Synthesis and Characterisation of Some New Substituted (α,α-diphenyl-α-hydroxymethyl)-1,2,4-triazoles-1,3,4-oxadiazoles and 1,3,4-thiadiazoles

Badie A. Ahmed and Salim J. Mohammed

Department of Chemistry, College of Science, University of Mosul

(NJC)

(Recevied on 25/2/2009) **(Accepted for publication 20/4/2010)**

Abstract

Several new substituted-4-alkyl/aryl semicarbazides (2a-d) were synthesized. Subsequent ring closure of substituted (2a-d) yield 2-amino alkyl/aryl-5-substituted-1,3,4-oxadiazoles (3a-d) and substituted-1,2,4-triazoles (4a-d) under acidic and basic media respectively. Methylation of compounds (4a-d) gave substituted methoxy-1,2,4-triazoles (5a-d). The reaction of benzilic acid hydrazide (I) with formic acid gave 1-formyl-2-(α,α-diphenyl-α-hydroxyacetyl) hydrazine (6). Refluxing of the later with phosphorus pentoxide and phosphorus pentasulfide gave oxa/thiadiazole (7 and 8) respectively. The structures of all products were elucidated by physical and Spectroscopic methods.

الخلاصة

في هذا البحث تم تحضير عدد من معوضات السيميكاربازيد (2a-d) الجديدة. عند استخدام الغلـق الحلقي لهذه المركبات باستخدام الوسط الحامضي والقاعدي تم الحصول على معوضات 1،3،4-أوكسادايازول (3a-d) ومركبات 1،2،4-ترايازول (4a-d) على التوالي، وعند مثيلة مركبات الترايازول (4a-d) بواسـطة يوديد المثيل تم الحصول على مركبات الميثوكسي ترايازول (5a-d). عند معاملة هيدرازيد حامض البنزيليك (1) مع حامض الفورميك تم الحصول على المركب 1-فورميل-2-($\alpha،\alpha$-ثنائي فنيل-α-هيدروكسـي اسيتيل) هيدرازين (6)، الذي عند معاملته مع خامس أوكسيد الفسفور وخامس كبريتيد الفسفور تم الحصـول على مركبي الأوكسا/الثيادايازول غير المعوضين (7 و 8) على التوالي.

تم إثبات الصيغ التركيبية للمركبات المحضرة الجديدة باستخدام الطرق الطيفية والفيزياوية المختلفة.

Introduction

Varied biological activities have been attributed to triazole, oxadiazole and thiadiazole compounds, including analgesic, antipyretic, antimicrobial, fungicidal and other central nervous system affecting activities[1, 2].

The use of benzilic acid hydrazide (I) as starting material for the synthesis of new heterocycle compounds with the aim of preparing potent biologically active compounds is a subject of recent interest[3].

Now we report a facile synthesis of several compounds such as semicarbazides, oxadiazoles, triazoles and thiadiazoles moiety, starting from benzilic acid hydrazide (I).

Experimental

Melting point were determined on Gallenkamp Melting point and are uncorrected. Infrared Spectra (ν cm^{-1}) were recorded on a Pye Unicam Sp200 Perkin-Elmer Spectrophotometer in KBr disc. ^{1}H-NMR Spectra were determined on Hitachi Perkin-Elmer Spectrophotometer (60 MHz) using TMS as internal reference. UV Spectra were measured in Shimadzu UV 160 Spectrophotometer. Elemental analysis were performed on Carlo Erba type 1106 CHN analyzer.

The methyl benzilate was prepared by the usual esterfication method, benzilic acid hydrazide (I) was prepared using the reported method[4], starting from methyl benzilate.

1-(α,α-Diphenyl-α-hydroxymethyl)-4-substituted Semicarbazides[5] (2a-d) (General Procedure):

Equimolar of benzilic acid hydrazide (I) (2.4 gm, 0.01 mole) and suitable alkyl/aryl isocyanate (0.01 mole) were refluxed in (30 ml) of absolute ethanol for (2-12 hours). The crystalline product which separated out on cooling was filtered and crystallized from ethanol to give the title compounds.

Physical data of the products are listed in (table 1). Their IR, UV and ^{1}H-NMR data are listed in (table 3).

5-(α,α-Diphenyl-α-hydroxymethyl)-2-alkyl/aryl amino-1,3,4-oxadiazoles[6] (3a-d):

Semicarbazides (2a-d) (0.01 mole) were added gradually with stirring during (20 minutes) to syrupy phosphoric acid (85%, 25 ml) at 20C^o.

The mixture was heated with stirring at the same temperature for further (30 minutes), then poured into ice-water and left overnight. The precipitate was filtered, washed with water and crystallized from aqueous ethanol.

Physical data of the products are listed in (table 2) their spectral data are listed in (table 4).

3-(α,α-Diphenyl-α-hydroxymethyl)-4-alkyl/aryl amino-1,2,4-triazoline-5-ones[5] **(4a-d):**

Semicarbazides (2a-d) (0.07 mole) were refluxed in 10% sodium hydroxide (25 ml) for three hours. The refluxing solution was treated with charcoal and filtered while hot, the filtrate was cooled and acidified with hydrochloric acid (pH 5-6). The solid was separated, dried and crystallized from aqueous ethanol to give the title compounds.

Physical data of the products are listed in (table 2), their spectral data are listed in (table 4).

5-(α,α-Diphenyl-α-hydroxymethyl)-4-alkyl/aryl amino-3-methoxy-1,2,4-triazols[7] **(5a-d):**

To a methanolic solution of 5-(α,α-diphenyl-α-hydroxy methyl)-4-alkyl/aryl-1,2,4-trizoline-5-ones (4a-d) (0.002 mole), fused sodium acetate (0.4 g) and methyl iodide (0.22 g, 0.002 mole) were added. The mixture was refluxed for four hours, then cooled in crushed ice and kept overnight in refrigerator the white solid precipitate was filtered off and crystallized from benzene.

Physical and spectral data of the products are listed in tables (2 and 4) respectively.

1-Formyl-2-(α,α-Diphenyl-α-hydroxyacetyl) hydrazine[8] **(6) :**

A solution of benzilic acid hydrazide (I) (2.4 gm, 0.01 mole) in formic acid (20 ml) was refluxed for three hours. The solvent was evaporated and the residue was crystallized from methanol to give (2.2 gm, 81%) of compound (6) (m.p. 147-49 ^{o}C).

Spectral data of the product are listed in table 5.

2-(α,α-Diphenyl-α-hydroxymethyl)-1,3,4-oxo/thiadaizole (7 and 8):

To a solution of formyl-2-(α,α-diphenyl-α-hydroxyacetyl) hydrazine (6) (0.27 gm, 0.001 mole) in xylene (200 ml), phosphorus pentoxide (0.14 gm, 0.001 mole) or phosphorus pentasulfide (0.17 gm, 0.001 mole) was added and the mixture was

refluxed for four hours. The solvent was removed and water (5 ml) was added to the residue. The crude product. Crystallization from methanol afforded compound (7) (m.p. 116-17 ^{o}C) (54%) and compound (8) (m.p. 165-67 ^{o}C) (65%).

Spectral data of the products (7 and 8) are shown in table 5.

Table 1: Physical data of compounds (2a-d)

Compd. No. 2	Ar(R)	m.p. C^{o}	Yield %	Crys. solvent	Mol. formula	Analysis % calcd. (found)		
						C%	H%	N%
a	Cyclohexyl	183-85	92	EtOH	$C_{21}H_{25}N_3O_3$	68.52 (68.66	6.70 6.81	11.33 11.44)
b	C_6H_5-	182-84	89	EtOH	$C_{21}H_{19}N_3O_3$	69.47 (69.60	5.31 5.26	11.54 11.63)
c	naphthyl	197-99	89	EtOH	$C_{24}H_{21}N_3O_3$	72.26 (72.18	5.37 5.26	10.43 10.52)
d	4-FC_6H_4-	171-73	85	eq.EtOH	$C_{21}H_{18}FN_3O_3$	66.37 (66.49	4.69 4.74	10.92 11.08)

Table 2: Physical data of compounds (3-5a-e)

Compd. No.	m.p. C°	Yield %	Mol. formula	Analysis calcd.			Anylsis found		
				C%	H%	N%	C%	H%	N%
3a	223-25	52	$C_{21}H_{23}N_3O_2$	71.83	6.64	11.89	72.20	6.59	12.03
3b	218-20	55	$C_{21}H_{17}N_3O_2$	73.29	4.81	12.12	73.46	4.95	12.24
3c	228-30	63	$C_{25}H_{19}N_3O_2$	76.27	4.81	10.49	76.33	4.83	10.68
3d	205-07	45	$C_{21}H_{16}FN_3O_2$	69.93	4.28	11.49	69.80	4.43	11.63
4a	232-34	64	$C_{21}H_{23}N_3O_2$	72.22	6.53	11.98	72.20	6.59	12.03
4b	207-09	60	$C_{21}H_{17}N_3O_2$	73.29	4.85	12.11	73.46	4.95	12.24
4c	297-99	56	$C_{25}H_{19}N_3O_2$	76.19	4.97	10.50	76.33	4.83	10.68
4d	219-21	45	$C_{21}H_{16}FN_3O_2$	69.71	4.32	11.51	69.80	4.43	11.63
5a	211-13	63	$C_{22}H_{25}N_3O_2$	72.48	6.67	11.62	72.72	6.88	11.57
5b	173-75	71	$C_{22}H_{19}N_3O_2$	73.83	5.28	11.56	73.94	5.32	11.76
5c	177-78	54	$C_{26}H_{21}N_3O_2$	76.31	5.19	10.33	76.65	5.15	10.31
5d	187-89	54	$C_{22}H_{18}FN_3O_2$	70.22	4.69	11.23	70.40	4.80	11.20

Results and Discussion

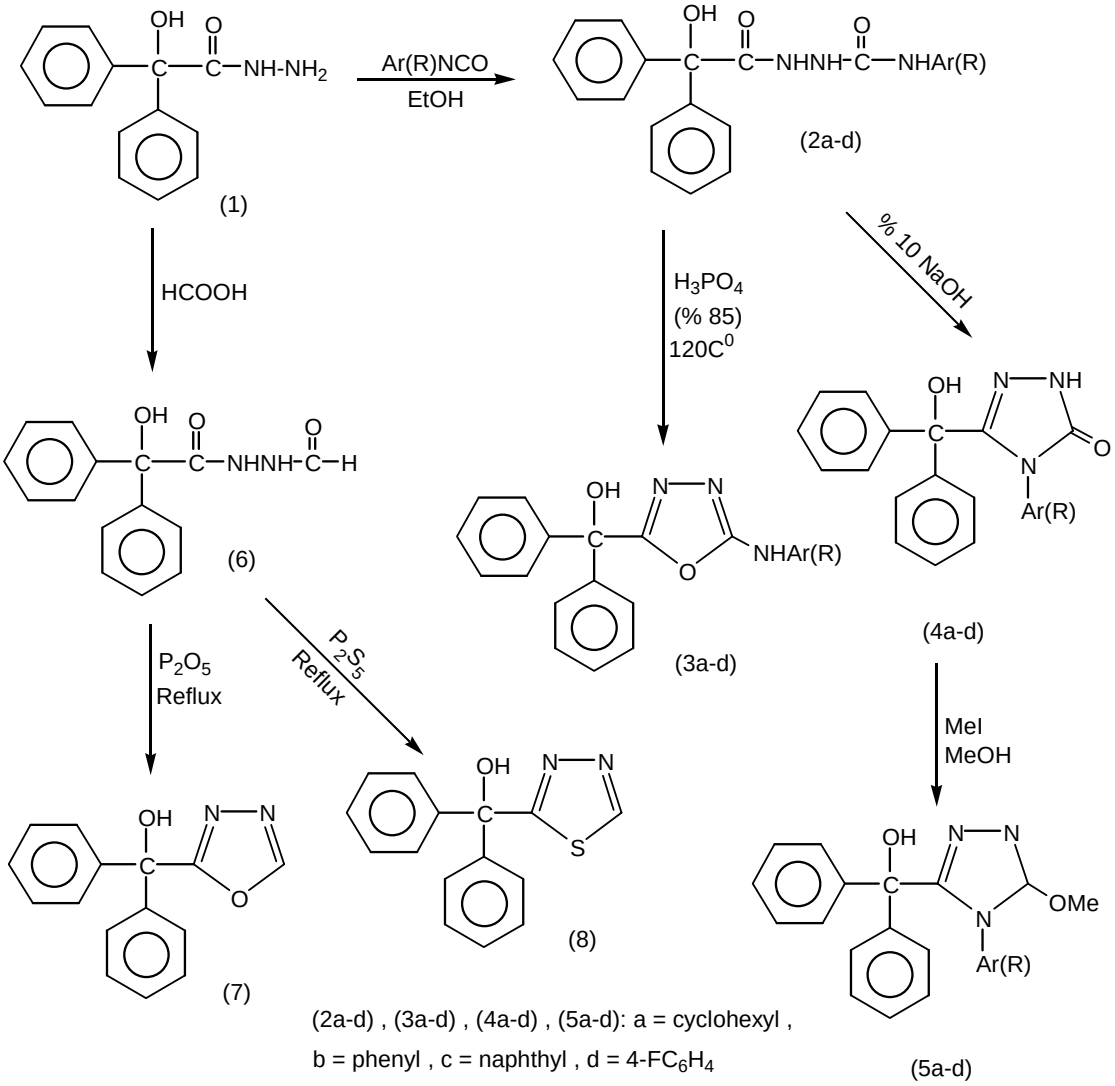
During the course of our extensive work towards the synthesis of new heterocyclic compounds of potential biological activity, acylsemicarbazides are used to synthesize many heterocyclic compounds, especially oxadiazoles and triazoles, which are well-known for their useful biological and pharmacological activities[9].

Acid hydrazide (I) is used for synthesis of new substituted semicarbazides (2a-d) by its reaction with suitable isocyanate. It has been found that this reaction was depend upon the nature of isocyanate substituents. Arylisocyanate needed longer reaction time than that of alkyl analogues, this probably due to steric factor[10].

The pharmacological interest attached to the substituted-1,3,4-oxadiazoles[11] led us to a great interest to synthesize 5-(α,α-diphenyl-α-hydroxymethyl)-1,3,4-oxadiazoles (3a-d). Thus, reaction of semicarbazides (2a-d) with phosphoric acid gave compounds (3a-d).

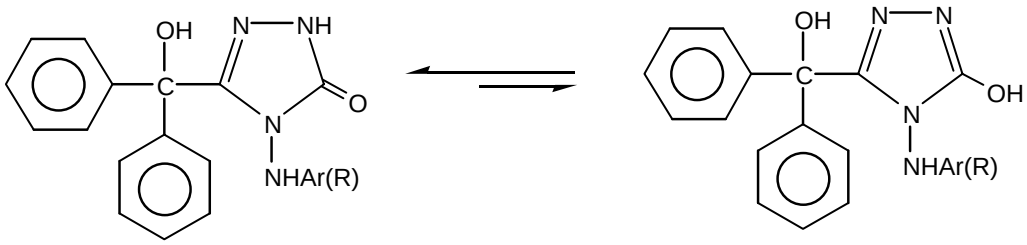
Structural assignment for these derivatives are strongly supported by elemental and spectral analyses (tables 2 and 4).

1,2,4-Triazole compounds have been found to possess several biological activities[12]. In connection with our continuous interest in the chemistry of benzilic acid, we now report a synthesis of a series of 1,2,4-triazole derivatives (4a-d) of this acid, by refluxing the corresponding semicarbazides (2a-d) in the presence of (10%) sodium hydroxide.



(Scheme)

1,2,4-Trizole-2-ones (4a-d) may exist in two toutomeric forms (enol and keto), the keto form of which are found to be predominates, since the IR spectra showed characteristic C=O bands in the range (3260-3190 cm^{-1}). UV spectra of these compounds have λ_{max} (MeOH) at (265-312 nm) which were presumably due to the carbonyl group. Finally, ^{1}H-NMR spectra showed no absorption of OH proton which proved that the keto form is favored. On the basis of these data it was concluded that triazoles (4a-d) exclusively present in the keto form both solid and in solution[13].



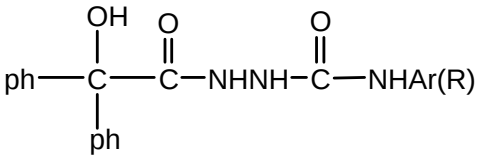
(keto form) (enol form)

Methylation of triazoles (4a-d) with methyl iodide in methanol under reflux afforded the corresponding methoxy derivatives (5a-d), probably via the enol toutomer. The O-methylation is confirmed by the singlet peak at (δ 3.8-3.9 ppm) in the NMR spectra of compounds (5a-d).

Generally heating the acid hydrazide (1) with formic acid yielded 1-formyl-2-substituted hydrazine (6).

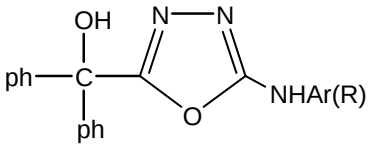
The UV spectrum of (6) (Table5) shows λ_{max} (MeOH) at (258nm). IR spectrum shows characteristic absorptions at: (3430 cm^{-1}) for NH group, (1695 cm^{-1}) for formyl carbonyl group and (1657 cm^{-1}) for bonded carbonyl group. The ^{1}H-NMR spectrum showed the expected signals of which the aromatic part showed multiplet in the range (δ 7.2-7.5 ppm); the two NH protons were observed at δ 8.2 and 8.8 ppm. Finally, the formyl proton appeared at δ 10.3 ppm.

Table 3: Spectral data of compounds (2a-d)

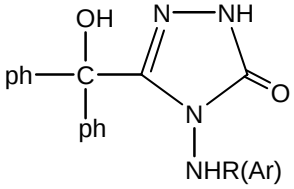


Compd. No.	UV (MeOH) λ_{max} (nm)	IR (KBr) υ cm^{-1}		^{1}H-NMR δ (ppm), DMSO-d_6
		C=O	NH	
2a	303	1657 1690	3220, 3380 3400	0.7-1.5(m,1H cyclohexyl); 6.3(s,1H,OH); 7.0(s,10H,2ph); 5.5(bs,1H,NH); 7.3 and 9.2 (each (s) each 1H,2NH)
2b	252	1660 1618	3195, 3350 3400	6.3(s,1H,OH); 6.8-7.4(m,10H,2ph); 7.7,8.25,9.4 (each(s), each 1H, 3NH)
2c	279	1670 1630	3200, 3315 3412	6.15(s,1H,OH); 6.5-7.4(m,17H,ArH+2ph); 7.8,8.0,9.3 (each(s) each 1H, 3NH)
2d	313	1682 1645	3210, 3315 3390	6.3(s,1H,OH); 6.9-7.4(m,15H,3ph); 7.7,8.4,9.4 (each(s) each 1H, 3NH)

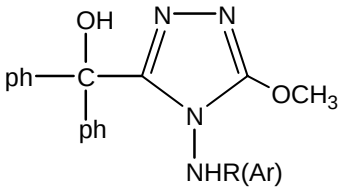
Table 4: Spectral data of compounds (3-5a-e)



(3a-d)



(4a-d)



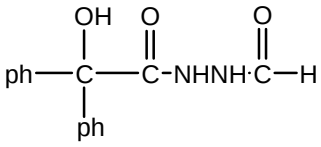
(5a-d)

Compd. No.	UV (MeOH) λ_{max} (nm)	IR (KBr) υ cm^{-1}			^{1}H-NMR δ (ppm), DMSO-d_6
		C=N	C=O	NH	
3a	283	1645	-----	3218	0.8-1.4(m,1H,cyclohexyl); 6.2(s,1H,OH); 6.8(bs,1H,NH); 7.1-7.6(m,10H,2ph)
3b	298	1632	-----	3260	6.4(s,1H,OH); 7.5(bs,1H,NH); 7.2-7.7(m, 14H,3ph)
3c	323	1660	-----	3180	6.25 (s,1H,OH); 7.6(bs,1H,NH); 6.5-7.4 (m,17H,ArH+2ph)
3d	312	1630	-----	3275	6.2(s,1H,OH); 7.2(s,1H,NH); 6.9-7.6(m, 15H,3ph)
4a	312	1613	1670	3230	0.6-1.2(m,1H,cyclohexyl); 6.15(s,1H,OH); 7.2(s,10H,2ph); 7.25(s,1H,NH)
4b	307	1615	1680	3260	6.2(s,1H,OH); 6.8-7.1(m,15H,3ph); 7.4(s,1H,NH)
4c	265	1603	1675	3190	6.2(s,1H,OH); 6.7-7.3(m,15H,3ph); 7.5(s,1H,NH)
4d	284	1595	1670	3211	6.3(s,1H,OH); 6.6-7.4(m,15H,2ph); 7.5(m,1H,NH)
5a	323	1590	------	------	0.9-1.3 (m, 11H, cyclohexyl); 3.8(s,3H, OCH_3); 6.2(s,1H,OH); 6.7-7.5(m,10H,2ph)
5b	318	1600	------	------	3.9(s,3H,OCH_3); 6.4(s,1H,OH); 6.8-7.4(m,15H,3ph)
5c	270	1635	------	------	3.85(s,3H,OCH_3); 6.4(2,1H,OH); 6.9-7.4(m,17H,ArH+2ph)
5d	291	1612	------	------	3.8 (s, 3H, OCH_3); 6.2 (s, H, OH); 6.9-7.6(m,14H,2ph+ ArH)

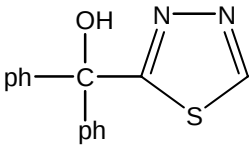
Another two new heterocyclic derivatives of benzilic acid namely mono substituted-1,3,4-oxa/thiadiazole (7 and 8) have been synthesized. Refluxing compound (6) in presence of phosphorus pentoxide or phosphorus pentasulfide afforded 2-(α,α-diphenyl-α-hydroxy methyl)-1,3,4-oxa/thiadiazole (7 and 8) respectively.

Structural assignment of these products are strongly supported by physical and spectral data. The UV spectra showed λ_{max} (MeOH) at (301nm) for compound (7) and (309 nm) for compound (8). IR spectra showed characteristic absorptions at (1592 cm^{-1}) and (1607 cm^{-1}) for C=N group. The ^{1}H-NMR spectrum (DMSO-d_6) showed the aromatic protons as multiplets in the range (δ 6.7-7.5 ppm); a singlet absorption at (δ 7.9 ppm) due to oxazole ring proton and a broad singlet at (δ 7.7 ppm) due to proton of thiazole ring. Finally, two singlet absorption appeared at (δ 6.3 and 6.7 ppm) were assigned for the two hydroxyle protons of compound (7 and 8) respectively.

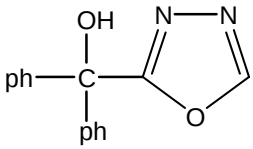
Table 5: Spectral data of compounds (6, 7 and 8)



(6)



(8)



(7)

Compd. No.	UV (MeOH) λ_{max} (nm)	IR (KBr) υ cm^{-1}			^{1}H-NMR δ (ppm), DMSO-d_6
		C=O	C=N	NH	
6	258	1657 1595	-----	3430	6.8(s,1H,OH); 7.2-7.5(m,10H,2ph); 8.2,8.8(s,2H2NH); 10.3(s,1H,CHO)
7	301	-----	1592	-----	6.3(s,1H,OH); 6.7-7.5(m,10H,2ph); 7.9(s,1H,oxazole ring)
8	309	-----	1607	-----	6.7(s,1H,OH); 6.9-7.5(m,10H,2ph); 7.7(bs,1H,thiazole ring)

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