, 10.14g) bromoethylacetate following the method describe in the literature[10], gave 96%, colorless oily product.

Themoxy acetic acid hydrazide (2)

This compound was prepared from the reaction of (0.05mole, 12.89g) ester (1) and (0.25 mole, 12.5g) hydrazine hydrate 99% as mentioned in the literature [10], yield 87%, m.p. (93-95° C), lit. (93-95° C)

Hydrazones [11] (3-10)

A mixture of hydrazide (3) (2.22g, 0.01mole) in 25ml ethanol, and substituted aromatic aldehyde (0.01mole) in 25ml ethanol was added. The reaction mixture was heated under reflux for 2 hours after completion of reaction; the reaction mixture was allowed to cool. The precipitate was filtered and recrystallized from ethanol, to give the hydrazones (3-10). Some physical and spectral data indicated in tables (1, 4).

Substituted azetidine-2-one (11-16)

General procedure for synthesis [12]

A solution of hydrazones derivatives(3-10) (0.005mole) and triethylamine (0.01mole) in 40ml 1, 4-dioxane, Chloroacetyl chloride (0.01 moles) was added as drop wise with stirring at room temperature for 20 minutes, and then the mixture was refluxed for 3hours. The reaction mixture concentrated then poured into ice-water and titled compounds were isolated by ethyl acetate, dried and recrystallized from absolute ethanol, yield the required products(11-16). The physical and spectral data were listed in tables (2, 5).

3- Thymoxy methyl acetamido-2-aryl -2, 3-dihydro 1, 3-oxazepine, 4, 7-dione [12] (17-22)

A mixture of hydrazone derivatives (3-7, 9) in 30ml dry benzene and maleic anhydride (0.29g, 0.003 moles) were refluxed for 2 hours, the solvent was evaporated, and precipitate was recrystallized from ethanol, giving the required products. The physical and spectral data were listed in table (3, 6).

RESULTS AND DISCUSSION

The hydrazides (2) were obtained from refluxing ester (1) with 99% hydrazine hydrate in absolute ethanol. These hydrazides were identified by IR which exhibits characteristic peak at (3316 cm^{-1}) for the (N-H) stretching, peak at for the carboxyl group appear at (1678 cm^{-1}) which lower than the carbonyl ester (1739 cm^{-1}) due to the presences of resonances effect[13]

Hydrazones (3-10) were prepared by reaction of the thymoxy acetic acid hydrazide (2) and different aryl aldehyde. The structure of hydrazones were elucidated from spectra evidence, peak at (1688-1697 cm^{-1}) for the carbonyl group, also the peak at (1604-1614 cm^{-1}) for C=N. In addition to that the stretching banding at (3317-3487 cm^{-1}) is assigned for N-H. The IR spectral data shows at table (4).

The reaction product of hydrazones derivatives (3-10) with chloroacetylchloride elucidated from IR and ^{1}HNMR. The IR shows the absence of stretching bands at (1604-1614 cm^{-1}) for C=N group and the bands at (1696-1733 cm^{-1}) for the carbonyl lactam stretching and banding at (1422-1433 cm^{-1}) for C-N ,while absorbing bands at (1503- 1508 cm^{-1}) for C=C in addition to that bands at (711-762 cm^{-1}) for C-CL. The IR as shows in table (5).

The ^{1}HNMR spectrum for compounds (16) shows bands as multiple at1.245ppm for CH $(CH_3)_2$, singlet band at 2.314 ppm for Ph-CH_3, multiple band at 3.272 ppm for CH<, singlet band at 4.132 ppm for CH_2, doublet band for CHCL at 4.613 also singlet band at 5.134 ppm for CH, multiple bands at 6.602-8.137 ppm for Ar-H finally band at 9.049 ppm for N-H, the ^{1}HNMR for compound (16) table (5).

Refluxing hydrazones (3-10) with maleic anhydride will produce oxazepine -4,7-dione derivatives (17-22) and their structure was confirmed by spectroscopic data. IR shows the carbonyl lactones at (1681-1700 cm^{-1}) and carbonyl amide at (1603- 1639 cm^{-1}) other absorption bands shows in table (6). The ^{1}HNMR spectrum for compound (18) showed results that confirm our expectation as mention in table (6).

Table (1): Some physical constant for compounds (3-10)

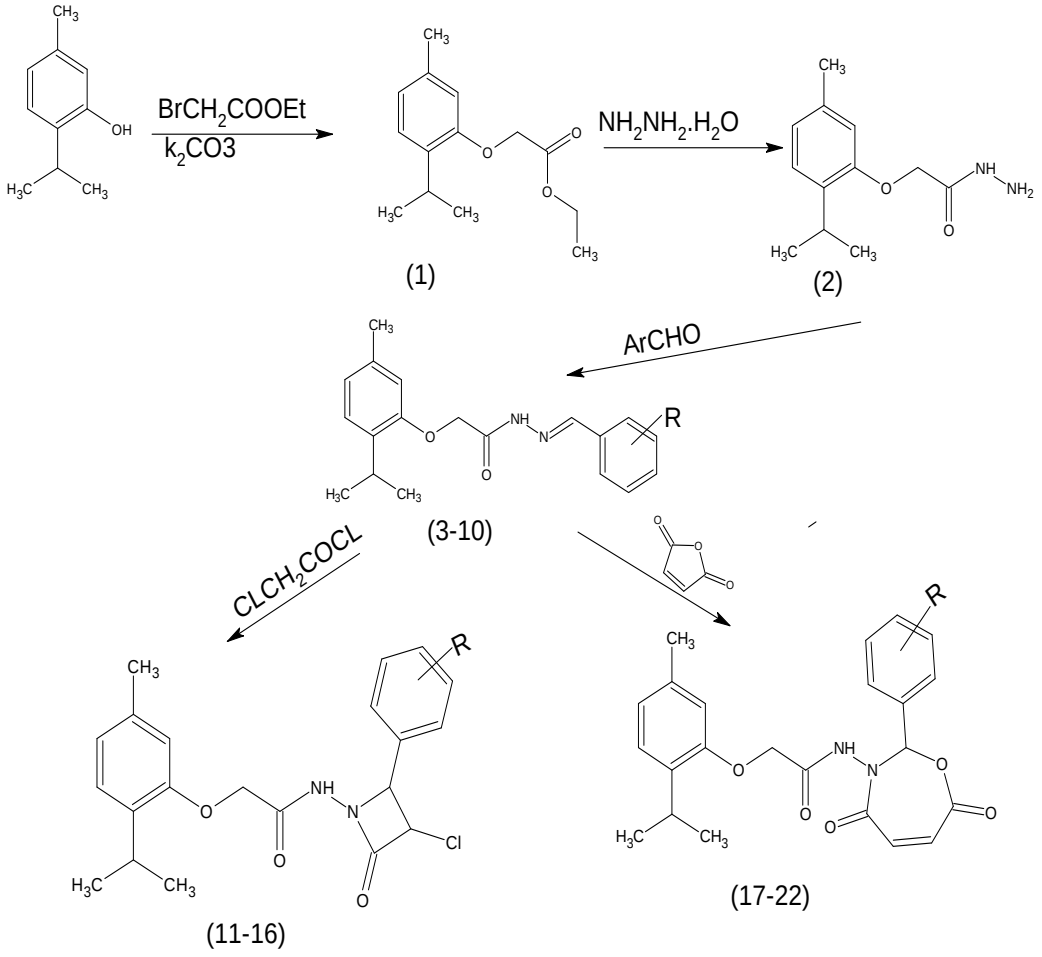
Comp. No.	R	M.p. (C°)	Yield(%)	Color
3	4-OH	111-113	85	yellow
4	4-CL	165-167	79	white
5	4-$N(CH_3)_2$	222-224	83	orange
6	H	156-158	89	white
7	4-No_2	136-138	77	Pale yellow
8	2-OMe	166-168	80	orange
9	4-OMe	151-153	84	white
10	2-CL	136-138	75	Pale yellow

Table (2): Some physical constant for compound (11-16)

Comp. No.	R	M.p. C°	Yield (%)	Color
11	4-CL	126-128	59	brown
12	4-$(NCH_3)_2$	142-144	67	Pale brown
13	H	120-122	75	Pale brown
14	4-NO_2	148-150	79	Pale brown
15	2-OMe	143-145	57	white
16	4-OMe	137-139	58	white

Table (3): Some physical constant for compounds (17-22)

Comp. No.	R	Mp (C°)	Yield (%)	Color
17	4-OH	115-117	73	yellow
18	4-CL	173-174	84	white
19	4-$(NH_3)_2$	103-107	75	red
20	H	148-150	69	white
21	4-No_2	151-153	53	yellow
22	4-CL	180-181	75	white



Scheme _1_

Table (4): Spectral data for hydrazones (3-10)

Comp. NO.	R	IRνcm^{-1}(KBr)			
		N-H	C=O	C=N	others
3	4-O-H	3317	1673	1614	3071(O-H)
4	4-CL	3444	1685	1613	726(C-CL)
5	4-N$(CH_3)_2$	3451	1692	1612	1257(C-N)
6	H	3444	1670	1604	
7	4-NO_2	3443	1687	1613	1284 sy.(NO_2) 1506 as.(NO_2)
8	2-OMe	3446	1697	1606	1104 sy.(C-O-C) 1256 ay.(C-O-C)
9	4-OMe	3487	1680	1612	1101 sy.(C-O-C) 1242 ay.(C-O-C)
10	2-CL	3445	1688	1604	758(C-CL)

Table (5): Spectral data for substituted azetidin-2-one derivative (11-16)

Comp. No.	R	IRν cm^{-1} (KBr)					
		C=O Lactone	C=O amide	C-N	Arc=c	C-CL	others
11	4-CL	1696	1647	1430	1504	762	
12	4-N$(CH_3)_2$	1717	1652	1424	1507	711	C-N(1245)
13	H	1700	1613	1433	1505	754	
14	4-NO_2	1733	1687	1435	1508	749	1315 sy.(NO_2) 1435 as.(NO_2)
15	2-OMe	1717	1652	1422	1507	750	1100 sy.(C-O-C) 1163 ay.(C-O-C)
16	4-OMe	1717	1650	1425	1503	745	1103 sy.(C-O-C) 1168 as.(C-O-C)

Comp.No.	R	^{1}HNMRδ(ppm) Solv.$CDCL_3$
16	4-OMe	1.245(m,6H)2$(CH_3)_2$ 2.314(s,3H)Ar-CH_3 3.272(m,1H)CH 3.838(s,3H)OCH_3 4.132(s,2H)CH_2 4.615(d,1H)CHCL 5134(s,1H)CH,cyclic 6.602-8.137(m,7H)Ar-H 9.049(s,1H)NH

Table (6): Spectral data for compounds (17-22)

Comp. No.	R	IRν Cm^{-1}(KBr)						
		C=O Lactone	C=O amide	C-N	C-O-C	C=C-C=O	Arc=c	others
17	4-OH	1681	1654	1417	sy⁄as 1167 1242	1611	1507	
18	4-CL	1693	1606	1413	1168 1253	1578	1504	C-CL 739
19	4-N(CH_3)	1697	1613	1434	1169 1257	1540	1506	C-N 1257
20	H	1700	1612	1414	1171 1256	1581	1504	
21	4-NO_2	1689	1505	1410	1168 1254	1586	1504	NO_2s y\as 1339 1379
22	2-CL	1693	1603	1420	1170 1261	1577	1506	C-CL 749
Comp.No.	R	^{1}HNMRδ(ppm) Solv.$CDCL_3$						
18	4-CL	1.286(m,6H)2(CH_3)$_2$ 2.303(s,3H) Ar-CH_3 3.289(m,1H)CH 4.648(s,2H)O-CH_2- 5.118(s,1H)-N-CH-O 6.458(d,1H)CH=COO 6.636-7.694 (m,7H)Ar-H 7.721(d,1H)CHCO 9.355(s,1H)NH						

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