Reaction of 1,3,4-Oxadiazolones with Free L-α-Amino Acids: A Facile Synthesis of Novel 3,5-Disubstituted Hydantoins

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A series of novel 3,5-disubstituted hydantoins **3a-l** were easily synthesized in one-step from the reaction of 2-phenyl-1,3,4-oxadiazolin-5-ones **1a-h** with various free L-α-amino acids **2a-e** in *m*-cresol at 150°. An alternative route leading to the formation of 3-benzamido-5-isopropylhydantoin **3c** was also developed to make clear the reaction mechanism.

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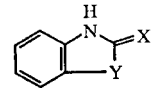
2-Substituted-1,3,4-oxadiazolin-5-ones and 2-substituted-1,3,4-oxadiazoline-5-thiones are of considerable interest for their synthesis, chemistry and pharmacological properties [1-36]. In the course of the studies disclosing the ring-opening ability of the oxadiazolines toward nucleophiles, we have recently found that the reactions of 2-aryl-1,3,4-oxadiazolin-5-ones and 2-aryl-1,3,4-oxadiazoline-5-thiones with *o*-substituted anilines such as *o*-phenylenediamine, *o*-amino(thio)phenol, *o*-aminobenzamide and methyl *o*-aminobenzoate were very promising as a novel system to prepare a variety of heterocyclic compounds possessing the following ring structures [37,38]:

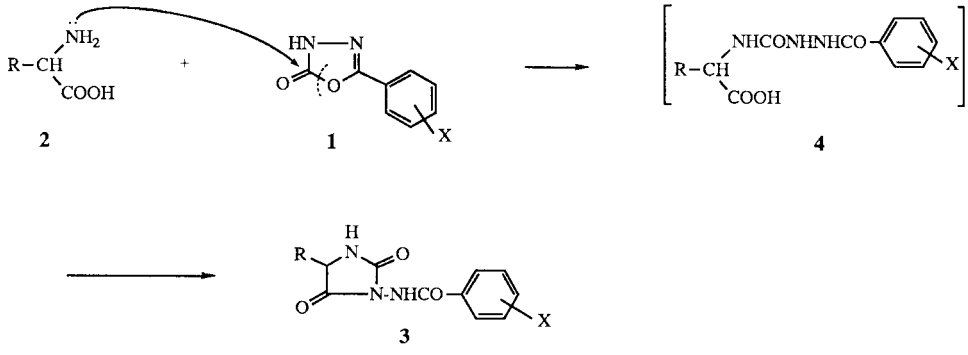


where X is O and S and Y is, for example, NH, O, S and CONNHCOAr. The heterocycle formation proceeds through the ring-opening of the oxadiazolines.

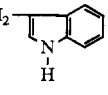
In order to further expand the synthetic utility of these oxadiazolines, it was applied to the preparation of hydantoins. We have found that 3,5-disubstituted hydantoins were conveniently synthesized from 2-aryl-1,3,4-oxadiazolin-5-ones and free L-α-amino acids.

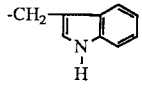
This article describes a facile one-step synthesis of a

Scheme I



1	X
a	H
b	2-Cl
c	4-Cl
d	2,4-Cl_2
e	3,5-Cl_2
f	4-CH_3
g	3-NO_2
h	4-NO_2

2	R
a	-CH_3
b	-$CH_2C_6H_5$
c	-$CH(CH_3)_2$
d	-$CH_2CH(CH_3)_2$
e	

3,4	X	R
a	H	-CH_3
b	H	-$CH_2C_6H_5$
c	H	-$CH(CH_3)_2$
d	H	-$CH_2CH(CH_3)_2$
e	H	
f	2-Cl	-$CH_2C_6H_5$
g	4-Cl	-$CH_2C_6H_5$
h	2,4-Cl_2	-$CH_2C_6H_5$
i	3,5-Cl_2	-$CH_2C_6H_5$
j	4-CH_3	-$CH_2C_6H_5$
k	3-NO_2	-$CH_2C_6H_5$
l	4-NO_2	-$CH_2C_6H_5$

series of novel hydantoins **3a-l** by the reaction of 2-aryl-1,3,4-oxadiazolin-5-ones **1a-h** with various free L-α-amino acids **2a-e**.

To elucidate the effects of reaction variables on these reactions, the reaction of 2-phenyl-1,3,4-oxadiazolin-5-one **1a** with free L-phenylalanine **2b** was firstly carried out in *m*-cresol under predetermined conditions. Tertiary amines such as triethylamine and pyridine were used to inhibit the formation of intramolecular zwitter ion of the amino acid.

Treatment of **1a** with **2b** in *m*-cresol in the presence of twice-molar quantity of triethylamine to **2b** at 80° for 48 hours afforded 3-benzamido-5-benzylhydantoin **3b** in 75% yield after purification. The use of pyridine was also effective for the formation of **3b**. No reaction occurred under the same conditions without any tertiary amine. At higher temperature of 150°, however, the reaction progressed much more rapidly even in the absence of any organic base and high conversion to hydantoin **3b** was achieved in 15 hours (Table I).

Table 1

Effect of Triethylamine on the Reaction between Oxadiazolone **1a** and L -α-Amino Acid **2b** [a]

Run	Molar ratio Triethylamine/**1a**	Reaction temperature °	Reaction time hours	Yield [b] %
1	1/1	80	48	45
2	2/1	50	72	-- [d]
3	2/1	80	48	75
4	2/1 [c]	80	48	33
5	3/1	80	48	69
6	0/1	80	48	-- [d]
7	0/1	150	15	74

[a] Reaction was carried out with each monomer (5 mmoles) in *m*-cresol (5 ml). [b] The value is that of after purification. [c] Pyridine was used instead of triethylamine. [d] Starting monomers could be recovered almost quantitatively.

Under the most simple conditions, a series of novel 3,5-disubstituted hydantoins **3a-l** were obtained in good yields from the combination of oxadiazolones **1a-h** and free L-α-amino acids **2a-e** (Scheme I, Table II). The structure of all the compounds were confirmed by elemental analyses and spectral data.

The formation of hydantoins **3a-l** undoubtedly proceeds *via* nucleophilic attack of the amino nitrogen of free L-α-amino acids on carbonyl C-5 of **1a-h** to give ring-opening adducts, acylsemicarbazides **4a-l**. Subsequent ring closure accompanied by the elimination of water completes the hydantoin structure. Attempts to isolate intermediates **4a-l** both by lowering the reaction temperature and shortening the reaction time below the lebel described above gave a trace amount of **3a-l** or only starting materials. A possible intermediate methyl L-α-benzamidocarbamidoisovalerate **4c** (X = H, Y = -$CH(CH_3)_2$), however, could be synthesized by treating methyl L-α-isocyanatoisovalerate (**5**) with benzoylhydrazide in dioxane at room temperature (Scheme II). The thermal cyclization of **4c** at 150° leading to the same product **3c** to that prepared from **1a** and **2c** proved indirectly the proposed mechanism.

EXPERIMENTAL

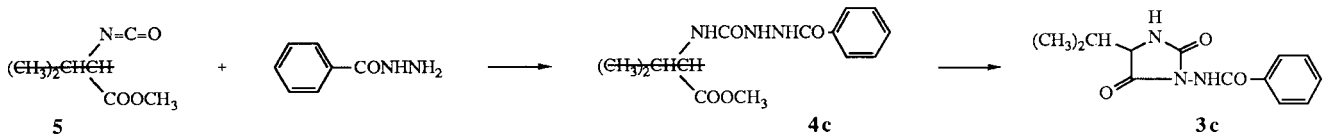
Melting points were determined in capillaries using an electrothermal melting point apparatus without correction. The ir and proton nmr spectra were recorded on a JASCO IR-810 spectrophotometer as potassium bromide disks and on a Hitachi R-24B spectrometer in DMSO-d_6 with TMS as an internal standard, respectively, unless otherwise noted. Electron impact mass spectra (ms) were obtained on a Hitachi M-2000 double focusing spectrometer at 70 eV by direct insertion. Elemental analyses were performed with a Perkin-Elmer 240C elemental analyzer.

2-Aryl-1,3,4-oxadiazolin-5-ones **1a-h** were prepared as previously reported [37]. Free L-α-amino acids **2a-e** (supplied by Ajinomoto Co., Inc.) were used without further purification. The other chemicals and solvents were obtained commercially and were used after purification by the usual manner.

General Procedure for Preparation of 3,5-Disubstituted Hydantoins **3a-l** from **1a-h**.

A mixture of **1** (0.01 mole) and **2** (0.01 mole) in *m*-cresol (10 ml) was heated with stirring at 150° for 15 hours and then allowed to cool to room temperature. Dilution with ether (*ca.* 100 ml) caused separation of a precipitate which was filtered off, washed subsequently with ether and water and recrystallized from water or dilute aqueous ethanol. The characteristic spectral features for all the products were ir bands at around 3260 (NH), 1790 (hydantoin 4-C=O), 1720 (hydantoin 2-C=O) and 1660 cm^{-1} (amide C=O) and ^1H nmr peaks at near δ 11 (broad s, 1H, amide NH),

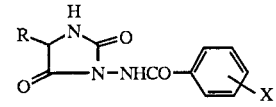
Scheme II



5 4c 3c

Table II

3,5-Disubstituted Hydantoins **3a-i**



Compound No.	X	R	Yield %	Mp° [a]	Formula	MS m/z	Analysis % Calcd./Found C	H	N
3a	H	$-CH_3$	45	158-160	$C_{11}H_{11}N_3O_3$	233 (M^+)	56.64 56.42	4.75 4.83	18.02 18.11
3b	H	$-CH_2C_6H_5$	74	172-173	$C_{17}H_{15}N_3O_3$	309 (M^+)	66.01 66.23	4.89 4.94	13.59 13.45
3c	H	$-CH(CH_3)_2$	81	159-161	$C_{13}H_{15}N_3O_3$	261 (M^+)	59.76 59.55	5.79 5.92	16.09 16.17
3d	H	$-CH_2CH(CH_3)_2$	61	161-162	$C_{14}H_{17}N_3O_3$	275 (M^+)	61.07 60.77	6.22 6.18	15.27 15.38
3e	H		71	199-202	$C_{19}H_{16}N_4O_3$	348 (M^+)	65.50 65.29	4.63 4.73	16.09 16.38
3f	2-Cl	$-CH_2C_6H_5$	78	207-208	$C_{17}H_{14}ClN_3O_3$	343 (M^+)	59.39 59.46	4.11 4.00	12.23 12.17
3g	4-Cl	$-CH_2C_6H_5$	81	250-251	$C_{17}H_{14}ClN_3O_3$	343 (M^+)	59.39 59.45	4.11 4.04	12.23 12.24
3h	2,4-Cl_2	$-CH_2C_6H_5$	82	220-222	$C_{17}H_{13}Cl_2N_3O_3$	377 (M^+)	53.98 53.76	3.46 3.26	11.11 11.09
3i	3,5-Cl_2	$-CH_2C_6H_5$	69	198-200	$C_{17}H_{13}Cl_2N_3O_3$	377 (M^+)	53.98 54.02	3.46 3.22	11.11 11.12
3j	4-CH_3	$-CH_2C_6H_5$	84	214-215	$C_{18}H_{17}N_3O_3$	323 (M^+)	66.86 66.87	5.30 5.11	13.00 12.89
3k	3-NO_2	$-CH_2C_6H_5$	77	217-218	$C_{17}H_{14}N_4O_5$	354 (M^+)	57.62 57.68	3.98 3.89	15.82 15.74
3l	4-NO_2	$-CH_2C_6H_5$	84	289-291	$C_{17}H_{14}N_4O_5$	354 (M^+)	57.62 57.76	3.98 3.99	15.82 15.76

[a] All compounds were recrystallized from water or dilute aqueous ethanol.

8.5 (s, 1H, hydantoin NH), 7-8 (m, C_6H_5 and/or C_6H_4) and 4.5 ppm (1H, hydantoin CH).

Methyl L-α-Isocyanatoisovalerate (**5**).

To an ice-cooled suspension of L-valine methylester hydrochloride (6.70 g, 0.04 mole) in dioxane (50 ml) trichloromethyl chloroformate (provided by Hodogaya Chemical Industries Ltd.) (6.0 ml, 0.05 mole) was added dropwise over a period of 20 minutes. After the addition, the reaction mixture was stirred at 80° for 10 hours. Removal of the solvent and excess trichloromethyl chloroformate afforded a tan yellow liquid material which was distilled *in vacuo* to give 5.12 g (82%) of **5** as colorless and clear liquid, bp 75-76°/9 mm; ir (neat): 2250 (N=C=O), 1745 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 4.12 (d, 1H, α-CH), 4.09 (s, 3H, $-OCH_3$), 2.43 (m, 1H, β-CH), 1.19 (d, 3H, CH_3), 1.06 ppm (d, 3H, CH_3); ms: m/z 157 (M^+).

Anal. Calcd. for $C_7H_{11}NO_3$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.38; H, 7.04; N, 8.83.

3-Benzamido-5-isopropylhydantoin **3c** from **5**.

To a solution of **5** (3.14 g, 0.02 mole) in dioxane (15 ml) was added in portions benzoylhydrazide (2.72 g, 0.02 mole) at ambient temperature followed by stirring at that temperature for 3 hours. Upon dilution with ether (*ca.* 50 ml), a white solid precipitated out. It was taken up with ether, rinsed several times with ether and recrystallized from dilute aqueous ethanol to produce 5.39 g (92%) of **4c** as white needles, mp 167-169°; ir: 3350, 3300 (NH), 1740 (ester C=O), 1680 (carbamide C=O), 1650 cm^{-1} (benzamide C=O); ^1H nmr: δ 10.19 (s, 1H, NH), 8.29-7.59 (m, 6H, NH and C_6H_5), 6.86 (d, 1H, NH), 4.25 (q, 1H, α-CH), 3.77 (s, 3H, $-OCH_3$), 2.02 (m, 1H, β-CH), 0.92 ppm (d, 6H, CH_3); ms: m/z 293 (M^+).

Anal. Calcd. for $C_{14}H_{19}N_3O_4$: C, 57.32; H, 6.53; N, 14.33. Found: C, 57.53; H, 6.32; N, 14.49.

Heating **4c** (1.47 g, 5 mmoles) in *m*-cresol (5 ml) at 150° for 10 hours provided 1.26 g (97%) of crude **3c**. This material was

recrystallized from dilute aqueous ethanol and identical in physical and spectral characteristics with a sample of **3c** prepared from **1a** and **2c**.

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