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Reaction of 2,2-Dimethyl-1,3-dioxin-4-ones with Imines, Carbodiimides, and Isocyanates

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The ring transformation of 2,2-dimethyl-1,3-dioxin-4-ones (**1**) to nitrogen heterocycles was studied. Heating of **1** with imines such as Schiff bases gave rise to [2+4] cycloadducts of imines to acylketenes (**2**), *i.e.*, 3,4-dihydro-1,3-oxazin-4-one derivatives (**4**). Similarly, **1** reacted with carbodiimides to yield 2-imino-1,3-oxazin-4-one derivatives (**11** and **12**). The reaction of **1** with phenyl isocyanate gave 3-phenyl-1,3-oxazine-2,4-diones (**15**), while the reaction with 2-pyridyl isocyanate gave pyrido[1,2-*a*]pyrimidin-4-one derivatives (**18**).

Keywords——1,3-dioxin-4-one; acylketene; masked acylketene; 1,3-oxazin-4-one; pyrido-[1,2-*a*]pyrimidine; ring transformation; cycloaddition; thermal fragmentation

2,2,6-Trimethyl-1,3-dioxin-4-one (**1a**), so-called diketene-acetone adduct, reacts with compounds which possess a C=N or C≡N moiety to give 6-methyl-1,3-oxazin-4-one derivatives.[1] The reaction involves thermal fragmentation of **1a** to acetylketene (**2a**: $R^1=H$, $R^2=Me$) followed by cycloaddition to the 1,2-dipoles.[1c] Similar methods have been reported for the formation of the 1,3-oxazin-4-one (**4**) from α-diazo-β-diketones[2] or furan-2,3-diones[3] as acylketene precursors, but, these methods seem to have limitations as regards substituents on the ketenes.

In the previous papers, we have reported a convenient and general method for the preparation of 2,2-dimethyl-1,3-dioxin-4-one derivatives (**1**)[4] and their reaction with some 1,3-dipoles and cyano compounds.[5] As a continuation of our studies on the synthesis of heterocycles *via* acylketene **2**, we investigated the thermal reaction of **1** with imines, carbodiimides, and isocyanates. The results are presented here.

When 2,2-dimethyl-6-phenyl-1,3-dioxin-4-one (**1b**) was heated with *N*-benzylideneaniline (**3a**) and *N*-benzylidene-*tert*-butylamine (**3c**) without any solvent at 130 °C, the corresponding 3,4-dihydro-1,3-oxazin-4-one derivatives (**4a** and **4c**) were obtained in good yields. The reaction of **1b** with *N*-benzylideneethylamine (**3b**) gave rise to 2-benzoyl-*N*-ethylcinnamamide (**5**) along with the 1,3-oxazine derivative (**4b**). 5,6-Disubstituted 1,3-dioxin-4-ones (**1c—e**) reacted similarly with imines at 165 °C to give the corresponding 1,3-oxazine derivatives (**4**). The transformation of **1c—e** to **4** did not take place at 130 °C. Apparently, 5,6-disubstituted dioxinones are less thermolabile than 6-substituted ones such as **1a**[1c] and **1b**, both of which undergo the ring transformation at 130 °C. The results of these reactions are summarized in Table I.

2-(Benzylideneamino)pyridine (**3d**) has a C=N bond conjugated with a ring C=N bond and reacts with diketene[6] or dichloroketene[7] as a 1,4-dipole to give pyrido[1,2-*a*]pyrimidine derivatives. However, the reaction of **3d** with acylketenes did not give the pyridopyrimidines. Namely, the thermal reaction of **3d** with **1c** gave the 1,3-oxazine derivative **4i**, while the reaction with **1a** and **1b** gave the cinnamamides **6** and **7**, respectively. The structures of these products **4—7** were fully supported by the spectral data. In addition, compound **6** was identified by comparison with a sample prepared from 2-acetoacetamidopyridine (**8**) and

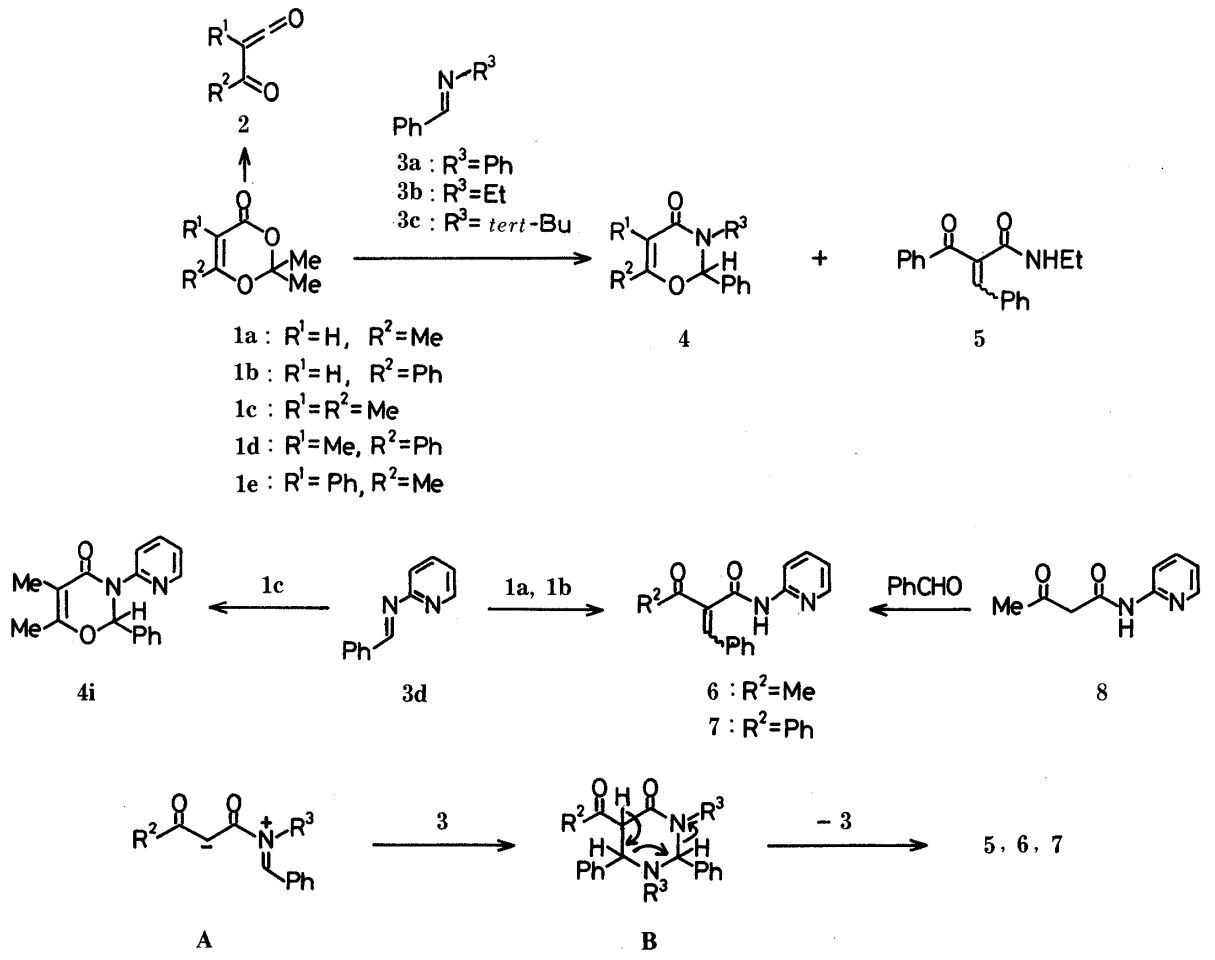

Chart 1

TABLE I. Reaction of 1,3-Dioxin-4-ones (**1**) with Imines (**3a—c**)

Product No.	Substituent			Reaction condition		Yield (%)	mp (°C)	Appearance (Recryst. solvent)[a]
	R^1	R^2	R^3	Temp. (°C)	Time (min)			
4a[b]	H	Ph	Ph	130	10	84	146—148	Needles (A)
4b	H	Ph	Et	130	30	43	117—119	Needles (B)
4c	H	Ph	*tert*-Bu	130	15	50	159—161	Needles (A)
4d	Me	Me	Ph	165	30	51	125.5—127.5	Prisms (B)
4e	Me	Me	Et	165	30	32	70.5—72	Prisms (A)
4f	Me	Me	*tert*-Bu	165	30	35	111—113	Prisms (B)
4g	Me	Ph	Ph	165	70	57	132—133	Prisms (B)
4h	Ph	Me	Ph	165	60	38	113—114	Prisms (B)

a) A, ethyl acetate; B, ether.
b) Reference 8.

TABLE II. Analytical and Spectral Data for **4**

Compd. No.	Formula	Analysis (%) Calcd (Found)			IR ($CHCl_3$) cm^{-1}		^{1}H-NMR ($CDCl_3$) δ		
		C	H	N	C=O	C=C	2-H	5-R^1	6-R^2
4b	$C_{18}H_{17}NO_2$	77.39 (77.25	6.13 6.00	5.01 4.97)	1653	1620 (sh)	6.36 (s)	5.91 (1H, s)	7.1—7.8 (5H, m)
4c	$C_{20}H_{21}NO_2$	78.14 (77.86	6.89 6.99	4.56 4.28)	1655	1613 (sh)	6.80 (s)	5.78 (1H, s)	7.2—7.8 (5H, m)
4d	$C_{18}H_{17}NO_2$	77.39 (77.13	6.13 6.10	5.01 5.03)	1660	1635 (sh)	6.52 (s)	1.77 (3H, s)	1.90 (3H, s)
4e	$C_{14}H_{17}NO_2$	72.70 (72.43	7.41 7.45	6.06 6.03)	1660	1630	6.06 (s)	1.77 (3H, s)	1.85 (3H, s)
4f	$C_{16}H_{21}NO_2$	74.10 (73.83	8.16 7.81	5.40 5.36)	1665	1625	6.45 (s)	1.64 (3H, s)	1.72 (3H, s)
4g	$C_{23}H_{19}NO_2$	80.91 (80.78	5.61 5.71	4.10 3.96)	1660	1610 (sh)	6.68 (s)	1.98 (3H, s)	7.1—7.75 (5H, m)
4h	$C_{23}H_{19}NO_2$	80.91 (80.77	5.61 5.76	4.10 3.91)	1660	1615	6.65 (s)	1.93 (3H, s)	7.2—7.65 (5H, m)

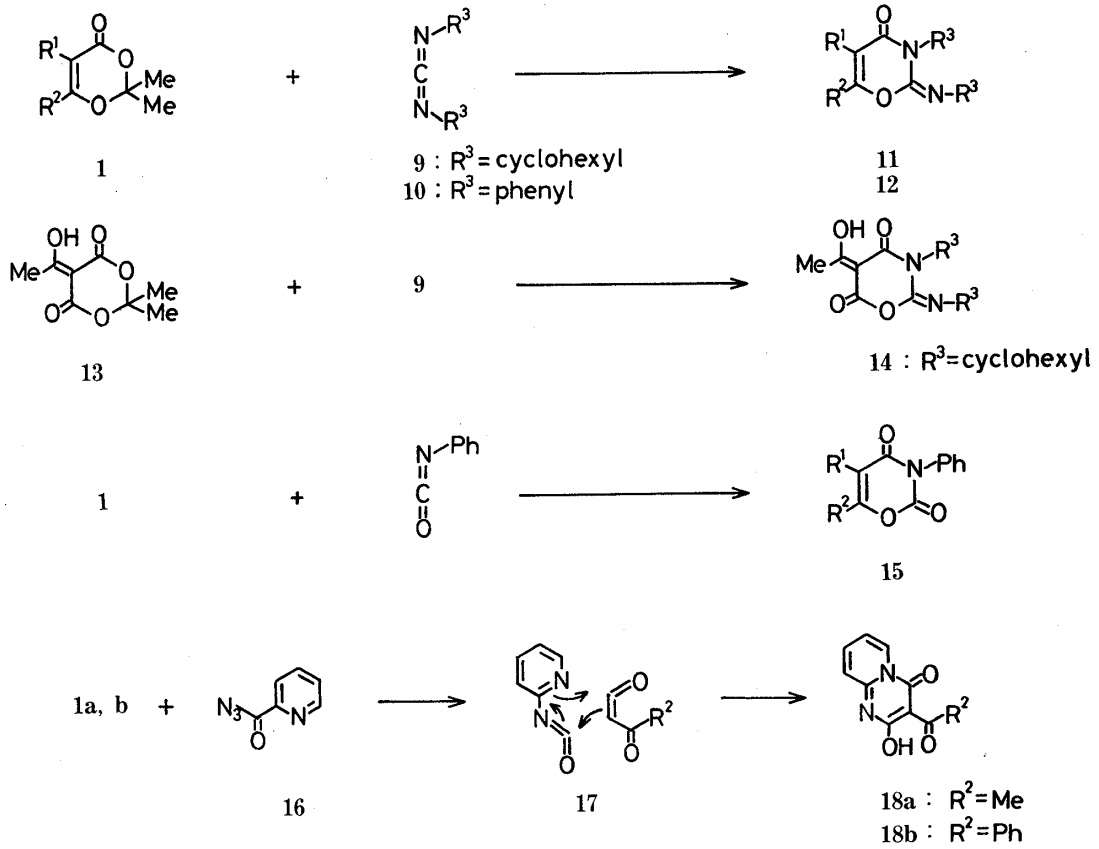

Chart 2

benzaldehyde. The geometry of the cinnamamides **5**—**7** was not determined.

Formation of these products **4**—**7** can be consistently explained in terms of the acylketene intermediate **2**. Namely, 1,3-oxazines **4** are formed by [2+4] cycloaddition of the imines **3** to the acylketenes **2**, and the cinnamamides **5**—**7** are formed from a zwitterionic intermediate **A**. The intermediate may be formed by addition of **2** to **3** or by ring fission of the

TABLE III. Reaction of **1** with Carbodiimides (**9** and **10**)

Product No.	Substituents			Reaction conditions		Yield (%)	mp (°C) (lit. mp)	Appearance (Recryst. solvent)[a]
	R^1	R^2	R^3	Temp. (°C)	Time (min)			
11a	H	Me	Cyclohexyl	130	60	81	81—82 (82—83)[b]	Prisms (A)
11b	H	Ph	Cyclohexyl	130	40	86	118—118.5	Needles (A)
11c	Me	Me	Cyclohexyl	165	70	76	132—133	Prisms (A)
11d	Me	Ph	Cyclohexyl	165	60	70	162—163	Prisms (A)
11e	Ph	Me	Cyclohexyl	165	60	64	126—127	Needles (C)
12a	H	Me	Ph	125	40	45	176—177 (184—185)[b]	Needles (A)
12b	H	Ph	Ph	130	40	64	163—165	Leaves (A)
12c	Me	Me	Ph	165	80	47	129—130 (141)[c]	Prisms (B)
12d	Me	Ph	Ph	165	60	35	175—177	Prisms (B)
12e	Ph	Me	Ph	165	70	67	165—166	Needles (A)

a) A, methanol; B, ether; C, ethyl acetate.
b) Reference 9.
c) Reference 10.

TABLE IV. Analytical and Spectral Data for **11** and **12**

Compd. No.	Formula	Analysis (%) Calcd (Found)			IR ($CHCl_3$) cm^{-1}		^{1}H-NMR ($CDCl_3$) δ	
		C	H	N	C=O	C=C	5-R^1	6-R^2
11b	$C_{22}H_{28}N_2O_2$	74.96 (74.85	8.01 7.97	7.95 7.80)	1700 1673	1633	6.06 (1H, s)	7.4—7.9 (5H, m)
11c	$C_{18}H_{28}N_2O_2$	71.01 (70.71	9.27 9.05	9.20 9.11)	1690	1640	1.82 (3H, s)	2.05 (3H, s)
11d	$C_{23}H_{30}N_2O_2$	75.37 (74.99	8.25 8.13	7.64 7.53)	1698 1670	1640	1.99 (3H, s)	7.50 (5H, s)
11e	$C_{23}H_{30}N_2O_2$	75.37 (75.33	8.25 8.19	7.64 7.50)	1700 1670	1640	7.30 (5H, s)	1.96 (3H, s)
12b	$C_{22}H_{16}N_2O_2$	77.63 (77.47	4.74 4.62	8.23 8.12)	1705 1675	1630	6.32 (1H, s)	6.85—7.75 (5H, m)
12d	$C_{23}H_{18}N_2O_2$	77.95 (77.73	5.12 5.08	7.91 7.68)	1710 1673	1640 (sh)	2.12 (3H, s)	6.8—7.8 (5H, m)
12e	$C_{23}H_{18}N_2O_2$	77.95 (77.76	5.12 5.08	7.91 7.70)	1700 1665	1640 (sh)	2.00 (3H, s)	6.76—7.66 (5H, m)

oxazine **4**. Addition of another molecule of **3** to **A** gives the pyrimidine intermediate **B**, from which the imine is eliminated to yield the cinnamamide derivative (**5**—**7**). As reported previously,[1c] 2,3,6-trisubstituted 1,3-oxazines are thermolabile and are converted to cinnamamides on heating. Presumably, the oxazine formed from **3d** and **1a** or **1b** is spon-

TABLE V. Reaction of **1** with Phenyl Isocyanate

Product No.	Substituents		Reaction conditions		Yield (%)	mp (°C) (lit. mp)	Appearance	Recryst. solvent[a]
	R^1	R^2	Temp. (°C)	Time (h)				
15b[c]	H	Ph	130	1	21	237—238	Needles	A
15c	Me	Me	165	2	42	143—145 (147)[b]	Needles	B
15d	Me	Ph	165	2	30	138—140	Prisms	B
15e	Ph	Me	165	2	59	164—165	Needles	A

a) A, methanol; B, ethyl acetate.
b) Reference 10.
c) Reference 12.

taneously isomerized to **6** or **7** *via* the intermediate **A** during the reaction. In contrast, 2,3,5,6-tetrasubstituted 1,3-oxazines are stable under these reaction conditions.

Acylketenes generated from **1** also added to dicyclohexyl- and diphenyl-carbodiimides (**9** and **10**) to produce the corresponding 1,3-oxazin-4-one derivatives (**11** and **12**). Interestingly, acetyl Meldrum's acid (**13**), on heating with **9**, underwent an analogous ring transformation to yield the 1,3-oxazine-4,6-dione derivative (**14**), though the mechanism of the reaction is not clear.

1,3-Dioxin-4-ones likewise reacted with phenyl isocyanate to give 1,3-oxazine-2,4-dione derivatives **15**. In contrast, 2-pyridyl isocyanate (**17**), which is thermally generated from 2-picolinoyl azide (**16**), reacted with 6-substituted 1,3-dioxin-4-ones (**1a** and **1b**) to give the corresponding 3-acyl-2-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (**18a** and **18b**). Apparently, 2-pyridyl isocyanate acted as a 1,4-dipole.

Interest in 1,3-oxazin-4-ones has been growing recently because of the potential biological properties of this class of heterocycle.[12] The ring transformation of the masked acylketene (**1**) provides a good method for preparing 1,3-oxazin-4-ones.

Experimental

All melting points were determined on a Yanagimoto micromelting point apparatus (MP-S3, hot-stage type) and are uncorrected. Infrared (IR) spectra were measured with a JASCO A-102 spectrometer. Proton nulcear magnetic resonance (^{1}H-NMR) spectra were measured on a JEOL JNM-PMX 60 spectrometer and are reported as δ values (ppm) relative to tetramethylsilane in deuteriochloroform or to sodium 2,2-dimethyl-2-silapentane-5-sulfonate in dimethylsulfoxide-d_6 (DMSO-d_6) as an internal standard. Mass spectra (MS) were obtained on a Hitachi M-52G mass spectrometer. 1,3-Dioxin-4-ones (**1**) were prepared according to the reported procedure.[4]

General Procedure for Reaction of 1,3-Dioxin-4-ones 1b—e with Imines 3a,[13] 3b,[14] and 3c[15]——A mixture of **1** (5 mmol) and **3** (5 mmol) was heated without any solvent. Products **4a**, **4c**, **4f**, and **4g** were crystallized from ether (**4a**, **4c**, and **4g**) or hexane (**4f**). Crystals were collected by suction and recrystallized. Other products were purified by silica gel column chromatography using mixtures of ethyl acetate and hexane as eluents (1 : 5 v/v for **4b** and **4h**; 1 : 3 v/v for **5**; 1 : 8 v/v for **4d** and **4e**). Reaction conditions, yields, recrystallization solvents, and melting points are shown in Table I. Elemental analyses and spectral data for the new compounds **4** are shown in Table II. Compound **5** was obtained in 28% yield as prisms of mp 89—91 °C (recrystallized from ether). *Anal.* Calcd for $C_{18}H_{17}NO_2$: C, 77.39; H, 6.13; N, 5.01. Found: C, 77.20; H, 6.19; N, 4.90. IR ($CHCl_3$): 3440 (NH), 1660 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.12 (3H, t, J=7 Hz, $CH_2\underline{CH_3}$), 3.40 (2H, quint, J=7 Hz, $\underline{CH_2}CH_3$), 6.26—6.60 (1H, br, NH), 7.15 (1H, s, =CH–), 7.15—8.06 (10H, m, 2 × Ph).

2-Acetyl-*N*-(2-pyridyl)cinnamamide (6)——a) A mixture of **3d**[16] (0.341 g, 2.4 mmol) and **1a** (0.364 g, 2 mmol) was heated without any solvent at 125—130 °C (bath temperature) for 15 min. Benzene (1 ml) was added to the mixture and separated crystals were collected by suction. Recrystallization from chloroform gave the product **6** as yellow needles of mp 157—159 °C. Yield, 0.34 g (64%). *Anal.* Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.14; H, 5.26; N, 10.44. IR ($CHCl_3$): 3400 (NH), 1680, 1660 (C=O), 1620 (C=C) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.50 (3H, s, Me), 7.0—8.5 (10H, m, olefinic protons), 11.0 (1H, br s, NH). The spectrum showed signals at δ 2.30 (Me)

and 10.50 (NH) indicating contamination (*ca.* 10%) by the geometrical isomer.

b) A solution of 2-acetoacetamidopyridine (**8**)[17] (0.89 g, 5 mmol), benzaldehyde (0.64 g, 6 mmol), and piperidine (20 mg) in benzene (6 ml) was refluxed for 30 min. The solvent was evaporated off *in vacuo*, and the residue was crystallized from ethyl acetate. Crystals were collected by suction and recrystallized from chloroform to give **6** as yellow needles of mp 157—160 °C. Yield, 0.82 g (62%). This product was identified by the comparison of its IR spectrum with that of the sample obtained in the above run.

2-Benzoyl-*N*-(2-pyridyl)cinnamamide (7)——A mixture of **3d** (0.546 g, 3 mmol) and **1b** (0.612 g, 3 mmol) was heated at 125—130 °C for 20 min. The oily reaction mixture was dissolved in methanol (3 ml) and the solution was placed in a refrigerator for 1 d. Precipitates were collected by suction and washed with methanol to give **7** as yellow needles of mp 129—133 °C. Yield, 0.68 g (69%). A portion of the product was recrystallized from methanol to give an analytical sample of mp 134—136 °C. *Anal.* Calcd for $C_{21}H_{16}N_2O_2$: C, 76.81; H, 4.91; N, 8.53. Found: C, 76.29; H, 4.90; N, 8.41. IR (KBr): 3200—2800 (NH), 1660, 1640 (sh) (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 6.93—8.40 (15H, m, olefinic protons), 9.30 (1H, br, NH).

3,4-Dihydro-5,6-dimethyl-2-phenyl-3-(2-pyridyl)-2*H*-1,3-oxazin-4-one (4i)——A mixture of **1c** (0.86 g, 5.5 mmol) and **3d** (0.91 g, 5 mmol) was heated at 165 °C for 50 min. The product was crystallized from hexane. Recrystallization from ether yielded **4i** as colorless prisms of mp 147—149 °C. Yield, 0.84 g (55%). *Anal.* Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.93; H, 5.83; N, 9.92. IR ($CHCl_3$): 1660 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.73 (3H, s, C_5–Me), 1.95 (3H, s, C_6–Me), 6.8—7.9 (2H, m, pyridine-H), 7.34 (5H, s, Ph), 7.60[18] (1H, s, C_2–H), 8.06—8.46 (2H, m, pyridine-H). MS *m/e*: 280 (M^+), 98 ($MeCO \cdot CMe=C=O)^+$).

General Procedure for Reaction of 1a—e with Dicyclohexylcarbodiimide (9) and Diphenylcarbodiimide (10)——A mixtue of **9** (1—5 mmol) and **1** (1.1 mol eq) in dry xylene (for **1a** and **1b**) or in dry mesitylene (for **1c**—**e**) was heated. The reaction mixture was concentrated to dryness *in vacuo*. The crystalline residue was collected by suction using a small amount of ether or hexane, and recrystallized to give the product **11**. Similar treatment of **10**[19] gave the product **12**. Reaction conditions, yields, melting points and recrystallization solvents are shown in Table III. Analytical and spectral data are listed in Table IV.

5-Acetyl-3-cyclohexyl-2-cyclohexylimino-3,4,5,6-tetrahydro-1,3-oxazine-4,6-dione (14)——Compound **13** (mp 82—85 °C) was prepared by the method described in the literature.[20] A solution of **13** (0.39 g, 2 mmol) and **9** (0.41 g, 2 mmol) in dry toluene (3 ml) was refluxed for 10 min. The mixture was concentrated to dryness *in vacuo*. The crystalline residue was washed with methanol and filtered. Recrystallization from methanol gave the product **14**[21] as colorless needles of mp 128—130 °C. Yield, 0.49 g (73%). The ferric chloride test showed an orange coloration. *Anal.* Calcd for $C_{18}H_{26}N_2O_4$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.36; H, 7.66; N, 8.27. IR ($CHCl_3$): 3400—3200 (OH), 1715, 1665 (C=O), 1615 (C=N) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.83—2.60 (20H, m, 2 × cyclohexyl), 2.66 (3H, s, Me), 4.40—5.03 (2H, m, 2 × NC<u>H</u><), 17.65 (1H, s, Me–C(O<u>H</u>)=). MS *m/e*: 334 (M^+).

General Procedure for Reaction of 1b—e with Phenyl Isocyanate——A mixture of **1** (2 mmol) and phenyl isocyanate (4 mmol) was heated under the conditions listed in Table V. After the removal of excess phenyl isocyanate under reduced pressure, the residue was washed with ether, and the resulting crystals were collected by suction. Recrystallization gave the products **15b** and **15c**. In the case of **15d** or **15e**, the resulting oil was crystallized from ether (**15d**) or ethyl acetate (**15e**) under ice-cooling. The results are summarized in Table V.

3,4-Dihydro-5-methyl-3,6-diphenyl-2*H*-1,3-oxazine-2,4-dione (**15d**): *Anal.* Calcd for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02. Found: C, 73.02; H, 4.66; N, 5.13. IR ($CHCl_3$): 1764, 1690 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.12 (3H, s, Me), 7.16—7.90 (10H, m, 2 × Ph).

3,4-Dihydro-6-methyl-3,5-diphenyl-2*H*-1,3-oxazine-2,4-dione (**15e**): *Anal.* Calcd for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02. Found: C, 72.83; H, 4.67; N, 4.74. IR ($CHCl_3$): 1768, 1698 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.18 (3H, s, Me), 7.13—7.66 (10H, , 2 × Ph).

Reaction of 1a and 1b with 2-Pyridyl Isocyanate (17)——A mixture of **1** and picolinoyl azide (**16**)[22] in dry xylene (1 ml/1 mmol of **1**) was heated at 120 °C for 30 min. After cooling, the separated crystals were collected by suction and recrystallized from methanol to give the product **18a** or **18b**.

3-Acetyl-2-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**18a**): Brown leaves of mp 216—218 °C (lit.[6] mp 210 °C). The IR spectrum was identical with that of an authentic specimen.[6]

3-Benzoyl-2-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**18b**): Brown needles of mp 237—238 °C (dec.). *Anal.* Calcd for $C_{15}H_{10}N_2O_3$: C, 67.66; H, 3.79; N, 10.52. Found: C, 67.74; H, 3.77; N, 10.54. IR ($CHCl_3$): 3200—2800 (br) (OH), 1710, 1695 (sh), 1640 (C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 7.26—8.50 (8H, m, $C_{6,7,8}$–H and Ph), 8.86—9.16 (1H, m, C_5–H), 12.0—13.0 (1H, br, OH).

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