

Formation of 4-Benzamidoisoxazole Derivatives¹⁾Shonosuke ZEN,* Kazuho HARADA, Hikaru NAKAMURA,[†] and Yoichi IITAKA[†]

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The titled compounds (**3**) were synthesized by the reaction of nitrile oxides with 1-azirines and also the reaction of aliphatic nitro compounds with dibenzoylmethane derivatives in the presence of acetyl chloride and sodium methoxide. The structure of **3** was established by single crystal X-ray analysis. A mechanism of the formation for **3** is proposed.

This is dealing with an one-pot synthesis of 4-benzamidoisoxazole derivatives **3** through the reaction of nitrile oxides **1**²⁾ with 1-azirines **2**,^{3,4)} **3** was synthesized by the two methods as follows: (I) Nitrile oxides **1a—1c**, which are isolated or generated in situ by the acylation⁵⁾ of aliphatic nitro compounds **4a—4c** with acetyl chloride, are allowed to react with 2-benzoyl-1-azirines (**2a—2c**) in the presence of NaOMe. In this case furazan 2-oxides (**6**),²⁾ dimers of **1**, were obtained as main products. (II) Dibenzoylmethanes (**5a, 5b**) are reacted with two molecular equivalents of **4a, b** in the presence of acetyl chloride and NaOMe also (Scheme 1). The results of these procedures are summarized in Table 1.

The structure of **3** was determined by single crystal X-ray analysis with **3e** (Fig. 1) and also by alternative preparations of **3c** and **3g** from **9f** and **9g**⁶⁾ respectively (III) (Scheme 1). Compound **3c** obtained via (I) was identical to that obtained from the reaction (III).

The postulated mechanism of the formation of **3** was illustrated by Scheme 2: Nitrile oxide **1** generated from **4** reacts with dibenzoylmethane derivative **5** in an 1,3-dipolar cycloaddition to give an isoxazoline intermediate **10**. A fission of N-O bond⁷⁾ of **10** in basic conditions followed by elimination of benzoic acid

affords nitrene intermediate **11**, which isomerizes⁸⁾ to 1-azirine **2**. Subsequently, nucleophilic attack of methoxide anion to **2** gives aziridine intermediate **12**. Furthermore a fission of C-C bond⁹⁾ of **12** gives olefinic intermediate **13**, which cyclizes with another **1** to finally lead to **3**.

This mechanism was also supported by the following experimental results: i) Isolated nitrile oxide **1b** reacts with **5a** to give the corresponding 1-azirine **2b**.¹⁰⁾ ii) Isoxazoles (**7** and **8**) were isolated as by-products in

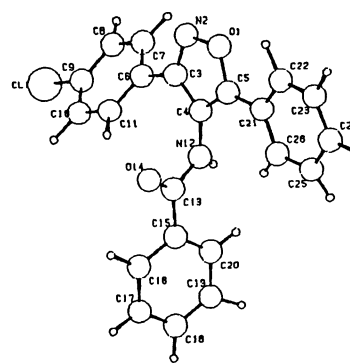
Fig. 1. Molecular structure of the compound **3e**.¹⁵⁾

Table 1. Yields and Spectral Data of the Derivatives of Benzamidoisoxazoles and Related Compounds

R ¹	R ²	R ³	Mp θ _m /°C	Yield/%			IR cm ⁻¹	MS, m/z	¹ H NMR δ/ppm (NH and Me)
				I	II	III			
3a	H	H	202—203	20 ^{b)}	16		3210, 1650	340(M ⁺)	7.60
3b	CH ₃	H	188—190	13, ^{a)} 23 ^{b)}			3240, 1640	354(M ⁺)	7.55, 2.37
3c	CH ₃	CH ₃	216—219	18 ^{a)}	28	76	3240, 1650	368(M ⁺)	7.53, 2.33, 2.40
3d	CH ₃	CH ₃	238—241	35 ^{b)}	41		3260, 1650	382(M ⁺)	7.42, 2.40, 2.37(2Me)
3e	Cl	H	176—178	5 ^{b)}			3260, 1660	374(M ⁺), 376(M ⁺ +2)	7.50
3g	CH ₃	H	223—224			91	3220, 1650	368(M ⁺)	7.45, 2.33(2Me)
14a	H	H	153—155		92		1660	354(M ⁺)	3.47
14b	CH ₃	H	155—157		76		1660	368(M ⁺)	2.45, 3.47
14c	CH ₃	CH ₃	176—178		83		1660	382(M ⁺)	2.22, 2.45, 3.45
14d	CH ₃	CH ₃	213—214		58		1660	396(M ⁺)	2.34(2Me), 2.43, 3.45
15a	—	—	222—224		64		3230, 1640	342(M ⁺)	7.50, 8.43, 8.80
15b	—	—	211—213		67		3370, 3300, 1630	356(M ⁺)	3.24, 6.63, 7.00
16a	—	—	173—175 ^{c)}		14		—	—	—
16b	—	—	130—132		60		3440, 1720, 1690	357(M ⁺)	—
17	—	—	201—202		74		3260, 1630	324(M ⁺)	—

a) The yields of **3** by the reaction of (1+2→3). b) The yields of **3** by the reaction of (4+2→3). c) Lit. 173.5—174.5 °C (Ref. 14). All compounds had elemental analyses (C,H,N) within ±0.3% of theoretical values.

Table 2. The Positional Parameters and Equivalent Isotropic Thermal Parameters with Their Estimated Standard Deviation in Parentheses

Atom	$x(\times 10^4)$	$y(\times 10^4)$	$z(\times 10^4)$	$B_{eq}/\text{\AA}^2$
O1	1679(1)	1789(4)	8110(2)	3.25(0.04)
N2	1978(1)	1606(5)	7109(3)	3.24(0.05)
C3	2560(2)	2069(6)	7470(3)	2.88(0.06)
C4	2657(2)	2564(6)	8681(3)	2.77(0.05)
C5	2095(2)	2389(6)	9048(3)	2.91(0.06)
C6	3013(2)	2080(6)	6642(3)	2.97(0.06)
C7	2854(2)	2795(7)	5502(4)	3.72(0.07)
C8	3289(2)	2858(7)	4742(4)	4.15(0.07)
C9	3881(2)	2222(7)	5135(4)	3.93(0.07)
C10	4050(2)	1468(7)	6243(4)	4.00(0.07)
C11	3610(2)	1409(6)	7006(4)	3.48(0.07)
C12	3217(1)	3230(5)	9339(3)	2.83(0.05)
C13	3615(2)	2077(6)	10035(3)	3.14(0.06)
C14	3510(1)	467(4)	10124(3)	4.86(0.06)
C15	4192(2)	2981(6)	10668(3)	3.06(0.06)
C16	4694(2)	1834(7)	11052(4)	4.07(0.07)
C17	5245(2)	2618(8)	11637(4)	4.96(0.08)
C18	5287(2)	4463(7)	11848(4)	4.10(0.07)
C19	4794(2)	5560(7)	11472(4)	3.97(0.07)
C20	4241(2)	4820(6)	10875(4)	3.64(0.07)
C21	1855(2)	2699(6)	10151(3)	3.24(0.06)
C22	1248(2)	2203(7)	10235(4)	4.41(0.08)
C23	1014(2)	2525(8)	11277(4)	5.34(0.09)
C24	1382(2)	3354(8)	12227(4)	5.24(0.09)
C25	1982(2)	3845(8)	12145(4)	4.88(0.09)
C26	2225(2)	3518(7)	11106(4)	4.30(0.08)
Cl	4433(1)	2391(2)	4191(1)	5.68(0.02)

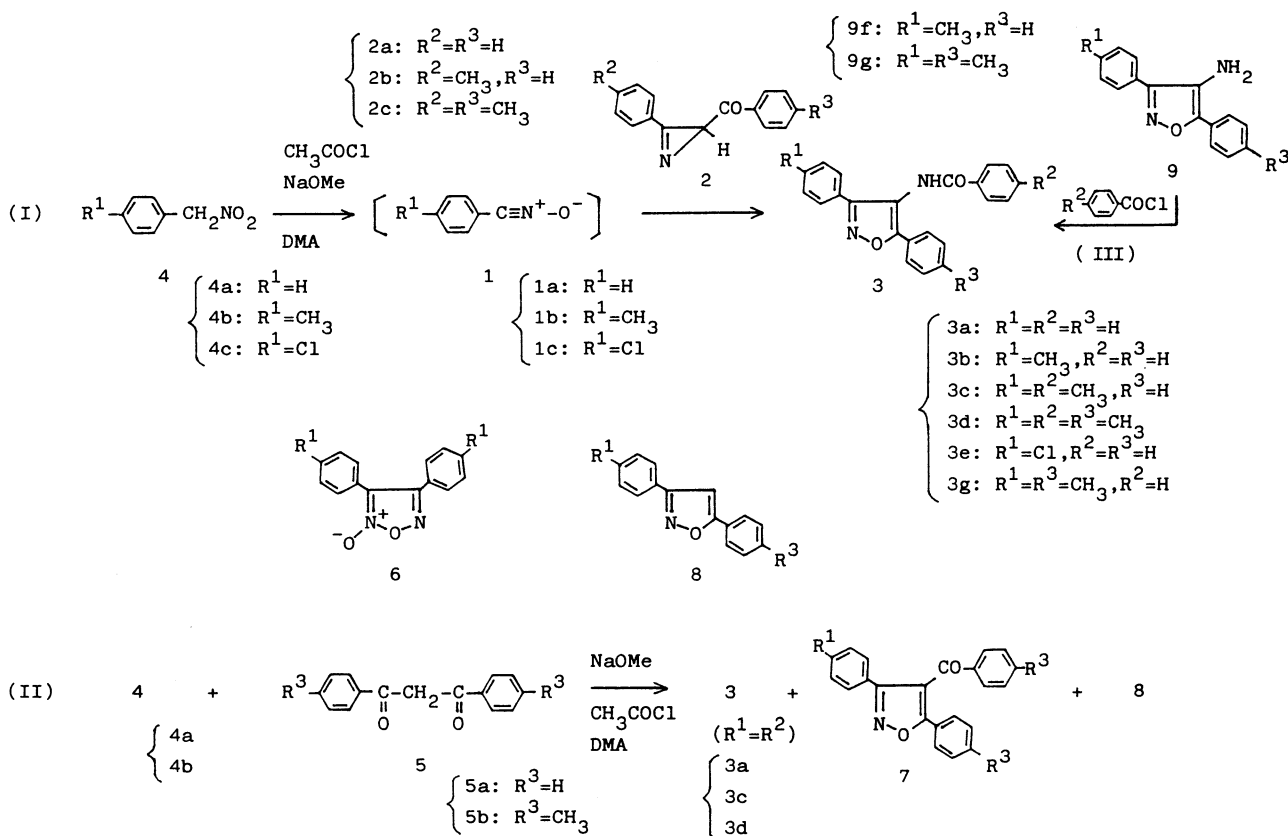
the reaction (II). This result shows that the above mechanism includes intermediate **10**, for **7** is a dehydroxy compound of **10**, and **8** is considered to be formed from **11**.⁸⁾

The reactivity of **3** was also studied as follows: i) *N*-Methylations of **3a**—**3d** were carried out with CH_3I to afford **14a**—**14d** in good yields as summarized in Table 1. ii) Hydrogenation of **3** with Raney Ni afforded β -aminoenone (**15**), which was hydrolyzed to give **16** and/or imidazole **17** (Scheme 3).

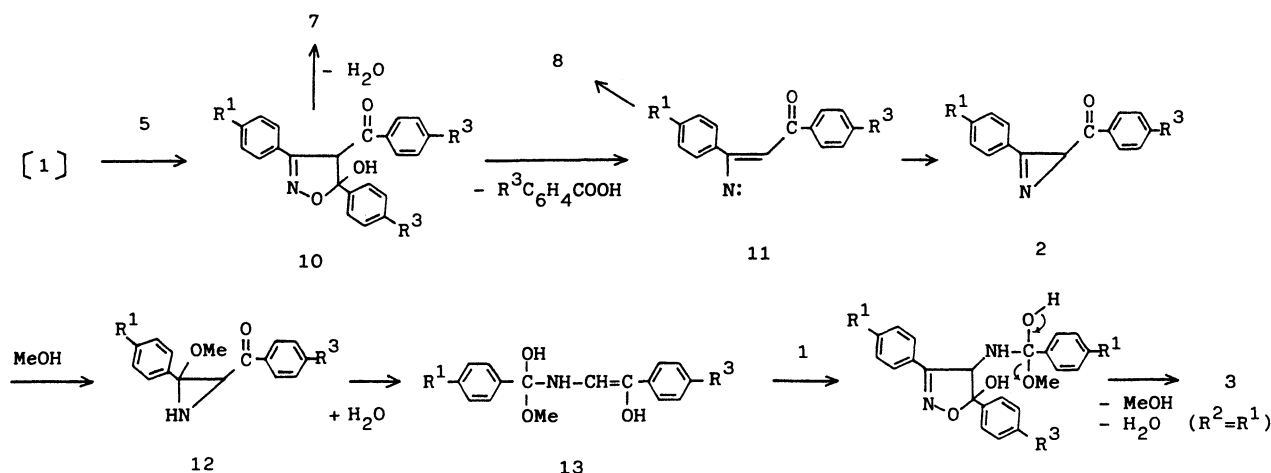
The authors (Z. and H.) reported¹¹⁾ previously the reaction of **1** with **2** to give **3** and assigned the structure of **3** to 4*H*-1,2,4-oxadiazine derivative based on spectroscopic analysis and also a ring opening reaction mentioned above. However, the structure of **3** was established to be 4-benzamido-3,5-diarylloxazole, as illustrated in Fig. 1 by X-ray analysis. Accordingly, the authors (Z. and H.) correct the structure of **3** herein.

Table 3. Bond Length and Torsional Angle for the Bond Connecting the Conjugated Groups

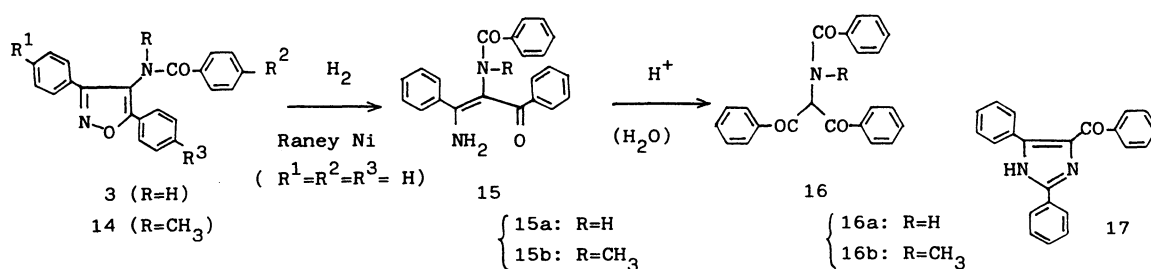
A-X-Y-B	Bond length (l/\AA) X-Y	Torsional angle ($\phi/^\circ$) along X-Y
N2-C3-C6-C7	1.474 (6)	42.9 (5)
O1-C5-C21-C22	1.458 (6)	6.6 (5)
C3-C4-N12-C13	1.419 (4)	-97.6 (4)
N12-C13-C15-C20	1.506 (5)	20.8 (5)



Scheme 1.



Scheme 2.



Scheme 3.

Experimental

Reaction of *p*-Tolunitrile Oxide (1b) with 3-Benzoyl-2-phenyl-1-azirine (2a). General Procedure for Method(I): To a solution of 2a¹²⁾ (57.0 mg, 0.26 mmol) in anhydrous *N,N*-dimethylacetamide (DMA) (5 cm³) was added freshly prepared 1b¹³⁾ (37.0 mg, 0.26 mmol) and 1 mol dm⁻³ NaOMe in MeOH (0.52 cm³) with ice-cooling. After stirring at room temperature overnight, the reaction mixture was partitioned between ice-water (20 cm³) and benzene (10 cm³). The aqueous phase was extracted with benzene (3×10 cm³), dried (Na₂SO₄) and concentrated to dryness. The residue (46.2 mg) was separated by column chromatography on silica gel with AcOEt-hexane (5:1) as an eluent to afford 3,4-di-*p*-tolylfurazan 2-oxide (6b) (20.1 mg, 54%) and 4-benzamido-5-phenyl-3-(*p*-tolyl)isoxazole (3b) (11.9 mg, 13%); mp 188–190 °C (EtOAc-hexane).

Reaction of Phenylnitromethane (4a) with 3-Benzoyl-2-phenyl-1-azirine (2a): To a solution of 4a (137 mg, 1.0 mmol) in anhydrous DMA (15 cm³) was added 1 mol dm⁻³ NaOMe in MeOH (1.0 cm³), acetyl chloride (0.70 cm³, 1.0 mmol), 2a (221.0 mg, 1.0 mmol) with ice-cooling. After further addition of 1 mol dm⁻³ NaOMe in MeOH (4.0 cm³), the reaction mixture was stirred at room temperature overnight. Then, the reaction mixture was poured into ice-water (20 cm³). After neutralization with 1 mol dm⁻³ HCl, the aqueous phase was extracted with benzene (3×15 cm³), dried (Na₂SO₄) and concentrated to dryness. The residue (284 mg) was chromatographed on silica gel with EtOAc-hexane (5:1) as an eluent to give 3,5-diphenylisoxazole (8a) (79.0 mg, 35%), 3,4-di-*p*-tolylfurazan 2-oxide (6a) (13.0 mg, 54%), and

4-benzamido-3,5-diphenylisoxazole (3a) (68.0 mg, 20%); mp 202–203 °C (MeOH-H₂O).

Reaction of Phenylnitromethane (4a) with Dibenzoylmethane (5a). General Procedure for Method(II): To a solution of 4a (548 mg, 4.0 mmol) in anhydrous DMA (20 cm³) was added 1 mol dm⁻³ NaOMe in MeOH (4 cm³), acetyl chloride (0.29 cm³, 4.1 mmol), 5a (448 mg, 2.0 mmol) with ice-cooling. After further addition of 1 mol dm⁻³ NaOMe in MeOH (16 cm³), the reaction mixture was poured into ice-water (120 cm³). After neutralization with 1 mol dm⁻³ HCl, the aqueous phase was extracted with benzene (3×40 cm³), dried (Na₂SO₄) and concentrated to dryness. The residue (887.5 mg) was chromatographed on silica gel with benzene-EtOAc (20:1) as an eluent to give 8a (140.5 mg, 32%), 4-benzoyl-3,5-diphenylisoxazole (7a) (195.3 mg, 30%), methyl benzoate (33.0 mg, 12%), acetophenone (28.0 mg, 12%) and 3a (108.2 mg, 16%).

X-Ray Analysis of 4-Benzamido-3-(*p*-chlorophenyl)-5-phenylisoxazole (3e): X-Ray specimen of 3e of approximate dimensions 0.35×0.1×0.06 mm was recrystallized from hexane-EtOAc. Diffraction intensities were measured using Cu Kα radiation monochromated by a graphite plate. The crystal data are: 4-Benzamido-3-(*p*-chlorophenyl)isoxazole, C₂₂H₁₅N₂O₂Cl, MW=374.8. Monoclinic, space group *P*2₁/*n*, *Z*=4. Unit cell dimensions, *a*=21.833(10), *b*=7.339(5), *c*=11.448(7) Å, β=99.02(6)°, *U*=1812 Å³. *D*_{cal}=1.374 g cm⁻³, μ for Cu Kα=31 cm⁻¹. Number of observed reflections as above the 2θ(I) level was 2390 out of 3947 within the 2θ range of 6° through 156°. The crystal structure was determined by the direct method and refined by the method of block-diagonal matrix least-squares to an *R* value of 0.058 including 27 heavier atoms and 42 hydrogen atoms. The hydrogens were

located on the difference electron-density map and their positional and isotropic temperature factors were included in the least-squares refinement. The molecular structure of **3e** is shown in Fig. 1. The molecule consists of an isoxazole ring(A), two phenyl groups (B and C, B ring bears a chlorine atom at *p*-position), and a benzamido group (D). The dimensions of each part of the molecule are quite normal. The torsional angles along the bonds connecting each group are listed in Table 3.

N-Benzoylation of 4-Amino-5-phenyl-3-(*p*-tolyl)isoxazole (9f): A mixture of **9f** (30 mg, 0.12 mmol), *p*-toluoyl chloride (19 mg, 0.12 mmol) and K_2CO_3 (18 mg, 0.12 mmol) in a ether-benzene- H_2O (1:3:1) mixed solution was stirred at 0–5 °C for 15 h. The mixture was poured into ice-water and extracted with toluene (5 cm³×3), dried (Na_2SO_4) and concentrated to dryness. The residue (47.4 mg) was chromatographed on silica gel with hexane-EtOAc (3:1) as an eluent to give **3c** (33.6 mg, 76%): mp 218–220 °C (MeOH- H_2O).

N-Methylation of 3a: A mixture of **3a** (20 mg, 0.06 mmol), KOH (3.9 mg, 0.06 mmol), and 18-crown-6 (0.25 mg, 0.001 mmol) in benzene (2 cm³) was refluxed for 2 h. After the addition of CH_3I (14 mg, 0.1 mmol) in benzene (1 cm³), the reaction mixture was refluxed for 4 h and concentrated in vacuo. After washing with H_2O , the crude product was recrystallized from EtOAc-hexane to give 4-(*N*-methylbenzamido)-3,5-diphenylisoxazole (**14a**) (19.0 mg, 92%).

Reductive Ring Opening Reaction of 3a: A solution of **3a** (100 mg, 0.26 mmol) in MeOH (30 cm³) was hydrogenated (1 atm, r.t.) for 3 h in the presence of activated Raney Ni-T1. After the solution was filtered, the filtrate was concentrated to dryness. The residue (95.2 mg) was chromatographed on silica gel with hexane-EtOAc (3:1) as an eluent to furnish 3-amino-2-benzamido-1,3-diphenyl-2-propen-1-one (**15a**) (64.6 mg, 64%).

Hydrolysis of 15a: A mixture of **15a** (50 mg, 0.15 mmol) and 1 mol dm⁻³ HCl (1 cm³) in MeOH (2 cm³) was refluxed for 2 h. After cooling, the reaction mixture was diluted with 5 cm³ of cooled H_2O , and the resultant precipitates were collected. 2-Benzamido-1,3-diphenyl-1,3-propanedione (**16a**) (7.0 mg, 14%): mp 173–175 °C (MeOH) (lit.¹⁴) 173.5–174.5 °C. The filtrate was neutralized with 2 mol dm⁻³ NaOH and the resultant precipitates were collected. 2-Benzoyl-3,5-diphenylimidazole (**17**) (37.0 mg, 74%): mp

201–202 °C (MeOH).

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