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Synthesis and Characterization of Some New Benzodiazepinium Salt Derivatives under microwave Irradiation

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Abstract:

An attempt to synthesize the benzoimidazol derivatives from the reaction of o-phenylenediamine and benzoic acid derivatives in the presence of ethanol and various ketones under microwave irradiation, 1 , 5 - benzodiazepinum salt derivatives were obtained instead of them. Unexpected reaction was happened for synthesis a new series of benzodiazepinium salt derivatives in a selective yield . The reaction mechanism was also discussed. The new compounds were purified and identified their structures were elucidated using various physical techniques like; FT- IR spectra, micro elemental analysis (C.H.N) and ^{1}H NMR spectra.

Key words: Benzodiazepinium Salt, Microwave Irradiation, Characterization.

Introduction:

Recent advances in technology have now made microwave energy more efficient means of heating reactions. Chemical transformations that took hours, or even days, to complete their organic reaction , can now be accomplished in minutes. Microwave assisted organic synthesis [1]. MAOS has emerged as frontier in pharmaceutical research for synthesis of newer drugs . MAOS is not only help in implementing GREEN chemistry but also led to the revolution in organic synthesis. Microwave irradiation is well known to promote the synthesis of a variety of organic compounds, where chemical reactions are accelerated because of selective absorption of microwave by polar molecules. The synthesis of diazepines via various synthetic procedures under catalyzed conditions has widely been reported[2-7].

Diazepines and benzodiazepines have various therapeutic applications. Many members of the diazepine family are widely used as anticonvulsants, antianxiolitics, analgesics, sedatives, antidepressives and hypnotic agents [8-11]. Benzodiazepine derivatives are used as dyes for acrylic fibers [12]. In addition, benzodiazepines are valuable intermediates for the synthesis of fused ring compounds such as triazolo-, oxadiazolo-, oxazino-, and furanobenzodiazepines [13-18]. Benzodiazepines are categorized as either short-, intermediate-, or long-

acting. Short- and intermediate-acting benzodiazepines are preferred for the treatment of insomnia; longer-acting benzodiazepines are recommended for the treatment of anxiety[19].

Material and Methods:

Melting points were determined in open capillary tubes , FT- IR spectra in the rang (4000-500 cm^{-1}) were recorded using KBr disk on FT - IR - 8300 Shimadzu spectrophotometer at Baghdad university in Iraq. ^{1}HNMR Spectra were recorded on varian spectrometer (300MHZ) in $CDCl_3$ or DMSO solvent and chemical shifts are given with respect to TMS (tetramethyl silane) as internal reference (chemical shift in δ ppm). Microelemental analysis (C. H. N. S) were conducted using a Carlo Erba 1106 elemental analyzer. The physical data of the compounds prepared are presented in table 1.

Typical procedure: 2,2,2-trimethyl-2,3-dihydro-1H-benzo[b][1,4]diazepin-5-ium-R-substituted benzoate (1-4)

A mixture of o-phenylenediamine(0.01 mole) and (0.01 mole)substituted benzoic acid were subjected to microwave irradiation at 180 watt(50 ◦c) for different time the mixture was fused ,then add the solvents (absolute ethanol, acetone; 2:1 ratio) to the fused mixture while hot. The reaction mixture was set aside for 24 hr at R.T during which a solid product was formed. The product was dried and recrystallized from ethanol and ethyl acetate with a ratio of (1 : 1) volume.

4-ethyl-2,2-dimethyl-2,3-dihydro-1*H*-benzo[b][1,4]diazepin-5-ium-R-substituted benzoate (5-8)

The same above procedure accept, it used 1-butanol instead of acetone.

2, 2-dimethyl -4-phenyl- 2, 3-dihydro-1 *H*-benzo [b] [1,4] diazepin -5-ium-R-substituted benzoate (9-12)

The same above procedure accept, it used acetophenone instead of acetone.

Table 1 .Physical properties of a new diazepinium salt derivatives

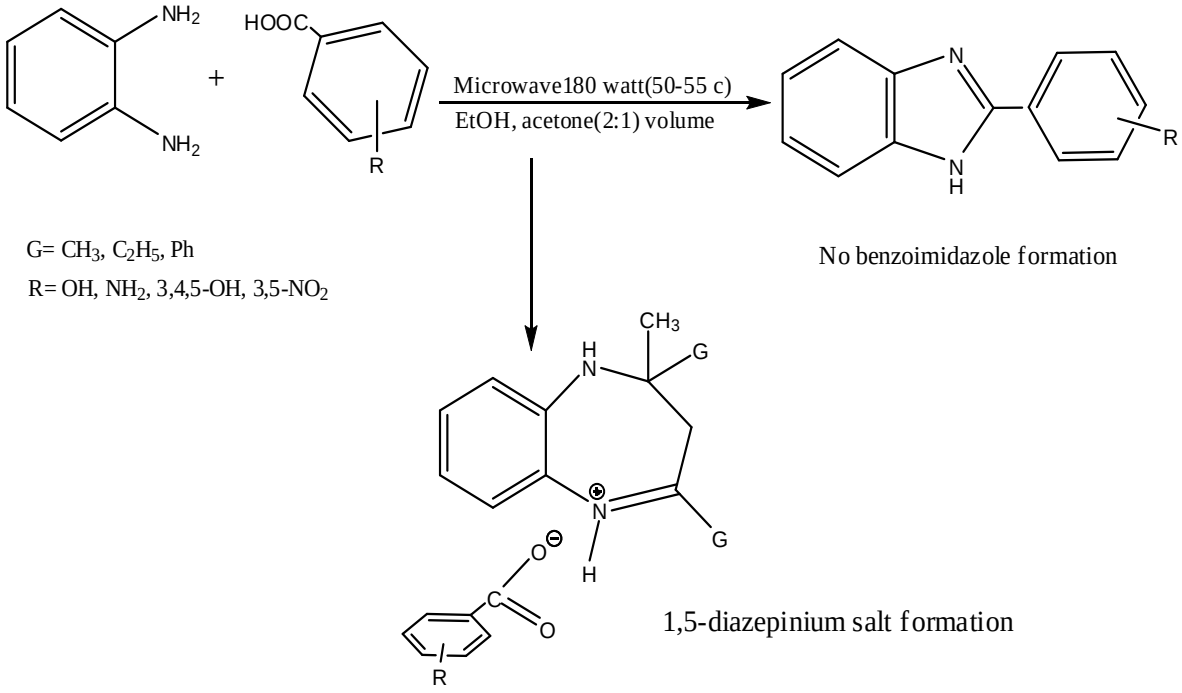
S. No.	R	Molecular Formula	M.P.,◦C	Yield, %	Time, min	Ketone
1	P-OH	$C_{19}H_{22}N_2O_3$	73-75	79	30	Acetone
2	O-NH_2	$C_{19}H_{23}N_3O_2$	45-47	81	16	Acetone
3	3,4,5-OH	$C_{19}H_{22}N_2O_5$	138-140	83	31	Acetone
4	3,5-NO_2	$C_{19}H_{20}N_4O_6$	90-92	85	40	acetone
5	P-OH	$C_{21}H_{26}N_2O_3$	76-78	81	25	1-butanone
6	O-NH_2	$C_{21}H_{27}N_3O_2$	52-54	80	13	1-butanone
7	3,4,5-OH	$C_{21}H_{24}N_2O_5$	125-126	78	11	1-butanone
8	3,5-NO_2	$C_{21}H_{24}N_4O_6$	99-102	83	16	1-butanone
9	P-OH	$C_{29}H_{24}N_2O_3$	51-53	82	15	Acetophenone
10	O-NH_2	$C_{29}H_{27}N_3O_2$	83-85	87	12	Acetophenone
11	3,4,5-OH	$C_{29}H_{24}N_2O_5$	118-120	84	12	Acetophenone
12	3,5-NO_2	$C_{29}H_{24}N_4O_6$	110-112	79	10	Acetophenone

2,2,2-trimethyl-2,3-dihydro-1H-benzo [b][1,4]diazepin-5-ium-4-hydroxy benzoate(1)
IR(KBr cm): 3344 (NH), 1674 (C=O), 1593 (C=N), 3421 (OH) and 3278(+NH). Anal. calcd. for $C_{19}H_{22}N_2O_3$: C, 69.92; H, 6.79; N, 8.58. found: C, 69.19; H, 6.54; N, 7.94.
2,2,2-trimethyl-2,3-dihydro-1H-benzo[b][1,4]diazepin-5-ium-2- amino benzoate(2)
IR(KBr cm): 3460 (NH), 1631 (C=O), 1612 (C=N), 3348-3321 (HN2) and 3433 (+NH). Anal. calcd. for $C_{19}H_{23}N_3O_2$: C, 70.13; H, 7.12; N, 12.91. found: C, 69.78; H, 6.97; N, 11.89.
2,2,2-trimethyl-2,3-dihydro-1H-benzo[b] [1,4]diazepin-5-ium-3,4,5 - trihydroxy benzoate(3)
IR(KBr cm): 3329 (NH), 1689 (C=O), 1616 (C=N), 3414 (OH) and 3155 (+NH). Anal. calcd. for $C_{19}H_{22}N_2O_5$: C, 63.67; H, 6.19; N, 7.82. found: C, 62.96; H, 5.97; N, 7.37.
2,2,2-trimethyl-2,3-dihydro-1H-benzo[b][1,4]diazepin-5-ium-3,5-dinitro benzoate(4)
IR(KBr cm): 3367 (NH), 1697 (C=O), 1620 (C=O), 1539-1345 (NO2) and 3236 (+NH). Anal.calcd. for $C_{19}H_{20}N_4O_6$: C, 57.00; H, 5.03; N, 13.99. found: C, 56.63; H, 4.76; N, 13.53.
4-ethyl-2,2-dimethyl-2,3-dihydro-1*H*-benzo[b][1,4]diazepin-5-ium-4-hydroxy benzoate(5)
IR(KBr cm): 3360 (NH), 1674 (C=O), 1593 (C=N), 3421 (OH) and 3275(+NH).
Anal. calcd. for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.39; N, 7.90. found: C, 70.63; H, 7.26; N, 7.46 .
4- ethyl-2,2-dimethyl-2,3-dihydro-1*H*-benzo[b][1,4]diazepin-5-ium-2-amino benzoate(6)
IR(KBr cm): 3348 (NH), 1651 (C=O), 1612 (C=N), 3456-3433 (NH2) and 3174 (+NH). Anal. calcd. for $C_{21}H_{27}N_3O_2$: C, 71.36; H, 7.70; N, 11.89. found: C, 71.09; H, 7.58; N, 11.23.
4- ethyl-2,2-dimethyl-2,3-dihydro-1*H*-benzo[b][1,4]diazepin-5-ium-3,4,5-trihydroxy benzoate(7)
IR(KBr cm): 3371 (NH), 1665 (C=O), 1612 (C=N), 3502 (OH) and 3136 (+NH).
Anal. calcd. for $C_{21}H_{26}N_2O_5$: C, 65.27; H, 6.78; N, 7.25. found: C, 64.9; H, 6.67; N, 6.92 .
4 -ethyl-2,2-dimethyl-2,3-dihydro-1*H*-benzo[b][1,4]diazepin-5-ium-3,5-dinitro benzoate(8)
IR(KBr cm): 3371 (NH), 1662 (C=O), 1620 (C=N), 1539-1346 (NO2) and 3109 (+NH). Anal. calcd. for $C_{21}H_{24}N_4O_6$: C, 58.87; H, 5.65; N, 13.08. found: C, 58.44; H, 5.48; N, 12.79.
2, 2-dimethyl -4-phenyl- 2,3-dihydro-1*H*-benzo[b][1,4]diazepin-5-ium-4-hydroxy benzoate(9)
IR(KBr cm): 3278 (NH), 1674 (C=O), 1635 (C=N), 3387 (OH) and 3059 (+NH).
Anal. calcd. for $C_{29}HN_2O_3$: C, 77.31; H, 5.82; N, 6.22. found: C, 77.12; H, 5.33; N, 5.86 .
2, 2-dimethyl -4-phenyl- 2,3-dihydro-1*H*-benzo[b][1,4]diazepin-5-ium-2-amino benzoate(10)
IR(KBr cm): 3400 (NH), 1761 (C=O), 1631 (C=N), 3390-3278 (NH2) and 3059 (+NH). Anal. calcd. for $C_{29}H_{27}N_3O_2$: C, 77.48; H, 6.05; N, 9.35. found: C, 77.26; H, 5.92; N, 8.83.
2, 2-dimethyl -4-phenyl- 2,3-dihydro-1*H*-benzo[b][1,4]diazepin-5-ium-3,4,5-trihydroxy benzoate(11)
IR(KBr cm): 3371 (NH), 1685 (C=O), 1600 (C=N), 3429 (OH) and 3278 (+NH).
Anal. calcd. for $C_{29}H_{26}N_2O_5$: C, 72.18; H, 5.43; N, 5.81. found: C, 72.31; H, 5.57; N, 6.24.
2, 2-dimethyl -4-phenyl- 2,3-dihydro-1*H*-benzo[b][1,4]diazepin-5-ium-3,5-dinitro benzoate(12)

IR(KBr cm): 3460 (NH), 1666 (C=O), 1624 (C=N), 1539-1346 (NO_2) and 3340 (+NH). Anal. calcd. for $C_{29}H_{24}N_4O_6$: C, 66.40; H, 4.61; N, 10.68. found: C, 66.27; H, 4.33; N, 9.98.

Results and Discussion:

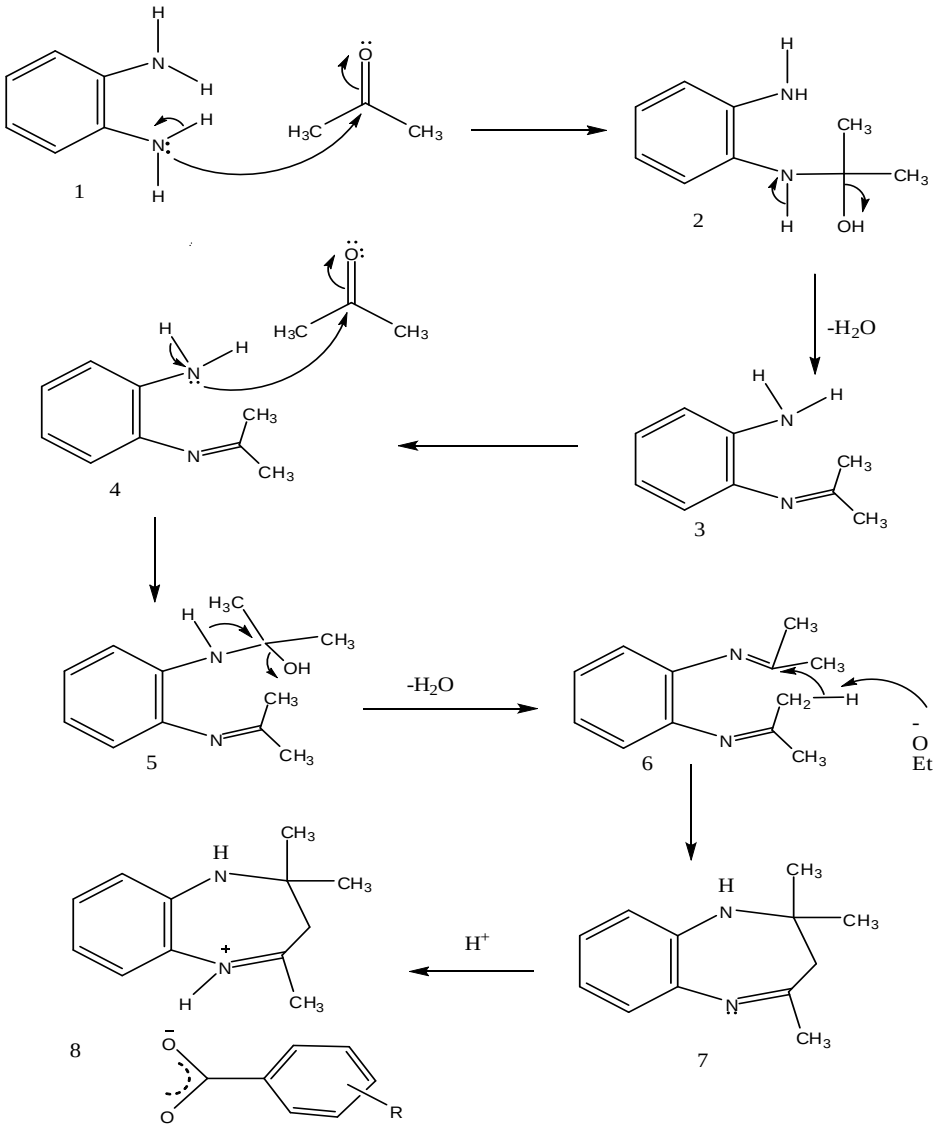
This research reports on the formation of 1,5-benzodiazepinium salt from the unexpected reaction of o-phenylenediamine and substituted benzoic acid under microwave irradiation in the presence of a (ethanol, acetone) mixture with a ratio of (2:1) volume and in the absence of a catalyst . We were planned to prepare a new set of benzoimidazole derivatives using a conventional method and it will publish in a separated paper, later on. When we would try to synthesize the same compounds using a microwave irradiation, an unexpected reaction was happened and it was given a new sets of 1,5-diazepinium salt instead of 2-substituted benzoimidazole derivatives. Equimolar quantities of the starting materials were irradiated at 180 watt (50-55 ◦c) for different times.



Scheme1. Synthesis of a new diazepinium salt derivatives

It was later observed that the benzoimidazole formation via a condensation reaction was not happened. The scheme 2 shows the proposed reaction mechanism for the formation of the benzodiazepine salt(1-12).It is proposed that the initial step is attack of the carbonyl carbon of acetone by the loin pair of electrons on the amino group. Due to the difference in electronegativity between the carbon atom and the oxygen atom of the carbonyl group, the electron density is than the carbon, making the oxygen acquire a partial negative charge and the carbon atom a partial positive charge. Also, the tendency of the nitrogen to attract electrons towards itself making the hydrogen (N-H) easily abstracted , thereby leaves the nitrogen with a negative charge, making it a better nucleophile to attack

the carbonyl in structure 1 Loss of a water molecule from structure 2 results in the formation of a C=N bond in structure 3. The second amine group attacks the carbonyl of anther acetone molecule in structure 4 resulting in the formation of structure 5, and the subsequent loss of a water molecule leads to the formation of the C=N group in structure 6 [20]. The ethoxide ion formed from the dissociation of ethanol, abstracts a proton from the methyl group, resulting in the formation of the enolate ion instructure 6. Since ethanol is a weak acid, it produces a strong conjugate base that can easily deprotonate a weakly acidic proton, in this case from a methyl group which is made acidic by the presence of unsaturation and a heteroatom on the adjoining carbon [6,21]. The loss of the proton by the methyl group makes it a good nucleophile which then attacks the carbon of the C=N bond because of the partial positive charge of the carbon as a result of the electron withdrawing effect of the nitrogen forming the benzodiazepine structure 7. In the case of compound one the benzodiazepine formed in structure 7 is then protonated by the benzoic acid to form an iminium ion which subsequently forms a salt with the benzoate ion in structure 8



Scheme 2.A proposed mechanism for the formation of compounds.

The new compounds were characterized using spectral data successfully. The practical microelement analysis (C. H. N) were fitted with the theoretical data. The ^{1}HNMR spectra were listed in table 2.

Table 2. The ^{1}HNMR spectra data for a new diazepinium salt derivatives

NO.	R	Data, DMSO-d_6 , δ (S,2.5 ppm), δ(ppm)
1	4-OH	1.2 (S,6H,2CH_3) ; 2.1 (S,2H,CH_2) ; 2.2 (S, 3H, CH_3); 4.2 (bs, 1H,$^{+}$NH); 6.7-8.2 (m, 8H, aromatic); 8.5 (S, 1H, NH); 9.5 (S, 1H, OH).
2	2-NH_2	1.1 (S, 6H, 2CH_3) ; 2.2 (S, 2H, CH_2) ; 2.3 (S, 3H, CH_3); 4.1 (bs, 1H,$^{+}$NH); 5.3 (S, 2H, NH_2) 6.6-8.1 (m, 8H, aromatic); 8.4 (S, 1H, NH).
3	3,4,5-OH	1.3 (S, 6H, 2CH_3) ; 2.2 (S, 2H, CH_2) ; 2.3 (S, 3H, CH_3) 4.3 (bs, 1H,$^{+}$NH); 6.8-8.4 (m, 6H, aromatic); 8.6 (S, 1H, NH); 9.6 (S, 3H, 3OH).
4	3,5-NO_2	1.2 (S, 6H, 2CH_3) ; 2.2 (S, 2H, CH_2) ; 2.3 (S, 3H, CH_3) 4.2 (bs, 1H,$^{+}$NH); 6.6-8.3 (m, 7H, aromatic); 8.6 (S, 1H, NH).
9	4-OH	1.2 (S, 3H, CH_3) ; 2.3 (S, 2H, CH_2) ; 4.3 (bs, 1H,$^{+}$NH); 6.6-8.2 (m, 8H, aromatic); 8.4 (S, 1H, NH); 9.5 (S, 1H, OH).
10	2-NH_2	1.1 (S, 3H, CH_3) ; 2.2 (S, 2H, CH_2) 4.2 (bs, 1H,$^{+}$NH); 5.2(S, 2H, NH_2); 6.7-8.1 (m, 18H, aromatic); 8.3 (S, 1H, NH).
11	3,4,5-OH	1.3 (S, 3H, CH_3) ; 2.2 (S, 2H, CH_2) ; 4.3 (bs, 1H,$^{+}$NH); 6.7-8.2 (m, 16H, aromatic); 8.4 (S, 1H, NH); 9.5 (S, 3H, 3OH).
12	3,5-NO_2	1.3 (S, 3H, CH_3) ; 2.3 (S, 2H, CH_2) ; 4.3 (bs, 1H,$^{+}$NH); 6.6-8.3 (m, 17H, aromatic); 8.4 (S, 1H, NH).

Conclusions:

The compounds of 1,5-diazepinium salt derivatives (1-12) have been synthesized with a good yield. An unexpected reaction was happened based on the reaction of 0-phenylenediamine and benzoic acid derivatives in the presence of acetone and ethanol under microwave irradiation without a catalyst . The synthesis method outlined here could be useful in the synthesis of derivatives of the seven membered benzodiazepine ring .

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تحضير وتشخيص بعض المشتقات الجديدة من املاح البنزوداي أزيبينيوم تحت ظروف تشعيع المايكروويف

عبدالامير مطلك فنجان **الاء شايع شبرم**

قسم الكيمياء - كلية العلوم للبنات- جامعة بغداد - بغداد - العراق

الخلاصة:

جرت محاولة لتحضير مشتقات البنزوأيميدازول من تفاعل اورثو فنيلين داي أمين ومشتقات حامض البنزويك بوجود الايثانول ومشتقات الكيتون تحت ظروف تشعيع المايكروويف ،إلا انه تعذّر الحصول على هذه المشتقات ، وبدلا" منها لقد تم الحصول على المشتقات الجديدة من ملح 5,1- بنزوداي أزيبينيوم . لقد تم مناقشة ميكانيكية التفاعل أيضا. حدث تفاعل غير متوقع لتحضير سلسلة جديدة من مشتقات أملاح 5,1- بنزوداي أزيبينيوم بمنتوج انتقائي . لقد تم تنقية وتشخيص تراكيب المركبات الجديدة باستعمال مختلف التقنيات الفيزيائية مثل: طيف الأشعة تحت الحمراء ،والتحليل الكمي الدقيق للعناصر وطيف الرنين النووي المغناطيسي للبروتون .

الكلمات المفتاحية: ملح بنزوداي أزيبينيوم، تشعيع المايكروويف، التشخيص.