New Synthesis of 4,5-Dihydro-1,2,4-triazin-3(2*H*)-one Derivatives through Cyclic Transformation of 1,3,4-Oxadiazol-2(3*H*)-one Derivatives

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Some 5-aryl(or benzyl)-2-oxo-1,3,4-oxadiazole-3(2*H*)-acetones or acetophenones **2** were easily prepared. These compounds reacted with hydrazine derivatives to give 4,5-dihydro-1,2,4-triazin-3(2*H*)-one derivatives **3**, **4** and **6** in good yields. With phenylhydrazine, the intermediate hydrazones **5** were obtained. Their conversion into triazinones necessitated the presence of sodium ethylate.

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In recent papers, we reported new ring transformations of 5-aryl-3-carbazoyl-1,3,4-oxadiazol-2(3*H*)-ones into 4-benzamido-1,2,4-triazolidine-3,5-diones [1] and ethyl 5-aryl(or benzyl)-2-oxo-1,3,4-oxadiazole-3(2*H*)-acetates into hydantoin derivatives [2]. These transformations followed a same general intramolecular reaction pathway (Scheme 1). "Z" represents a chain of 2 or 3 carbon or heteroelement units. The nucleophilic center NuH could be obtained by *N*-alkylation of oxadiazolone **1** or formed as an intermediate in a reaction of a functionalized N-3 substituent with a nucleophilic reagent.

Scheme 1

Scheme 2

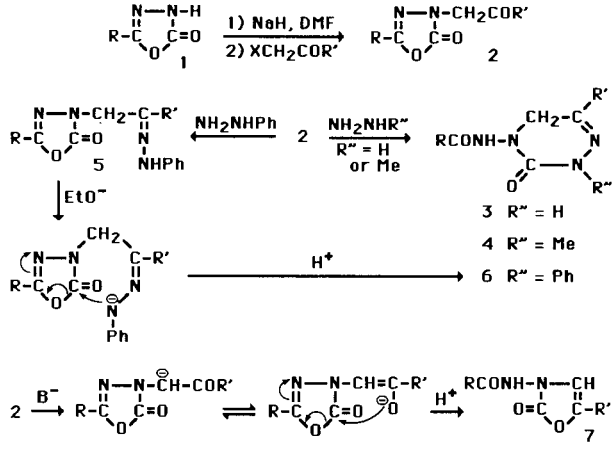

Table I

1,3,4-Oxadiazol-2(3*H*)-one Derivatives **2**

2	R	R'	Yield % [a]	Mp °C	Formula	Analyses, % Calcd./Found C	H	N	IR, ν cm^{-1}	^{1}H NMR [b] δ ppm
a	Ph	Me	60	114 [c]	$C_{11}H_{10}N_2O_3$ (218.20)	60.54 60.64	4.62 4.64	12.84 12.81	1770, 1720	2.2 (s, 3H), 4.85 (s, 2H), 7.5-7.9 (m, 5H)
b	Ph	Ph	76	147 [c]	$C_{16}H_{12}N_2O_3$ (280.27)	68.56 68.69	4.32 4.30	10.00 10.07	1780, 1690	5.55 (s, 2H), 7.4-8.2 (m, 10H)
c	4-MePh	Me	65	139 [d]	$C_{12}H_{12}N_2O_3$ (232.23)	62.06 61.92	5.21 5.25	12.06 12.11	1785, 1725	2.2 (s, 3H), 2.4 (s, 3H), 4.85 (s, 2H) 7.4 and 7.7 (2d, 4H)
d	4-MePh	Ph	67	148 [c]	$C_{17}H_{14}N_2O_3$ (294.30)	69.38 69.36	4.80 4.73	9.52 10.00	1770, 1685	2.35 (s, 3H), 5.5 (s, 2H), 7.3 (d, 2H), 7.45-7.8 (m, 5H), 8 (d, 2H)
e	4-ClPh	Me	79	160 [c]	$C_{11}H_9ClN_2O_3$ (252.65)	52.29 52.41	3.59 3.56	11.09 11.12	1795, 1725	2.2 (s, 3H), 4.85 (s, 2H), 7.6 and 7.8 (2d, 4H)
f	4-ClPh	Ph	54	165 [e]	$C_{16}H_{11}ClN_2O_3$ (314.71)	61.06 61.21	3.52 3.51	8.90 8.87	1775 (b), 1690	5.55 (s, 2H), 7.55-7.95 (m, 7H), 8.05 (d, 2H)
g	Ph-CH_2	Me	61	68 [f]	$C_{12}H_{12}N_2O_3$ (232.23)	62.06 62.01	5.21 5.24	12.06 12.05	1780, 1720	2.15 (s, 3H), 4 (s, 2H), 4.7 (s, 2H), 7.4 (s, 5H)
h	Ph-CH_2	Ph	70	78 [f]	$C_{17}H_{14}N_2O_3$ (294.30)	69.38 69.25	4.80 4.78	9.52 9.55	1775, 1690	4.05 (s, 2H), 5.45 (s, 2H), 7.4 (s, 5H), 7.6-8.1 (m, 5H)

[a] Non optimized yields. [b] In DMSO-d_6. [c] 1-Propanol. [d] 1-Butanol. [e] Ethanol. [f] Diethyl ether.

Table II

4-Acylamino-6-methyl(or phenyl)-4,5-dihydro-1,2,4-triazin-3(2*H*)-ones **3**

3	R	R'	Yield % [a]	Mp °C	Formula	Analyses, % Calcd./Found C	H	N	IR, ν cm^{-1}	^{1}H NMR [b] δ ppm
a	Ph	Me	51	194 [c]	$C_{11}H_{12}N_4O_2$ (232.23)	56.89 56.83	5.21 5.15	24.13 24.19	3330, 3250, 1690, 1655	1.85 (s, 3H), 4.2 (s, 2H), 7.45-8 (m, 5H), 9.9 (s, 1H), 10.7(s, 1H)
b	Ph	Ph	33	240 [c,d]	$C_{16}H_{14}N_4O_2$ (294.30)	65.29 65.08	4.80 4.91	19.04 18.90	3240 (b), 1700 1660	4.75 (s, 2H), 7.4-8.05 (m, 10H), 10.5 (s, 1H), 10.85 (s, 1H)
c	4-MePh	Me	57	198 [c]	$C_{12}H_{14}N_4O_2$ (246.26)	58.52 58.42	5.73 5.68	22.75 22.81	3280, 3220, 1695, 1655	1.85 (s, 3H), 2.35 (s, 3H), 4.15 (s, 2H), 7.35 and 7.8 (2d, 4H), 9.85 (s, 1H), 10.6 (s, 1H)
d	4-MePh	Ph	48	275 [c]	$C_{17}H_{16}N_4O_2$ (308.33)	66.22 66.13	5.23 5.21	18.17 18.26	3250 (b), 1685, 1660	2.35 (s, 3H), 4.75 (s, 2H), 7.2-8.05 (m, 9H), 10.55 (s, 1H), 10.8 (bs, 1H)
e	4-ClPh	Me	61	230 [c]	$C_{11}H_{11}ClN_4O_2$ (266.68)	49.54 49.68	4.16 4.14	21.01 21.08	3330, 3270, 1700, 1655	1.85 (s, 3H), 4.15 (s, 2H), 7.6 and 7.9 (2d, 4H), 9.85 (s, 1H), 10.7 (s, 1H)
f	4-ClPh	Ph	52	289 [e]	$C_{16}H_{13}ClN_4O_2$ (328.74)	58.45 58.28	3.99 3.96	17.04 17.09	3320, 3250, 1675, 1635	4.7 (s, 2H), 7.35-8.05 (m, 9H), 10.5 (s, 1H), 10.9 (s, 1H)
g	$PhCH_2$	Me	66	195 [e]	$C_{12}H_{14}N_4O_2$ (246.26)	58.52 58.42	5.73 5.77	22.75 22.80	3220 (b), 1675, 1655	1.85 (s, 3H), 3.5 (s, 2H), 4.05 (s, 2H), 7.3 (s, 5H), 9.7 (s, 1H), 10.25 (s, 1H)
h	$PhCH_2$	Ph	50	236 [f,g]	$C_{17}H_{16}N_4O_2$ (308.33)	66.22 66.07	5.23 5.20	18.17 18.24	3240 (b), 1690, 1675	3.5 (s, 2H), 4.6 (s, 2H), 7.1-7.8 (m, 10H), 10.4 (bs, 2H)

[a] Non optimized yields. [b] In DMSO-d_6. [c] 1-Propanol. [d] Lit [5b] mp 232°. [e] 1-Butanol. [f] Methanol. [g] Lit [5b] mp 234-235°.

Table III

4-Acylamino-2-methyl-6-methyl(or phenyl)-4,5-dihydro-1,2,4-triazin-3(2*H*)-ones **4**

4	R	R'	Yield % [a]	Mp °C	Formula	Analyses, % Calcd./Found C	H	N	IR, ν cm^{-1}	^{1}H NMR [b] δ ppm
a	Ph	Me	70	199 [c]	$C_{12}H_{14}N_4O_2$ (246.26)	58.52 58.71	5.73 5.72	22.75 22.81	3280, 1680 1650	1.9 (s, 3H), 3.15 (s, 3H), 4.2 (s, 2H), 7.45-8 (m, 5H), 10.7(s, 1H)
b	Ph	Ph	70	190 [c]	$C_{17}H_{16}N_4O_2$ (308.33)	66.22 66.29	5.23 5.20	18.17 18.23	3300, 1680, 1655	3.4 (s, 3H), 4.75 (s, 2H), 7.35-8 (m, 10H), 10.9 (s, 1H)
c	4-MePh	Me	65	205 [c]	$C_{13}H_{16}N_4O_2$ (260.29)	59.98 60.01	6.20 6.18	21.53 21.57	3280,1675, 1645	1.95 (s, 3H), 2.35 (s, 3H), 3.2 (s, 3H), 4.2 (s, 2H), 7.3 and 7.8 (2d, 4H), 10.6 (s, 1H)
d	4-MePh	Ph	61	182 [c]	$C_{18}H_{18}N_4O_2$ (322.35)	67.06 67.18	5.63 5.60	17.38 17.45	3300, 1690, 1660	2.35 (s, 3H), 3.35 (s, 3H), 4.75 (s, 2H), 7.25-7.95 (m, 9H), 10.75 (s, 1H)
e	4-ClPh	Me	82	234 [c]	$C_{12}H_{13}ClN_4O_2$ (280.70)	51.34 51.21	4.67 4.69	19.96 20.01	3250, 1660 1650	1.9 (s, 3H), 3.15 (s, 3H), 4.25 (s, 2H), 7.65 and 7.95 (2d, 4H), 10.8 (s, 1H)
f	4-ClPh	Ph	62	197 [e]	$C_{17}H_{15}ClN_4O_2$ (342.77)	59.57 59.44	4.41 4.40	16.35 16.41	3300 (b), 1680, 1660	3.35 (s, 3H), 4.75 (s, 2H), 7.4-7.9 (m, 7H), 8 (d, 2H), 11 (s, 1H)
g	$PhCH_2$	Me	73	170 [e]	$C_{13}H_{16}N_4O_2$ (260.29)	59.98 59.88	6.20 6.17	21.53 21.61	3250 (b), 1690, 1645	1.9 (s, 3H), 3.15 (s, 3H), 3.5 (s, 2H), 4.1 (s, 2H), 7.3 (s, 5H), 10.3 (s, 1H)
h	$PhCH_2$	Ph	60	191 [c]	$C_{18}H_{18}N_4O_2$ (322.35)	67.06 67.12	5.63 5.65	17.38 17.31	3250 (b), 1695, 1650	3.3 (s, 3H), 3.5 (s, 2H), 4.6 (s, 2H), 7.2-7.8 (m, 10H), 10.45 (s, 1H)

[a] Non optimized yields. [b] In DMSO-d_6. [c] 1-Propanol.

In this third report, we describe reactions of 5-aryl(or benzyl)-2-oxo-1,3,4-oxadiazole-3(2*H*)-acetones or acetophenones **2** with hydrazine, methylhydrazine and phenylhydrazine (Scheme 2). Ketones **2** were prepared by a classical method using alkylation with chloroacetone or 2-bromoacetophenone of the corresponding oxadiazolones **1** sodium salts in anhydrous dimethylformamide. They are presented in Table I.

Table IV

Phenylhydrazones **5**

5	R	R'	Yield % [a]	Mp °C	Formula	Analyses, % Calcd./Found C	H	N	IR, ν cm^{-1}	^{1}H NMR [b] δ ppm
a	Ph	Me	91	180 [c]	$C_{17}H_{16}N_4O_2$ (308.33)	66.22 66.29	5.23 5.21	18.17 18.22	3310, 1755	1.9 (s, 3H), 4.55 (s, 2H), 7.7-7.9 (m, 10H), 9 (s, 1H)
b	Ph	Ph	73	180 [d]	$C_{22}H_{18}N_4O_2$ (370.39)	71.34 71.41	4.90 4.86	15.13 15.10	3300, 1760	5.15 (s, 2H), 7.1-7.95 (m, 15H), 9.1 (s, 1H)
c	4-MePh	Me	72	169 [d]	$C_{18}H_{18}N_4O_2$ (322.35)	67.06 67.12	5.63 5.60	17.38 17.43	3320, 1755	1.9 (s, 3H), 2.35 (s, 3H), 4.55 (s, 2H), 6.6-7.2 (m, 5H), 7.4 and 7.75 (2d, 4H), 9.05 (s, 1H)
d	4-MePh	Ph	87	168 [c]	$C_{23}H_{20}N_4O_2$ (384.42)	71.86 71.76	5.24 5.22	14.57 14.61	3300, 1750	2.3 (s, 3H), 5.15 (s, 2H), 7.25-7.95 (m, 14H), 9.9 (s, 1H)
e	4-ClPh	Me	74	195 [c]	$C_{17}H_{15}ClN_4O_2$ (342.77)	59.57 59.65	4.41 4.38	16.35 16.42	3330, 1770	1.9 (s, 3H), 4.55 (s, 2H), 6.6-7.3 (m, 5H), 7.6 and 7.85 (2d, 4H), 9 (s, 1H)
g	$PhCH_2$	Me	90	124 [d]	$C_{18}H_{18}N_4O_2$ (322.35)	67.06 66.89	5.63 5.64	17.38 17.41	3340, 1770	1.85 (s, 3H), 3.95 (s, 2H), 4.45 (s, 2H), 6.6-7.4 (m, 10H), 9 (s, 1H)

[a] Non optimized yields. [b] In DMSO-d_6. [c] 1-Butanol. [d] 1-Propanol.

Table V

4-Acylamino-6-methyl(or phenyl)-2-phenyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-ones **6**

6	R	R'	Yield % [a]	Mp °C	Formula	Analyses, % Calcd./Found C	H	N	IR, ν cm^{-1}	^{1}H NMR [b] δ ppm
a	Ph	Me	70	183 [c]	$C_{17}H_{16}N_4O_2$ (308.33)	66.22 66.10	5.23 5.20	18.17 18.28	3250, 1690, 1645	2 (s, 3H), 4.4 (s, 2H), 7.15-8 (m, 10H), 10.8 (s, 1H)
b	Ph	Ph	67	210 [c]	$C_{22}H_{18}N_4O_2$ (370.39)	71.34 71.31	4.90 4.88	15.13 15.22	3250 (b), 1690, 1660	4.95 (s, 2H), 7.2-8.05 (m, 15H), 11.05 (s, 1H)
c	4-MePh	Me	63	160 [c,d]	$C_{18}H_{18}N_4O_2$ (322.35)	67.06 67.00	5.63 5.60	17.38 17.44	3200, 1690, 1640	2.05 (s, 3H), 2.35 (s, 3H), 4.35 (s, 2H), 7-7.6 (m, 7H), 7.85 (2d, 4H), 10.8 (bs, 1H)
d	4-MePh	Ph	69	215 [c]	$C_{23}H_{20}N_4O_2$ (384.42)	71.86 71.91	5.24 5.21	14.57 14.63	3200, 1700, 1655	2.4 (s, 3H), 4.9 (s, 2H), 7.1-7.95 (m, 14H), 10.9 (bs, 1H)
e	4-ClPh	Me	64	152 [e]	$C_{17}H_{15}ClN_4O_2$ (342.77)	59.57 59.70	4.41 4.42	16.35 16.30	3240, 1680, 1655	2.05 (s, 3H), 4.55 (s, 2H), 7.3-7.6 (m, 5H), 7.7 and 8 (2d, 4H), 11 (bs, 1H)
g	$PhCH_2$	Me	62	152 [e]	$C_{18}H_{18}N_4O_2$ (322.35)	67.06 67.11	5.63 5.68	17.38 17.32	3250 (b), 1690, 1655	1.95 (s, 3H), 3.5 (s, 2H), 4.2 (s, 2H), 7.2-7.6 (m, 10H), 10.45 (s, 1H)

[a] Non optimized yields. [b] In DMSO-d_6. [c] Ethanol. [d] Water. [e] Cyclohexane.

When these compounds **2** were treated with hydrazine hydrate at a 2:1 hydrazine/ketone molar ratio for 3 hours in boiling 1-propanol, 4-acylamino-6-methyl(or phenyl)-4,5-dihydro-1,2,4-triazin-3(2*H*)-ones **3** were obtained in good yields (Table II). With benzyl derivatives **2g** and **2h**, this reaction occurred at room temperature (Scheme 2).

In a recent patent [3], an example of that reaction with R = trifluoromethyl has been reported. Only two other synthetic methods are known in the literature for the preparation of 4-amino-4,5-dihydro-1,2,4-triazin-3(2*H*)-one derivatives, one by reacting bases with phenacylhydrazine semicarbazone [4] and the second by treatment with hydrazine hydrate of the salts formed between 2-amino-5-aryl-1,3,4-oxadiazoles and halogenoketones [5].

In the same experimental conditions as with hydrazine hydrate but at a 1.5:1 hydrazine/ketone molar ratio, methylhydrazine converted compounds **2** to new 4-acylamino-2-methyl-6-methyl(or phenyl)-4,5-dihydro-1,2,4-triazin-3(2*H*)-ones **4** (Table III). The intermediate methylhydrazones were not isolated.

At last, when phenylhydrazine was reacted with ketones **2** for 2 hours in boiling 1-propanol, the corresponding phenylhydrazones **5a-e,g** were obtained (Table IV). The cyclic transformation of **5** into 4-acylamino-6-methyl(or

phenyl)2-phenyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-ones **6** (Table V) necessitated the presence of sodium ethylate in absolute ethanol. With ketones **2f** or **2h**, the reaction of phenylhydrazine gave, respectively, a mixture of compounds which could not be isolated (probably due to a cycle opening) or an unstable oil which could not be cyclized.

In these reactions, very small amounts of other heterocyclic compounds, 3-acylamino-1,3-oxazol-2(3*H*)-one derivatives **7** have been detected. They were the result of an other base-catalyzed cyclic transformation of ketones **2**. They will be presented in a next paper.

Assignment for the structures of new products was provided by elemental analysis and ir and ^{1}H-nmr spectra.

EXPERIMENTAL

Melting points (uncorrected) were determined with a Buchi oil heated apparatus. The ir spectra were recorded on a Perkin Elmer 1310 spectrophotometer as potassium bromide disks. The ^{1}H-nmr spectra were obtained in DMSO-d_6 on a Brucker WP 80 spectrometer and are reported as δ values (ppm) relative to tetramethylsilane as an internal standard.

Oxadiazolones **1**.

These compounds were prepared by the classical method by reaction of phosgen with the corresponding hydrazides [6].

5-Aryl(or benzyl)-2-oxo-1,3,4-oxadiazole-3(2*H*)-acetones and 5-Aryl(or benzyl)-2-oxo-1,3,4-oxadiazole-3(2*H*)-acetophenones **2**.

To a stirred solution of 10 mmoles of **1** in 40 ml of dry dimethylformamide at 0°, 0.24 g (10 mmoles) of sodium hydride was added. When hydrogen gas evolution ceased, the mixture was heated at 60-80° for 10 minutes. After cooling at 0°, a solution of 0.93 g (10 mmoles) of chloroacetone or 1.99 g (10 mmoles) of 2-bromoacetophenone in 10 ml of dry dimethylformamide was added slowly. The reaction mixture was stirred for 30 minutes at room temperature, then for 30 minutes at 60-80°. After cooling, it was poured onto 150 ml of ice-water. Compound **2** precipitated, was filtered and recrystallized from adequate solvent (Table I).

4-Acylamino-6-methyl(or phenyl)-4,5-dihydro-1,2,4-triazin-3(2*H*)-ones **3** and 4-Acylamino-2-methyl-6-methyl(or phenyl)-4,5-dihydro-1,2,4-triazin-3(2*H*)-ones **4**.

To a solution of 10 mmoles of **2** in 40 ml of 1-propanol was added 1 g (20 mmoles) of hydrazine hydrate (to prepare **3**) or 0.7 g (15 mmoles) of methylhydrazine (to prepare **4**). The reaction mixture was refluxed for 3 hours. Solvent was evaporated under reduce pressure and the resulting solid **3** or **4** was recrystallized from adequate solvent (Table II and III).

Phenylhydrazones **5**.

To a solution of 10 mmoles of **2** in 40 ml of 1-propanol was added 1.1 g (10 mmoles) of phenylhydrazine and the reaction mixture was refluxed for 2 hours. After removal of the solvent under reduced pressure, the resulting solid **5** was recrystallized from adequate solvent (Table IV).

4-Acylamino-6-methyl(or phenyl)-2-phenyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-ones **6**.

To a solution of 10 mmoles of sodium ethylate in 40 ml of absolute ethanol was added at room temperature 10 mmoles of **5**. The reaction mixture was refluxed for 90 minutes. After cooling at room temperature, it was poured onto 100 ml of ice-water and 2 ml of acetic acid. Compound **6** precipitated, was filtered and recrystallized from adequate solvent (Table V).

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