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Facile Preparations of 1,4-(Diphenylmethyleneamino)piperazine-2,5-diones and *N*-Phenylmethyleneamino-β, γ, and δ-lactams from Benzylidene Hydrazines and α, β, γ, and δ-Haloacyl Halides

TADASHI OKAWARA, RIE KATO, and MITSURU FURUKAWA*

Faculty of Pharmaceutical Sciences, Kumamoto University, 5-1, Oe-hon-machi, Kumamoto 862, Japan

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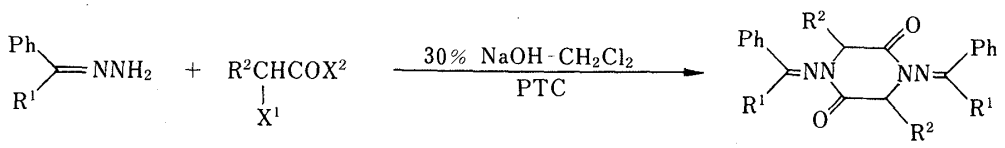
The reaction of benzylidene hydrazines (**1**) with various haloacyl halides (**2**) was carried out in aqueous NaOH–CH_2Cl_2 in the presence of a phase transfer catalyst to afford 1,4-(diphenylmethyleneamino)piperazine-2,5-diones (**3**) and *N*-phenylmethyleneamino-β, γ, and δ-lactams in yields of 31—84%.

Keywords——benzylidene hydrazine; alpha, beta, gamma, and delta-haloacyl halide; phase transfer catalyst; 1,4-(diphenylmethyleneamino)piperazine-2,5-dione; *N*-phenylmethyleneamino-β, γ, and δ-lactam

Several methods for the preparation of lactams by intramolecular *N*-alkylation of amide under phase transfer conditions have been reported.[1] We have exploited one-pot syntheses of β-lactams by the reaction of amines,[2] α-amino acids,[3] and 1-substituted thioureas[4] with β-haloacyl halides under phase transfer conditions. This method is convenient and has the advantage of making the work-up easier.

We report here the reaction of benzylidene hydrazines with α, β, γ, and δ-haloacyl halides in the presence of a phase transfer catalyst (PTC). Recently, Taylor[5] found that the chloroacetylhydrazone of benzophenone underwent an intramolecular cyclization on treatment with sodium hydride in anhydrous THF to give 1-(diphenylmethylene)-3-oxo-1,2-diazetidinium ylide. In contrast, we obtained the 1,4-(diphenylmethyleneamino)piperazine-2,5-diones (**3**) from benzylidene hydrazine and α-haloacyl halides.

The reaction was carried out by slowly adding α-haloacyl halide (**2**) to a stirred solution

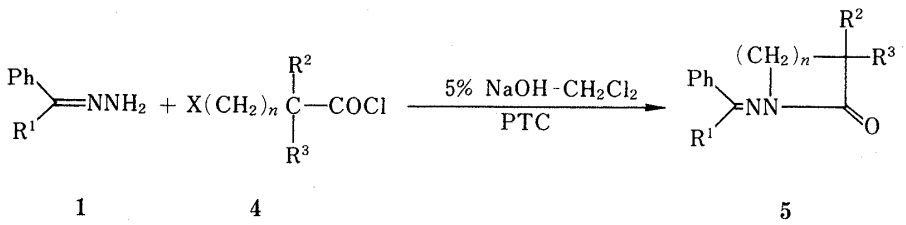


1 2 3

Chart 1

TABLE I. 1,4-(Diphenylmethyleneamino)piperazine-2,5-diones (**3**)

	R^1	R^2	X^1	X^2	mp (°C)	Yield (%)
3a	Ph	H	Cl	Cl	189—190	51
3b	Ph	CH_3	Br	Br	146—147	42
3c	Ph	C_2H_5	Br	Cl	150—151	53



1 4 5

Chart 2

TABLE II. *N*-Phenylmethyleneamino-β, γ, and δ-lactams (**5**)

	R^1	R^2	R^3	X	*n*	mp (°C)	Yield (%)
5a	H	CH_3	Br	Br	1	94—95	38
5b	H	CH_3	CH_3	Cl	1	85—86	31
5c	Ph	CH_3	Br	Br	1	133—134	41
5d	Ph	CH_3	CH_3	Cl	1	158—159	51
5e	H	H	Br	Br	2	158—159	36
5f	Ph	H	Br	Br	2	147—148	84
5g	Ph	H	Br	Br	3	124—125	74

of benzylidene hydrazine (**1**) in 30% NaOH–CH_2Cl_2 in the presence of a small amount of benzyltriethylammonium chloride, followed by stirring for 12 h at room temperature to afford **3** in 42—52% yields. The results are shown in Table I. The IR spectra of the products showed carbonyl absorption at 1760 cm^{-1}. The possible structures are piperazine-2,5-dione and α-lactam, but the latter can be excluded because the above frequency is low for such a carbonyl group on a three-membered ring. A probable structure is considered to be the piperazine-2,5-dione (**3**); the observed frequency of the carbonyl band seems to be attributable to steric strain. The ^{1}H-NMR and mass spectra, and elemental analyses also support this structure. This reaction did not proceed when 5% NaOH was used instead of 30% NaOH.

Next, the β, γ, and δ-lactams were synthesized from benzylidene hydrazines (**1**) and β, γ, and δ-haloacyl halides (**4**) in 5% NaOH–CH_2Cl_2 in the presence of PTC. The results are summarized in Table II.

In the reaction of α, ω-dihaloacyl chlorides (**4**) with **1**, the corresponding piperazine-2,5-diones (**3**) were not detected. The β-lactams ($n=1$) were produced in 31—51% yields. The assignment of the structures (**5a—d**) was based on IR and mass spectra data. The IR spectra showed the carbonyl absorption at 1760—1770 cm^{-1}, and the mass spectra had fragments typical of ketones, azomethines, alkenes, and isocyanates derived from β-lactams.

In the course of preparation of the pyrazolidinium ylide from the 3-chloro-2,2-dimethylpropionyl hydrazone of benzophenone, Taylor[5] also isolated 1-diphenylmethyleneamino-3,3-dimethylazetidin-2-one (**5d**) under anhydrous conditions.

In the cases of $n=2$ and 3, the corresponding γ and δ-lactams (**5e—g**) were isolated. These products gave satisfactory IR, ^{1}H-NMR, and mass spectral data, and elemental analyses.

This reaction is considered to provide a useful one-pot synthesis of lactams from hydrazones.

Experimental

All the melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded with a JASCO IRA-1 grating infrared spectrometer. Nuclear magnetic resonance

Table III. 1-(Diphenylmethyleneamino)piperazine-2,5-diones (3)

	IR ν_{max}^{KBr} cm^{-1} C=O	^{1}H-NMR (δ) in $CDCl_3$	*m/e* (M^+)	Analysis (%) Calcd (Found)		
				C	H	N
3a	1760	5.33 (s, $CH_2 \times 2$, 4H) 7.66 (m, Ph × 4, 20H)	472	76.30 (76.71	5.12 5.22	11.86 11.96)
3b	1760	1.25 (d, $CH_3 \times 2$, 6H, J=7.0 Hz), 5.90 (q, CH × 2, 2H, J=7.0 Hz), 7.66 (m, Ph × 4, 20H)	250[a]	76.78 (76.48	5.64 5.62	11.20 11.10)
3c	1760	0.80—1.90 (m, $C_2H_5 \times 2$, 10H), 5.90 (m, CH × 2, 2H), 7.66 (m, Ph × 4, 20H)	528	77.25 (77.12	6.10 6.19	10.60 10.56)

a) The parent ion was not detected under any conditions tested.

Table IV. *N*-Phenylmethyleneamino-β, γ, and δ-lactams (5)

	IR ν_{max}^{KBr} cm^{-1} C=O	^{1}H-NMR (δ) in $CDCl_3$	*m/e* (M^+)	Analysis (%) Calcd (Found)		
				C	H	N
5a	1770	2.00 (s, CH_3, 3H), 3.89 (d, CHH, 1H, J=6.0 Hz), 4.11 (d, CHH, 1H, J=6.0 Hz), 7.53 (m, Ph, 5H), 7.97 (s, CH, 1H)	266, 268	49.46 (49.65	4.15 4.14	10.49 10.52)
5b	1760	1.33 (s, $CH_3 \times 2$, 6H), 3.37 (s, CH_2, 2H), 7.67 (m, Ph, 5H), 8.65 (s, CH, 1H)	202	71.26 (71.48	6.98 7.21	13.85 13.48)
5c	1760	1.83 (s, CH_3, 3H), 3.20 (m, CH_2, 2H), 7.38 (m, Ph × 2, 10H)	342, 344	59.50 (59.25	4.41 4.42	8.16 7.93)
5d	1760	1.23 (s, $CH_3 \times 2$, 6H), 2.75 (s, CH_2, 2H), 7.36 (m, Ph × 2, 10H)	278	77.67 (77.49	6.52 6.67	10.06 10.06)
5e	1710	2.61 (m, CH_2, 2H), 3.80 (m, CH_2, 2H) 4.55 (q, CH, 1H), 7.55 (m, Ph, 5H), 8.18 (s, CH, 1H)	266, 268	49.46 (49.90	4.15 4.32	10.49 10.36)
5f	1700	2.40 (m, CH_2, 2H), 3.50 (m, CH_2, 2H), 4.33 (q, CH, 1H), 7.42 (m, Ph × 2, 10H)	342, 344	59.50 (59.84	4.41 4.49	8.16 8.10)
5g	1660	2.12 (m, $CH_2 \times 2$, 4H), 3.50 (m, CH_2, 2H), 4.42 (m, CH, 1H), 7.48 (m, Ph × 2, 10H)	356, 358	60.52 (60.32	4.80 4.58	7.84 7.72)

(^{1}H-NMR) spectra were determined with a JEOL 60H high resolution NMR instrument. Mass spectra were measured with a JEOL 01SG mass spectrometer.

2,3-Dibromo-2-methylpropionyl Chloride (4, X=R^2=Br, R^3=CH_3, n=1) and 3-Chloro-2,2-dimethylpropionyl Chloride (4, X=Cl, R^2=R^3=CH_3, n=1)——These compounds were obtained from 2,3-dibromo-2-methylpropionic acid and 3-chloro-2,2-dimethylpropionic acid.[2)]

Dibromoacyl Chloride (4,X=R^2=Br, R^3=H, n=2, 3 and 4)——These compounds were prepared from the corresponding lactones and bromine, followed by treatment with $SOCl_2$.[2)]

General Procedure for Preparation of 1,4-(Diphenylmethyleneamino)piperazine-2,5-diones (3)——An α-haloacyl chloride **2** (5 mmol) was added dropwise to a stirred solution of benzophenone hydrazone **1** (5 mmol) in 30% NaOH (5 ml) and CH_2Cl_2 (20 ml) under cooling with ice-water. When the addition was over, benzyltriethylammonium chloride (10 mg) was added. The reaction mixture was stirred for 12 h at room temperature. The CH_2Cl_2 layer was

separated, washed with H_2O (10 ml × 2), dried over anhydrous Na_2SO_4, and evaporated to dryness. The residue was purified by recrystallization from EtOH. The IR, ^{1}H-NMR and mass spectral data, and elemental analyses are listed in Table III.

General Procedure for Preparation of *N*-Phenylmethyleneamino-*β*, *γ*, and *δ*-lactams (5)——By the same method as described above, compounds (**5**) were obtained from **1** and **4** with 5% NaOH–CH_2Cl_2. Compounds **5a** and **5b** were purified by silica gel column chromatography ($CHCl_3$). Compounds **5c**—**g** were recrystallized from EtOH. The IR, ^{1}H-NMR, and mass spectral data, and elemental analyses are summarized in Table IV.

References

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