Cyclic Transformations of 5-Aryl(or Benzyl)-3-(2-bromoethyl-1,3,4-oxadiazol-2(3*H*)-ones into 1-Aminoimidazolidin-2-one and 5,6-Dihydro-4*H*-1,3,4-oxadiazine Derivatives

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5-Aryl(or benzyl)-3-(2-bromoethyl)-1,3,4-oxadiazol-2(3*H*)-ones **3** have been prepared. They were reacted with secondary alkylamines without any change of the heterocycle to give amino derivatives **6**, but with primary alkylamines, cyclic transformation occurred to give 1-acylamino-3-alkylimidazolidin-2-ones **7**. In the presence of sodium alcoholate, bromo compounds **3** were transformed into 2-aryl(or benzyl)-4-alkoxycarbonyl-5,6-dihydro-4*H*-1,3,4-oxadiazines **9**.

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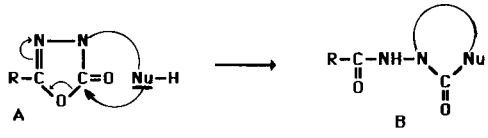
Reactions of various nucleophilic reagents such as amines, hydrazines or alcohols with 3-unsubstituted 1,3,4-oxadiazol-2(3*H*)-ones to give semicarbazide [1-7], carbonohydrazide or hydrazine derivatives and some heterocyclic compounds have been reported [1,2,8,9]. On the other hand, intramolecular nucleophilic reactions using some functionalized N-3 substituents of the oxadiazolone cycle and conducting to cyclic transformations into various heterocycles are less known. In recent papers, we reported some examples [10-12] (Scheme 1).

Scheme 1



In this way, Kristinsson *et al.* [13] have studied the reactions of secondary amines and thiols with a particular compound, the 3-(2-bromoethyl)-5-trifluoromethyl-1,3,4-oxadiazol-2(3*H*)-one (**1**). These authors have obtained some 4-carbamoyl-5-trifluoromethyl-5,6-dihydro-4*H*-1,3,4-oxadiazines **2** (Scheme 2).

Our purpose was the more general study of reactions of primary and secondary amines or alcohols (in the presence of sodium alcoholate) with 5-aryl(or benzyl)-3-(2-bromoethyl)-1,3,4-oxadiazol-2(3*H*)-ones **3**.

Compounds **3** were prepared in good yields by reaction of 1,2-dibromoethane in excess with the sodium salts of 5-aryl(or benzyl)-1,3,4-oxadiazol-2(3*H*)-ones **4** in anhydrous dimethylformamide (Table I). As attempted, the corresponding 3,3'-ethylenedi(5-aryl-1,3,4-oxadiazol-2(3*H*)-ones) **5** were formed as by-products in these reactions except for

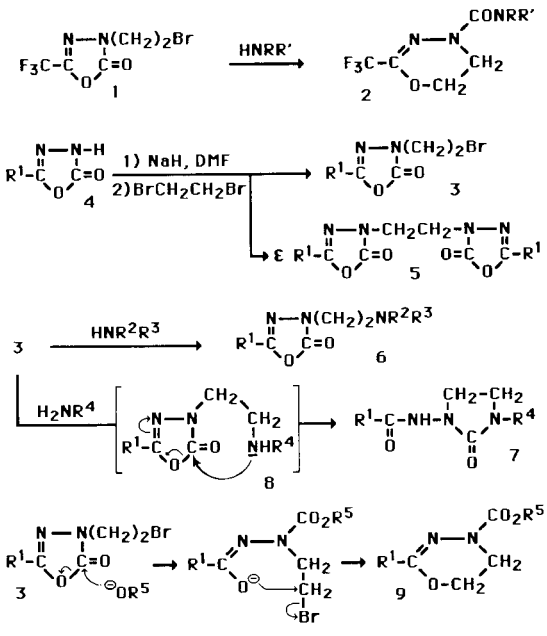
Table I

5-Aryl(or Benzyl)-3-(2-bromoethyl)-1,3,4-oxadiazol-2(3H)-ones **3**

3	R^1	Yield %[a]	Mp °C	Formula	Analyses, % Calcd./Found C	H	N	IR, ν cm^{-1}	^{1}H NMR [b] δ ppm
a	Ph	74	104 [c,d]	$C_{10}H_9BrN_2O_2$ (269.09)	44.63 44.53	3.37 3.40	10.41 10.35	1770	3.8 (t, 2H), 4.15 (t, 2H), 7.4-7.9 (m, 5H)
b	4-MeOPh	71	112 [e]	$C_{11}H_{11}BrN_2O_3$ (299.11)	44.17 44.12	3.71 3.71	9.37 9.40	1775	3.75 (t, 2H), 3.8 (s, 3H), 4.15 (t, 2H), 7.6 and 7.8 (2d, 4H)
c	4-MePh	74	119 [e]	$C_{11}H_{11}BrN_2O_2$ (283.11)	46.66 46.80	3.92 3.90	9.90 9.86	1765	2.35 (s, 3H), 3.8 (t, 2H), 4.15 (t, 2H), 7.35 and 7.7 (2d, 4H)
d	4-ClPh	42	111 [c]	$C_{10}H_8BrClN_2O_2$ (303.53)	39.57 39.50	2.66 2.69	9.23 9.19	1775	3.8 (t, 2H), 4.15 (t, 2H), 7.5-7.85 (m, 4H)
e	$PhCH_2$	65	[f]	$C_{11}H_{11}BrN_2O_2$ (283.11)	46.66 46.71	3.92 3.87	9.90 9.92	1785	3.75 (t, 2H), 4 (s, 2H), 4.05 (t, 2H), 7.35 (s, 5H)

[a] Non optimized yields. [b] In DMSO-d_6. [c] Cyclohexane. [d] Benzene. [e] Petroleum ether 40-60. [f] This compound was obtained as an oil.

Scheme 2



the R^1 benzyl group. Low solubility of **5** in organic solvents permitted a facile separation from bromoethyl derivatives **3**.

When compounds **3** were treated with secondary amines in acetonitrile at room temperature, no opening of the oxadiazolone ring occurred in opposition to the results reported with 4-unsubstituted oxadiazolones which gave semicarbazide derivatives. Actually, 3-(2-aminoethyl)-5-aryl(or benzyl)-1,3,4-oxadiazol-2(3*H*)-ones derivatives **6** were obtained as the result of a classical alkylation of amines (Table II). Some known amino compounds of type **6**, used for industrial purpose, were prepared by direct alkylation of non-substituted oxadiazolones with β-halogenoamines [14]. Our result represent a new general way to these products. The same reaction with $R^1 = CF_3$ which gave 4-substituted oxadiazines **2** [13] could be attributed to the electron-withdrawing effect of R^1 which increases the electrophile character of the cyclic carbonyl group (Scheme 2).

When primary alkyl amines reacted with bromoethyl derivatives **3** in boiling acetonitrile, 1-acylamino-3-alkylimidazolidin-2-ones **7** were produced in excellent yields (Table III). The probable reaction mechanism could be in a first step the classical alkylation of the amine by the bromoethyl derivative **3** to give a nonisolated secondary amine **8** observed by a thin layer chromatographic method. The second step could be a nucleophilic intramolecular attack of the cyclic carbonyl group by the amino group with ring opening of the oxadiazolone and simultaneous imidazolidinone ring closure (Scheme 2).

At last, compounds **3** were treated for 30 minutes with refluxing alcohol in the presence of sodium alcoholate. In these conditions, the corresponding 2-aryl(or benzyl)-4-alkoxycarbonyl-5,6-dihydro-4*H*-1,3,4-oxadiazines **9** were obtained (Table IV). In this case, alcoholate ion could attack at first the cyclic carbonyl group to give an iminoalcoholate ion which then effected an intramolecular S_N2 reaction on the bromoethyl group with formation of the oxadiazine ring (Scheme 2).

Table II

3-(2-Aminoethyl)-5-aryl(or Benzyl)-1,3,4-oxadiazol-2(3H)-ones Derivatives **6**

6	R^1	R^2	R^3	Yield %[a]	Mp °C	Formula	Analyses, % Calcd./Found C	H	N	IR, ν cm^{-1}	^1H NMR [b] δ ppm
a	Ph	Et	Et	55	[c]	$C_{14}H_{19}N_3O_2$ (261.31)	64.34 / 64.47	7.33 / 7.30	16.08 / 16.02	1780	0.95 (t, 6H), 2.5 (q, 4H), 2.8 (t, 2H), 3.8 (t, 2H), 7.3-7.95 (m, 5H)
b	Ph	-$(CH_2)_4$-		69	65 [d,e]	$C_{14}H_{17}N_3O_2$ (259.30)	64.84 / 64.97	6.61 / 6.62	16.21 / 16.17	1760	1.55-1.85 (m, 4H), 2.35-2.65 (m, 4H), 2.85 (t, 2H), 3.9 (t, 2H), 7.35-8 (m, 5H)
c	Ph	-$(CH_2)_5$-		78	68 [e]	$C_{15}H_{19}N_3O_2$ (273.32)	65.91 / 65.98	7.01 / 6.98	15.37 / 15.45	1775	1.3-1.65 (m, 6H), 2.3-2.55 (m, 4H), 2.7 (t, 2H), 3.9 (t, 2H), 7.4-8 (m, 5H)
d	$PhCH_2$	Et	Et	61	[c]	$C_{15}H_{21}N_3O_2$ (275.34)	65.43 / 65.36	7.69 / 7.69	15.26 / 15.22	1785	0.95 (t, 6H), 2.5 (q, 4H), 2.7 (t, 2H), 3.7 (t, 2H), 3.85 (s, 2H), 7.35 (s, 5H)
e	$PhCH_2$	-$(CH_2)_4$-		61	[c]	$C_{15}H_{19}N_3O_2$ (273.32)	65.91 / 65.92	7.01 / 6.96	15.37 / 15.35	1780	1.5-1.8 (m, 4H), 2.35-2.6 (m, 4H), 2.8 (t, 2H), 3.8 (t, 2H), 3.85 (s, 2H), 7.35 (s, 5H)
f	$PhCH_2$	-$(CH_2)_5$-		58	[c]	$C_{16}H_{21}N_3O_2$ (287.35)	66.87 / 66.77	7.37 / 7.33	14.62 / 14.68	1780	1.3-1.6 ((m, 6H), 2.25-2.5 (m, 4H), 2.65 (t, 2H), 3.8 (t, 2H), 3.85 (s, 2H), 7.35 (s, 5H)

[a] Non optimized yields. [b] In deuteriochloroform. [c] This compound was obtained as an oil. [d] Ethyl ether. [e] Petroleum ether 40-60.

Table III

1-Acylamino-3-alkylimidazolidin-2-ones **7**

7	R^1	R^4	Yield %[a]	Mp °C	Formula	Analyses, % Calcd./Found C	H	N	IR, ν cm^{-1}	^1H NMR [b] δ ppm
a	Ph	Pr	73	161 [c,d]	$C_{13}H_{17}N_3O_2$ (247.29)	63.14	6.93	16.99	3260, 1700	0.9 (t, 3H), 1.25-1.7 (m, 2H), 3.2 (t, 2H), 3.3
						63.27	6.87	16.92	1660	(t, 2H), 3.55 (t, 2H), 7-7.95 (m, 5H), 10.2 (s, 1H)
b	Ph	Bu	61	164 [e,f]	$C_{14}H_{19}N_3O_2$ (261.31)	64.34	7.33	16.08	3260, 1700	0.95 (t, 3H), 1.2-1.6 (m, 4H), 3.25 (t, 2H), 3.3
						64.44	7.30	16.12	1660	(t, 2H), 3.6 (t, 2H), 7.1-8 (m, 5H), 10.2 (s, 1H)
c	Ph	$PhCH_2$	63	143 [e,f]	$C_{17}H_{17}N_3O_2$ (295.33)	69.13	5.80	14.23	3260, 1700	3.25 (t, 2H), 3.65 (t, 2H), 4.4 (s, 2H),
						68.91	5.83	14.28	1670	7.2-7.9 (m, 10H), 9.95 (s, 1H)
d	4-MeOPh	Pr	75	146 [g,h]	$C_{14}H_{19}N_3O_3$ (277.31)	60.63	6.91	15.15	3265, 1710	0.95 (t, 3H), 1.4-1.75 (m, 2H), 3.3 (t, 2H),
						60.67	6.87	15.19	1660	3.5 (t, 2H), 3.65 (t, 2H), 3.8 (s, 3H),
										6.8 and 7.85 (2d, 4H), 10.1 (s, 1H)
e	$PhCH_2$	Pr	55	149 [i]	$C_{14}H_{19}N_3O_2$ (261.31)	64.34	7.33	16.08	3200, 1690	0.9 (t, 3H), 1.2-1.65 (m, 2H), 3.15 (t, 2H),
						64.49	7.38	16.02	1670	3.35 (t, 2H), 3.5 (s and t, 4H), 7.35 (s, 5H),
										9.25 (s, 1H)

[a] Non optimized yields. [b] In deuteriochloroform. [c] Cyclohexane. [d] Benzene. [e] Ethyl acetate. [f] Petroleum ether 40-60. [g] Ethanol. [h] Water. [i] Ethyl ether.

Table IV

2-Aryl(or Benzyl)-4-alkoxycarbonyl-5,6-dihydro-4*H*-1,3,4-oxadiazines **9**

9	R^1	R^5	Yield %[a]	Mp °C	Formula	Analyses, % Calcd./Found C	H	N	IR, ν cm^{-1}	^1H NMR [b] δ ppm
a	Ph	Et	79	86 [c,d]	$C_{12}H_{14}N_2O_3$ (234.25)	61.53	6.02	11.96	1710, 1620	1.25 (t, 3H), 3.85 (t, 2H), 4.2 (q, 2H), 4.45 (t, 2H),
						61.40	6.04	12.02		7,3-7.9 (m, 5H)
b	Ph	Me	81	69 [c,d]	$C_{11}H_{12}N_2O_3$ (220.22)	59.99	5.49	12.72	1690, 1615	3.75 (s, 3H), 3.85 (t, 2H), 4.5 (t, 2H),
						59.89	5.50	12.76		7,3-7.95 (m, 5H)
c	4-MeOPh	Et	82	100 [c,d]	$C_{13}H_{16}N_2O_4$ (264.27)	59.08	6.10	10.60	1685, 1605	1.25 (t, 3H), 3.8 (s, 3H), 3.85 (t, 2H), 4.2 (q, 2H),
						59.17	6.13	10.63		4.45 (t, 2H), 7 and 7.75 (2d, 4H)
d	4-MePh	Et	77	95 [c,d]	$C_{13}H_{16}N_2O_3$ (248.27)	62.89	6.50	11.28	1720, 1690,	1.2 (q, 3H), 2.3 (s, 3H), 3.8 (t, 2H), 4.15 (q, 2H),
						62.72	6.50	11.31	1615	4.35 (t, 2H), 7.2 and 7.65 (2d, 4H)
e	4-ClPh	Et	91	120 [e,f]	$C_{12}H_{13}ClN_2O_3$ (268.69)	53.64	4.88	10.43	1710, 1620	1.25 (t, 3H), 3.85 (t, 2H), 4.2 (q, 2H), 4.45 (t, 2H),
						53.71	4.92	10.39		7.6 and 7.9 (2d, 4H)
f	$PhCH_2$	Et	63	88 [c,d]	$C_{13}H_{16}N_2O_3$ (248.27)	62.89	6.50	11.28	1680, 1640	1.2 (t, 3H), 3.5 (s, 2H), 3.8 (t, 2H), 4.2 (q, 2H),
						62.86	6.53	11.33		4.45 (t, 2H), 7.35 (s, 5H)

[a] Non optimized yields. [b] In DMSO-d_6. [c] Ethyl ether. [d] Petroleum ether 40-60. [e] Ethanol. [f] Water.

No reaction occurred between primary or secondary arylamines and bromoethyl derivatives **3** in boiling acetonitrile .

Physicochemical data of new compounds **3,6,7,9** are listed in Tables I-IV. Assignment for the structures of new products was provided by elemental analysis and ir and ^1H-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 on a Brucker WP 80 spectrometer and are reported as δ values (ppm) relative to tetramethylsilane as an internal standard.

5-Aryl(or benzyl)-3-(2-bromoethyl)-1,3,4-oxadiazol-2(3*H*)-ones **3** and 3,3'-Ethylenedi(5-aryl-1,3,4-oxadiazol-2(3*H*)-ones) **5**.

A solution of 10 mmoles of 5-aryl(or benzyl)oxadiazolone **4** in 30 ml of dry dimethylformamide was added slowly to a cold suspension of 0.24 g (10 mmoles) of sodium hydride in 40 ml of dry dimethylformamide. After addition and heating for 30 minutes on a water bath at 50-60°, hydrogen gas evolution ceased. After cooling at 0°, 4.7 g (25 mmoles) of dibromoethane were added quickly under strong stirring. After addition, the temperature was raised slowly to 70-80° in 30 minutes and maintained for 30 minutes. After removal of the solvent under reduce pressure, the resulting crop was treated with 100 ml of boiling ethyl acetate. By filtration, sodium bromide and **5** were obtained as a solid mixture which was treated with 50 ml of water to isolate compound **5**. The ethyl acetate solution was evaporated *in vacuo* to give compound **3** which was recrystallized from adequate solvent (Table I).

Only aryl derivatives of compounds **5** were obtained in this reaction. They were soluble as a very small amount in boiling 1-butanol, diethyleneglycol or dimethylformamide. They were insoluble in ^{1}H-nmr solvents.

3,3'-Ethylenedi(5-phenyl-1,3,4-oxadiazol-2(3*H*)-one) (**5a**).

This compound was recrystallized from 1-butanol, mp 266°; ir: 1770, 1620 cm^{-1}.

Anal. Calcd. for $C_{18}H_{14}N_4O_4$ (350.32): C, 61.71; H, 4.03; N, 15.99. Found: C, 61.61; H, 4.05; N, 15.95.

3,3'-Ethylenedi(5-(4-methoxyphenyl)-1,3,4-oxadiazol-2(3*H*)-one) (**5b**).

This compound was recrystallized from 1-butanol, mp 252°; ir: 1760, 1610 cm^{-1}.

Anal. Calcd. for $C_{20}H_{18}N_4O_6$ (410.37): C, 58.53; H, 4.42; N, 13.65. Found: C, 58.65; H, 4.45; N, 13.60.

3,3'-Ethylenedi(5-(4-methylphenyl)-1,3,4-oxadiazol-2(3*H*)-one) (**5c**).

This compound was recrystallized from 1-butanol, mp 236°; ir: 1790, 1765, 1605 cm^{-1}.

Anal. Calcd. for $C_{20}H_{18}N_4O_4$ (378.37): C, 63.48; H, 4.80; N, 14.81. Found: C, 63.37; H, 4.81; N, 14.77.

3,3'-Ethylenedi(5-(4-chlorophenyl)-1,3,4-oxadiazol-2(3*H*)-one) (**5d**).

This compound was recrystallized from 1-butanol, mp 270°; ir: 1785, 1770, 1610 cm^{-1}.

Anal. Calcd. for $C_{18}H_{12}Cl_2N_4O_4$ (419.20): C, 51.57; H, 2.89; N, 13.37. Found: C, 51.47; H, 2.93; N, 13.30.

3-(2-Aminoethyl)-5-aryl(or benzyl)-1,3,4-oxadiazol-2(3*H*)-ones Derivatives **6**.

A solution of 10 mmoles of bromoethyl derivative **3** and 30 mmoles of secondary alkylamine (diethylamine for **6a,d**, pyrrolidine for **6b,e**, piperidine for **6c,f**) in 20 ml of acetonitrile was stirred at room temperature for 72 hours (**6a-c**) or 4 hours (**6d-f**). Acetonitrile and the residual amine were evaporated *in vacuo*. The oily mixture was treated with 100 ml of diethyl ether. The solution was washed twice with 50 ml of water, then dried over anhydrous sodium sulfate. After removal of the solvent, the resulting oil was chromatographied over neutral alumine with diethyl ether/petroleum ether (1/1) as the eluent to obtain very pure products. Compounds **6b,c** were solids; they were recrystallized from an adequate solvent (Table II).

Synthesis of compounds **6** could be effected in boiling acetonitrile for some hours but the resulting compounds were mixed with several by-products.

1-Acylamino-3-alkylimidazolidin-2-ones **7**.

A solution of 10 mmoles of bromoethyl compound **3** and 20 mmoles of primary alkylamine (propylamine for **7a,d,e**, butylamine for **7b**, benzylamine for **7c**) in 20 ml of acetonitrile was refluxed at room temperature for 90 minutes. After cooling, the reaction mixture was poured onto 100 ml of ice water. Compound **7** precipitated. It was filtered, dried and recrystallized from the adequate solvent (Table III).

2-Aryl(or benzyl)-4-alkoxycarbonyl-5,6-dihydro-4*H*-1,3,4-oxadiazines **9**.

To 40 ml of anhydrous ethanol or methanol was added 0.23 g (10 mmoles) of sodium. When sodium had disappeared, the resulting alcoholate solution was cooled to 25° and 10 mmoles of bromoethyl compound **3** was added under strong stirring. The reaction mixture was refluxed for 30 minutes. Alcohol was evaporated *in vacuo* and the oily residue was treated with 50 ml of diethyl ether. The etheral solution was filtered, washed twice with 20 ml of water and dried over anhydrous calcium sulfate. Solvent was evaporated and the crude oil crystallized slowly at 0°. Oxadiazines **9** were recrystallized from an adequate solvent (Table IV).

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