Synthesis of 3-Acylamino-2-oxazolidinone Derivatives through Cyclic Transformations of 5-Aryl (or Benzyl)-1,3,4-oxadiazol-2(3*H*)-one Derivatives

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New 3-acylamino-2-oxazolidinone derivatives **3** were obtained in good yields by reaction of 5-aryl (or benzyl)-3-(2-hydroxyethyl)-1,3,4-oxadiazol-2(3*H*)-ones **1** with sodium ethylate. Treatment of ethyl 5-aryl-2-oxo-1,3,4-oxadiazole-3(2*H*)-acetates **7** with aromatic aldehydes in the presence of sodium ethylate or sodium hydride afforded 3-acylamino-5-aryl-4-ethoxycarbonyl-2-oxazolidinone derivatives as two *trans*-**5** and *cis*-**6** racemics. Only *RS,SR*-racemates were obtained with acetophenone under the same conditions.

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In some recent papers, we reported ring transformations of derivatives of various 3-substituted 5-aryl (or benzyl)-1,3,4-oxadiazol-2(3*H*)-ones into derivatives of 4-amino-1,2,4-triazolidine-3,5-dione [1], 1-amino or 1,3-diamino-2,4-imidazolidinedione [2], 4-amino-4,5-dihydro-1,2,4-triazin-3(2*H*)-one [3], 1-aminoimidazolidin-2-one or 5,6-dihydro-4*H*-1,3,4-oxadiazine [4]. All these reactions followed a general intramolecular reaction pathway (Scheme 1). "*Z*" represents a chain of 2 or 3 carbon or heteroelement units.

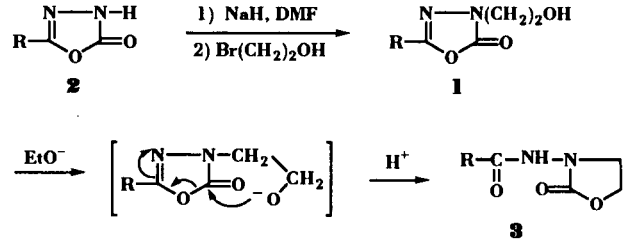
Scheme 1

A **B**

Two new examples of this ring transformation are presented here.

The 5-aryl (or benzyl)-3-(2-hydroxyethyl)-1,3,4-oxadiazol-2(3*H*)-ones **1** (Table I), which were easily prepared by reaction of 2-bromoethanol with the sodium salts of 5-aryl (or benzyl)-1,3,4-oxadiazol-2(3*H*)-ones **2**, have been transformed into the corresponding 3-acylamino-2-oxazolidinones **3** in the presence of sodium ethylate at room temperature in very good yields (Scheme 2) (Table II). The heterocyclic alcoholate ion attacked at the oxo group of the oxadiazolone cycle conducting to its opening with formation of the oxazolidinone ring.

Scheme 2



By a similar reaction mechanism, the alcoholate ion formed in the reaction between the carbanion **4** and an aromatic aldehyde could attack at the cyclic oxo group to give a ring transformation into a mixture of two *trans*-**5** and *cis*-**6** racemates of 3-acylamino-5-aryl-4-ethoxycarbonyl-2-oxazolidinones (Scheme 3). As expected, the mixture was formed by a large part of the *trans*-**5** racemate along with a minor amount of the *cis*-**6** racemate which has not

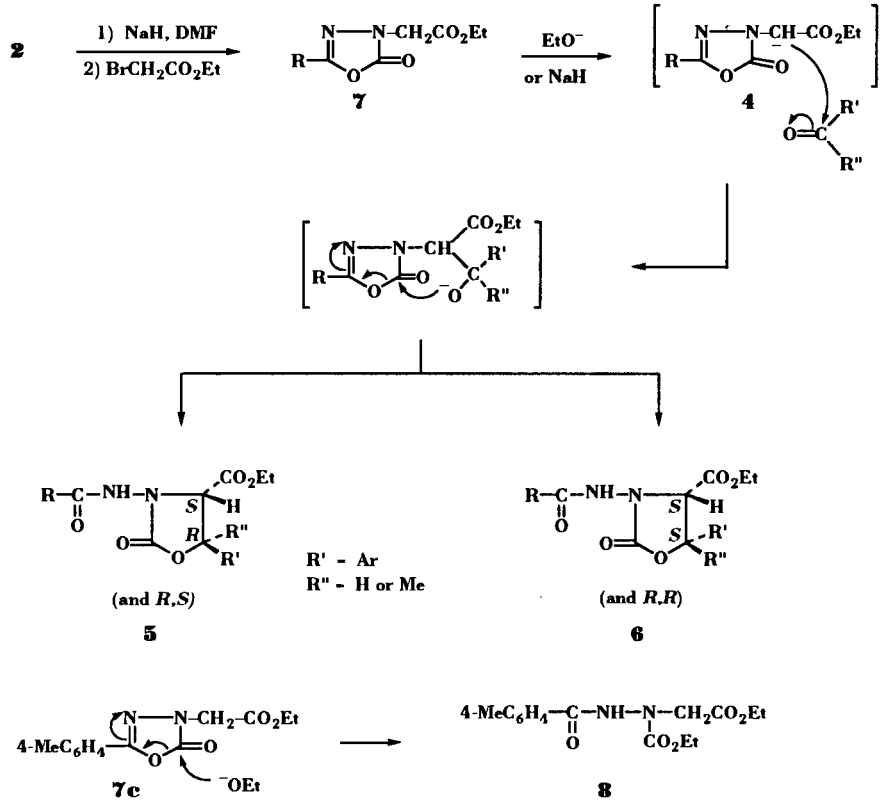
Table I

5-Aryl (or benzyl)-3-(2-hydroxyethyl)-1,3,4-oxadiazol-2(3*H*)-ones **1**

1	R	Yield % [a]	Mp °C	Formula	Analyses, % Calcd./Found C	H	N	IR, ν cm^{-1}	^{1}H NMR [b] δ ppm
a	Ph	68	78 [c]	$C_{10}H_{10}N_2O_3$ (206.19)	58.25 58.38	4.89 4.94	13.59 13.51	3495, 1750	3.7 (2t, 4H), 4.85 (t, 1H), 7.35-7.85 (m, 5H)
b	4-MeOPh	55	105 [c]	$C_{11}H_{12}N_2O_4$ (236.22)	55.93 55.78	5.12 5.10	11.86 11.90	3490, 1750	3.7 (2t, 4H), 3.8 (s, 3H), 5 (t, 1H), 7.05 and 7.7 (2d, 4H)
c	4-MePh	67	122 [c]	$C_{11}H_{12}N_2O_3$ (220.22)	59.99 59.84	5.49 5.53	12.72 12.75	3490, 1750	2.35 (s, 3H), 3.75 (2t, 4H), 4.95 (t, 1H), 7.4 and 7.8 (2d, 4H)
d	4-ClPh	60	114 [c]	$C_{10}H_9ClN_2O_3$ (240.64)	49.91 49.98	3.77 3.80	11.64 11.52	3490, 1740	3.75 (2t, 4H), 4.8 (t, 1H), 7.6 and 7.8 (2d, 4H)
e	$PhCH_2$	40	[d]	$C_{11}H_{12}N_2O_3$ (220.22)	59.99 59.91	5.49 5.47	12.72 12.78	3450, 1760	3.7 (2t, 4H), 3.9 (s, 2H), 4.95 (t, 1H), 7.35 (s, 5H)

[a] Non optimized yields. [b] In DMSO-d_6. [c] Ethyl acetate. [d] This compound was obtained as an oil.

Scheme 3



been isolated in two cases (Table III). Separation of racemates was effected by several recrystallizations or by chromatographic methods. Only *RS,SR*-racemates **5g,h** were obtained in this reaction when using acetophenone in place of an aromatic aldehyde.

Ethyl 5-aryl-2-oxo-1,3,4-oxadiazole-3(2*H*)-acetates **7** were prepared by the same process as compounds **1** [2] using ethyl bromoacetate in place of 2-bromoethanol. Carbanion **4** was generated by treatment of ester **7** either with sodium alcoholate in absolute ethanol (method A) or with sodium hydride in dry dimethylformamide (method B). It should be indicated that this last reaction afforded higher yields and more pure products than the first one.

In some cases, a secondary reaction occurred with sodium ethylate. Besides carbanion **4** formation ring opening of the oxadiazolone *via* a preferential attack at the oxo group with formation of an acyclic compound was observed. Thus, the ethyl (2-(4-methylbenzoyl)-1-ethoxycar-

Table II

3-Acylamino-2-oxazolidinones **3**

	R	Yield % [a]	Mp °C	Formula	Analyses, % Calcd./Found C	H	N	IR, ν cm^{-1}	^{1}H NMR [b] δ ppm
a	Ph	63	184 [c,d,e]	$C_{10}H_{10}N_2O_3$ (206.19)	58.25 58.41	4.89 4.91	13.59 13.52	3360, 1740, 1670	3.75 (t, 2H), 4.45 (t, 2H), 7.4-7.8 (m, 5H), 10.8 (s, 1H)
b	4-MeOPh	65	173 [c,d]	$C_{11}H_{12}N_2O_4$ (236.22)	55.93 55.80	5.12 5.08	11.86 11.84	3240, 1760, 1650	3.8 (s+t, 5H), 4.4 (t, 2H), 7 and 7.85 (2d, 4H), 10.6 (s, 1H)
c	4-MePh	71	178 [c,d]	$C_{11}H_{12}N_2O_3$ (220.22)	59.99 60.12	5.49 5.51	12.72 12.65	3300, 1745, 1670	2.35 (s, 3H), 3.75 (t, 2H), 4.4 (t, 2H), 7.25 and 7.75 (2d, 4H), 10.8 (s, 1H)
d	4-ClPh	67	175 [c,d]	$C_{10}H_9ClN_2O_3$ (240.64)	49.91 49.82	3.77 3.80	11.64 11.55	3300, 1755, 1680	3.8 (t, 2H), 4.45 (t, 2H), 7.65 and 7.95 (2d, 4H), 10.9 (s, 1H)
e	$PhCH_2$	32	141 [c]	$C_{11}H_{12}N_2O_3$ (220.22)	59.99 59.86	5.49 5.54	12.72 12.67	3240, 1735, 1685	3.45 (s, 2H), 3.6 (t, 2H), 4.35 (t, 2H), 7.25 (s, 5H), 10.3 (s, 1H)

[a] Non optimized yields. [b] In DMSO-d_6. [c] Ethyl acetate. [d] Petroleum ether 40-60° bp. [e] Lit [5] mp 178-180°.

Table III

3-Acylamino-5-aryl-4-ethoxycarbonyl-2-oxazolidinone *trans*-**5** and *cis*-**6**

No.	R	R'	R"	Yield % [a]	Mp °C	Formula	Analyses, % Calcd./Found C	H	N	IR, ν cm^{-1}	^{1}H NMR [b] δ ppm
5a-*trans*	Ph	Ph	H	52 (B) 30 (A)	178 [c,d]	$C_{19}H_{18}N_2O_5$ (354.35)	64.40 64.55	5.12 5.10	7.91 7.85	3300, 1785, 1750, 1655	0.75 (t, 3H), 3.7 (m, 2H), 5.15 and 6.2 (2d, 2H, J = 9 Hz), 7.2-8.2 (m, 10H), 11.2 (s, 1H)
6a-*cis*	Ph	Ph	H	5 (B)	154 [d,e]	$C_{19}H_{18}N_2O_5$ (354.35)	64.40 64.48	5.12 5.15	7.91 7.81	3225, 1790, 1750, 1655	1.2 (t, 3H), 4.2 (m, 2H), 4.65 and 5.8 (2d, 2H, J = 7 Hz), 7.4-8.2 (m, 10H), 11.3 (s, 1H)
5b-*trans*	4-MeOPh	Ph	H	45 (B)	158 [c,d]	$C_{20}H_{20}N_2O_6$ (384.37)	62.49 62.60	5.24 5.26	7.29 7.33	3360, 1795, 1735, 1650	0.75 (t, 3H), 3.7 (m, 2H), 3.85 (s, 3H), 5.15 and 6.25 (2d, 2H, J = 10 Hz), 7-7.45 (m+d, 5+2H), 7.9 (d, 2H), 11.05 (s, 1H)
6b-*cis*	4-MeOPh	Ph	H	7 (B)	107 [f]	$C_{20}H_{20}N_2O_6$ (384.37)	62.49 62.58	5.24 5.20	7.29 7.24	3190, 1785, 1735, 1635	1.15 (t, 3H), 3.8 (s, 3H), 4.15 (m, 2H), 4.6 and 5.7 (2d, 2H, J = 8 Hz), 7-7.45 (m+d, 5+2H), 7.9 (d, 2H), 11 (s, 1H)
5c-*trans*	4-MePh	Ph	H	66 (B) 35 (A)	170 [d,e]	$C_{20}H_{20}N_2O_5$ (368.37)	65.21 65.08	5.47 5.43	7.60 7.60	3220, 1780, 1735, 1660	0.75 (t, 3H), 2.35 (s, 3H), 3.7 (m, 2H), 5.4 and 6.2 (2d, 2H, J = 10 Hz), 7.25-7.5 (m+d, 5+2H), 7.85 (d, 2H), 11.1 (s, 1H)
5d-*trans*	4-NO_2Ph	Ph	H	67 (B)	191 [f]	$C_{19}H_{17}N_3O_7$ (399.35)	57.14 57.04	4.29 4.33	10.52 10.55	3310, 1800, 1740, 1660	0.75 (t, 3H), 3.7 (m, 2H), 5.2 and 6.25 (2d, 2H, J = 10 Hz), 7.4 (m, 5H), 8.25 (q, 4H), 11.6 (s, 1H)
5e-*trans*	Ph	4-NO_2Ph	H	61 (B) 51 (A)	242 [f]	$C_{19}H_{17}N_3O_7$ (399.35)	57.14 57.10	4.29 4.31	10.52 10.47	3270, 1810, 1755, 1655	0.8 (t, 3H), 3.7 (m, 2H), 5.15 and 6.4 (2d, 2H, J = 11 Hz), 7.4-8.1 (m+d, 5+2H), 8.3 (d, 2H), 11.2 (s, 1H)
6e-*cis*	Ph	4-NO_2Ph	H	5 (B)	215 [c,d]	$C_{19}H_{17}N_3O_7$ (399.35)	57.14 57.27	4.29 4.26	10.52 10.44	3200, 1780, 1745, 1645	1.15 (t, 3H), 4.2 (m, 2H), 4.55 and 5.95 (2d, 2H, J = 8 Hz), 7.3-8.1 (m+d, 5+2H), 8.35 (d, 2H), 11.2 (s, 1H)
5f-*trans*	4-MePh	4-NO_2Ph	H	70 (B)	228 [c]	$C_{20}H_{19}N_3O_7$ (413.37)	58.11 57.90	4.63 4.60	10.17 10.21	3270, 1810, 1740, 1655	0.8 (t, 3H), 2.4 (s, 3H), 3.7 (m, 2H), 5.15 and 6.4 (2d, 2H, J = 11 Hz), 7.35 (d, 2H), 7.65 and 7.85 (2d, 4H), 8.3 (d, 2H), 11.15 (s, 1H)
6f-*cis*	4-MePh	4-NO_2Ph	H	4 (B)	190 [f]	$C_{20}H_{19}N_3O_7$ (413.37)	58.11 57.99	4.63 4.66	10.17 10.15	3240, 1795, 1745, 1650	1.2 (t, 3H), 2.35 (s, 3H), 4.2 (m, 2H), 4.6 and 6 (2d, 2H, J = 8 Hz), 7.35 (d, 2H), 7.7 and 7.85 (2d, 4H), 8.3 (d, 2H), 11.1 (s, 1H)
5g	Ph	Ph	Me	72 (B)	205 [g]	$C_{20}H_{20}N_2O_5$ (368.37)	65.21 65.10	5.47 5.52	7.60 7.70	3210, 1785, 1745, 1650	1.2 (t, 3H), 1.7 (s, 3H), 4.25 (q, 2H), 4.85 (s, 1H), 7.3-8.1 (m, 10H), 11.25 (s, 1H)
5h	4-MePh	Ph	Me	74 (B)	162 [g]	$C_{21}H_{22}N_2O_5$ (382.40)	65.95 65.70	5.80 5.71	7.33 7.42	3215, 1790, 1745, 1650	1.2 (t, 3H), 1.75 (s, 3H), 2.35 (s, 3H), 4.3 (q, 2H), 4.85 (s, 1H), 7.2-8 (m, 9H), 11.2 (s, 1H)

[a] Non optimized yields with methods A or B. [b] In DMSO-d_6. [c] Ethyl acetate. [d] Petroleum ether 40-60° bp. [e] Diethyl ether. [f] Ethanol. [g] 1-Propanol.

bonylhydrazino)acetate **8** has been isolated (Scheme 3).

Few methods of synthesis of 3-amino-2-oxazolidinone derivatives are known. One method [6,7] consists in the treatment with diethyl carbonate of 2-hydroxyethylhydrazine derivatives prepared from hydrazine and substituted oxiranes. An other one [8] is the reaction of the *O*-(2,4-dinitrophenyl)hydroxylamine with *N*-lithium salts of 2-oxazolidinone.

Physicochemical data of the new compounds are consistent with the assigned structures [7,9]. Protons on car-

bons **4** and **5** have coupling constants around 10 Hz in the *trans*-**5** racemates and 8 Hz in *cis*-**6** racemates. By analogy with the results obtained in the reaction with aldehydes, we suggest that compounds **5g,h** from reaction with acetophenone are *RS,SR*-racemates. Further investigation shall be necessary to assure this proposal.

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 Bruker WP 80 spectrometer and are reported as δ values (ppm) relative to tetramethylsilane as an internal standard.

5-Aryl (or benzyl)-3-(2-hydroxyethyl)-1,3,4-oxadiazol-2(3*H*)-ones **1**.

A solution of 10 mmoles of 5-aryl (or benzyl)oxadiazolone **2**, prepared by the classical method of Dornow and Bruncken [10], in 10 ml of dry dimethylformamide was added slowly to a cold suspension of 0.24 g (10 mmoles) of sodium hydride in 50 ml of dry dimethylformamide. The reaction mixture was heated at 50° until hydrogen gas evolution had ceased. After cooling at 0-10°, a solution of 1.87 g (15 mmoles) of 2-bromoethanol in 5 ml of dry dimethylformamide was added with stirring and the reaction mixture was heated at 50-60° for 30 minutes. After cooling at 0-10°, it was poured onto 200 ml of ice-water. The precipitated compound **1** was recovered and recrystallized from a suitable solvent (Table I).

3-Acylamino-2-oxazolidinones **3**.

To a solution of 12 mmoles of sodium ethylate in 40 ml of absolute ethanol was added a solution of 10 mmoles of oxadiazolone **1**. The mixture was stirred at 40° for 3 hours. After cooling at 0-10°, the reaction mixture was poured onto a solution of 3 ml of acetic acid in 200 ml of ice-water. The precipitated compound **3** was filtered, dried and recrystallized from a suitable solvent (Table II).

3-Acylamino-5-aryl-4-ethoxycarbonyl-2-oxazolidinone *trans*-**5** and *cis*-**6** Racemates.

Method A.

To a solution of 10 mmoles of ester **7** and of 15 mmoles of aromatic aldehyde in a mixture of 20 ml of dry benzene and of 20 ml of absolute ethanol was added dropwise a cold solution of 15 mmoles of sodium ethylate in 10 ml of absolute ethanol. After complete addition, the mixture was stirred for a variable time at room temperature. Then, a solution of 1 ml of acetic acid in 10 ml of absolute ethanol was added cautiously. After removal of solvents under reduced pressure, the resulting oil was treated with 200 ml of diethyl ether. The ethereal solution was filtered and the ether was evaporated. The resulting oil was stirred with 20 ml of petroleum ether 40-60° bp, and the mixture was decanted (for extraction of excess aldehyde). The resulting greasy product crystallized slowly at 0°. It was filtered and the *trans*-**5** racemate was obtained by several recrystallizations from diethyl ether (Table III). Attempts to obtain the *cis*-**6** racemate in a very pure state by column chromatography was often unsuccessful. Using this procedure, an acyclic hydrazinoacetate **8** was isolated besides the **5c** racemate.

Ethyl (2-(4-Methylbenzoyl)-1-ethoxycarbonylhydrazino)acetate (**8**).

This compound was isolated by column chromatography and recrystallized from diethyl ether-petroleum ether 40-60° bp, mp 89°; ir: 3310, 1735, 1705, 1670 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 1.1 (2t, 6H), 2.35 (s, 3H), 4.1 (2q, 4H), 4.2 (s, 2H), 7.3 and 7.85 (2d, 4H), 10.9 (s, 1H).

Anal. Calcd. for $C_{15}H_{20}N_2O_5$: (308.32): C, 58.43; H, 6.54; N, 9.09. Found: C, 58.40; H, 6.50; N, 9.18.

Method B.

To a solution of 15 mmoles of aromatic aldehyde or acetophenone in 25 ml of dry dimethylformamide was added 0.24 g (10 mmoles) of sodium hydride. Then, a solution of 10 mmoles of ester **7** in 15 ml of dry dimethylformamide was added dropwise. The mixture was stirred for 3 hours at room temperature. It was poured onto 150 ml of cold water acidified with 1 ml of concentrated hydrochloric acid. A greasy mixture was obtained which crystallized after several hours. The precipitated compounds **5** and **6** were filtered and dried. By recyrstallization from a suitable solvent, the *trans*-**5** racemate was obtained (Table III). The *cis*-**6** racemate present in small amount, was isolated by column chromatography on silica gel 60 0.05-0.2 mm (Macherey-Nagel) using diethyl ether-petroleum ether 40-60° bp (1:1) as the eluent.

Ethyl 5-Aryl-2-oxo-1,3,4-oxadiazole-3(2*H*)-acetates **7**.

Using the procedure described for the preparation of compound **1** with ethyl bromoacetate in place of 2-bromoethanol compounds **7a** (R = Ph) and **7c** (R = 4-MePh) have been reported in a recent paper [2].

Ethyl 5-(4-Methoxyphenyl)-2-oxo-1,3,4-oxadiazole-3(2*H*)-acetate (**7b**).

This compound was recrystallized from 1-propanol and obtained in 65% yield, mp 122°; ir: 1780, 1735, 1615 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 1.2 (t, 3H), 3.85 (s, 3H), 4.2 (q, 2H), 4.7 (s, 2H), 7.15 and 7.8 (2d, 4H).

Anal. Calcd. for $C_{13}H_{14}N_2O_5$ (278.26): C, 56.11; H, 5.07; N, 10.07. Found: C, 56.01; H, 5.04; N, 10.15.

Ethyl 5-(4-Nitrophenyl)-2-oxo-1,3,4-oxadiazole-3(2*H*)-acetate (**7d**).

This compound was recrystallized from 1-propanol and obtained in 61% yield, mp 134°; ir: 1780, 1745, 1605 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 1.25 (t, 3H), 4.25 (q, 2H), 4.8 (s, 2H), 8.15 and 8.45 (2d, 4H).

Anal. Calcd. for $C_{12}H_{11}N_3O_6$ (293.23): C, 49.15; H, 3.78; N, 14.33. Found: C, 49.29; H, 3.77; N, 14.23.

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