REACTIONS OF METHACRYLOYL ISOCYANATE WITH IMINES DERIVED FROM KETONES AND ALKYL AMINES

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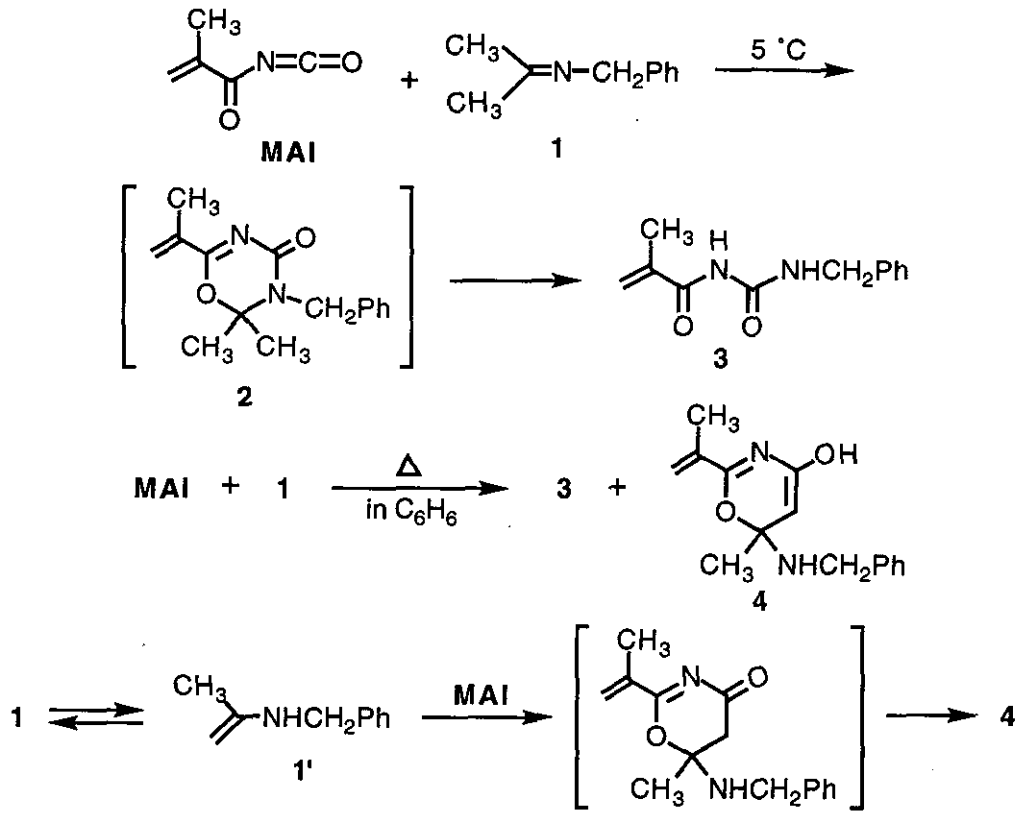
Abstract - The reactions of methacryloyl isocyanate (**MAI**) with imines derived from ketones and alkyl amines led to the formation of the corresponding 2*H*-1,3,5-oxadiazin-4(3*H*)-one, 1,3-oxazine, piperidinedione, and/or 1-alkyl-1-alkenyl-3-methacryloylurea, whose relative yields greatly depended on the reaction conditions as well as the nature of imine. The latter three compounds correspond to products arising from the reacion of **MAI** with enamine tautomers of imines.

Methacryloyl isocyanate (**MAI**) is a versatile polyfunctional reagent bearing an enone moiety as well as a highly reactive acyl isocyanato group.[1] Recently, it has been found that enamines added not only to the acyl isocyanato moiety, but also to the enone moiety in **MAI**: At a higher reaction temperature initial [4 + 2] cycloadducts to acyl isocyanato moiety in **MAI** dissociate into two original substrates and then regenerated enamine adds to the enone moiety in **MAI**.[1a] In addition, 2*H*-1,3,5-oxadiazin-4(3*H*)-ones produced by the [4 + 2] cycloaddition of **MAI** to imines derived from aromatic aldehydes were found to dissociate into **MAI** and imine in solution even at low temperature.[1b] To the best of our knowledge, such dissociation phenomena have not been observed in [4 + 2] cycloadducts of acyl isocyanates.

It has been reported that 2-alkyl-2-thiazoline and -oxazoline participated as their corresponding enamine tautomers in the reaction of phenyl,[2] benzoyl[3] and thiobenzoyl isocyanate.[3] Thus, it seemed to be interest to study the reaction of **MAI** with isomerizable imines to enamines. We report here the reaction of **MAI** with imines derived from methyl ketones, propiophenone or cyclohexanone and alkyl amines.[4]

Reaction of Imines Derived from Acetone. The reaction of **MAI** with isopropylidenebenzylamine (**1**) in Et_2O at 5 °C for 1 h gave a good yield of 1-benzyl-3-methacryloylurea (**3**), mp 95-96 °C, which was identical with an authentic sample prepared from **MAI** and benzylamine.[5] On the basis of the following observations, it was clarified that urea (**3**) was the compound arising from hydrolysis of an unstable initial [4+2] cycloadduct, 3-benzyl-2,2-dimethyl-6-isopropenyl-2*H*-1,3,5-oxadiazin-4(3*H*)-one



Scheme 1

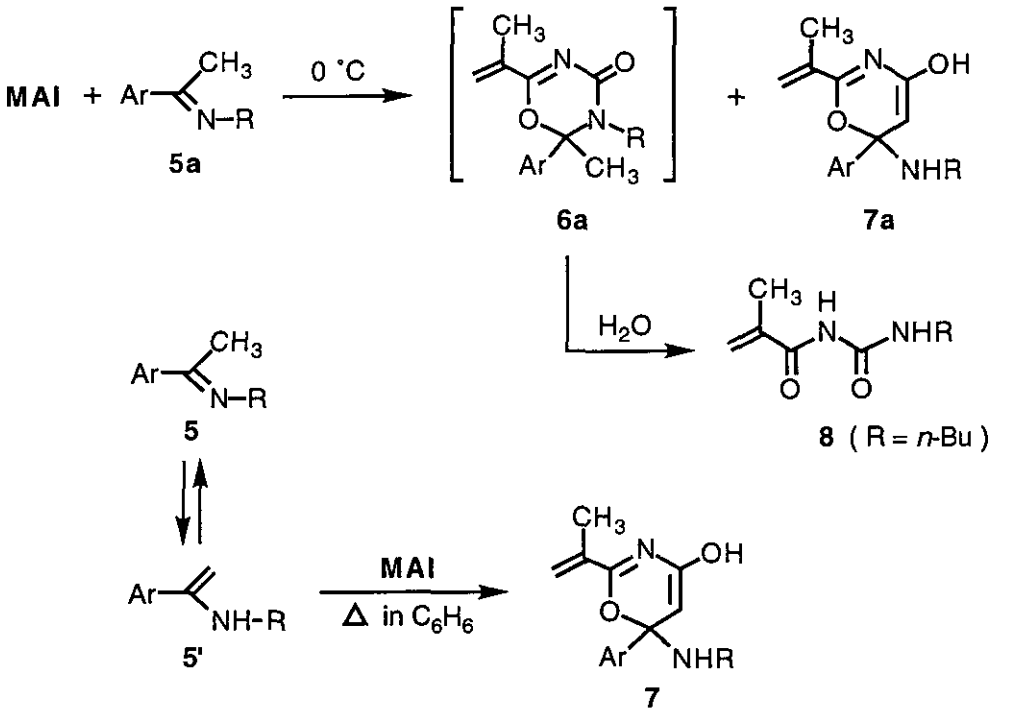
(**2**). The ir spectrum of the reaction mixture of **MAI** with an equivalent of **1** in CCl_4 at 0 °C for 1 h exhibited characteristic bands assignable to 2*H*-1,3,5-oxadiazin-4(3*H*)-one structure[6] at 1688 (C=O) and 1640 cm^{-1} (C=N), respectively. Since **2** was very sensitive to moisture, its isolation was unsuccessful; the reaction mixture was readily hydrolyzed with a 5% ethanolic hydrochloric acid to give **3** in good yield.

On the other hand, the reaction of **MAI** with imine (**1**) in benzene under reflux for 2 h afforded 6-benzylamino-4-hydroxy-2-isopropenyl-6-methyl-1,3-oxazine (**4**) as colorless needles, mp 147-148 °C, in 45% yield, together with a 43% yield of urea (**3**). It should be emphasized that **4** corresponds to the tautomer[1a] of the initial [4 + 2] cycloadduct of **MAI** to enamine tautomer (**1'**) of imine (**1**) as shown in Scheme 1.

Reaction of Imines Derived from Acetophenones. The reaction of **MAI** with α-methyl-*p*-chlorobenzylidene-*n*-butylamine (**5a**) was conducted in CCl_4 at 0 °C for 26 h. The ir spectrum of the reaction mixture in CCl_4 showed the presence of two cycloadducts, 1,3,5-oxadiazinone (**6a**) and 1,3-oxazine (**7a**).[7] In fact, the reaction mixture was treated with a 3% aqueous ethanol at room temperature for 12 h to give a 39% yield of **7a** as colorless needles, mp 110-110.5 °C, together with urea (**8**) (36%) and *p*-chloroacetophenone (38%) which arise from hydrolysis of **6a**; in this case **MAI** partially reacted with enamine tautomer (**5a'**) of **5a** even at low temperature.

In the reaction of **MAI** with **5a** in refluxing benzene for 1 h, however, **7a** was formed quantitatively.

Similarly, the reaction of **MAI** with imine **5b**, **5c** or **5d** in benzene under reflux for 1 h gave the corresponding 1,3-oxazine, **7b** (mp 123-124 °C), **7c** (mp 155-155.5 °C) or **7d** (mp 151-152 °C) in 90, 90 or 86% yield, respectively.[8] The above facts indicate that the tendency of tautomerization of imines (**5**) to their enamines (**5'**) is much stronger than that of imine (**1**) to its enamine (**1'**) (Scheme 2).

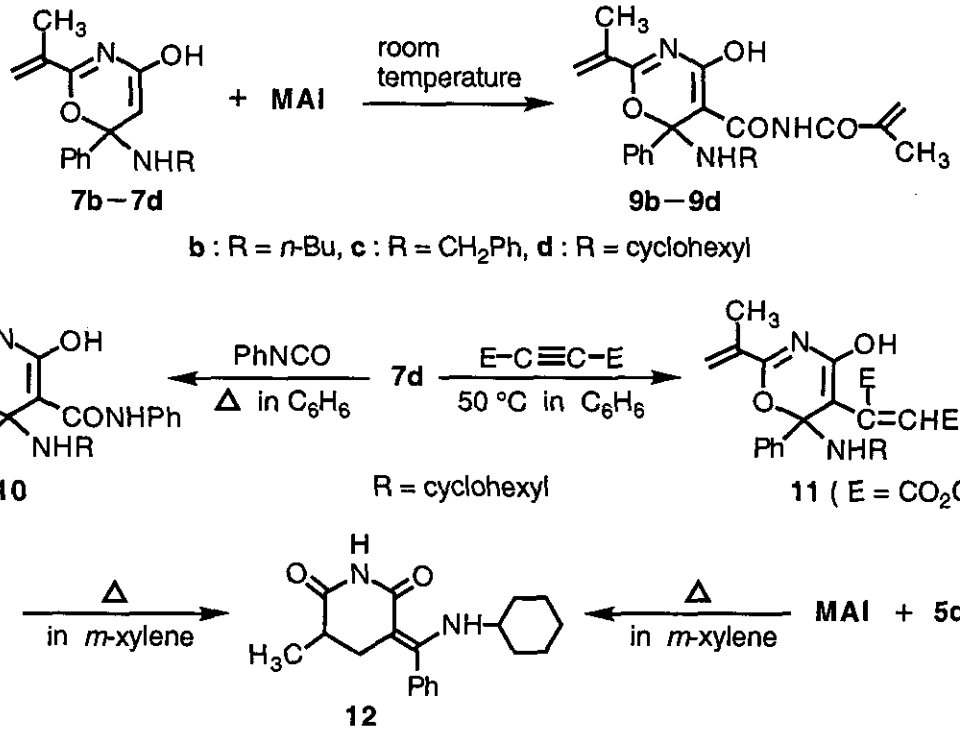


a : Ar = *p*-ClC$_6$H$_4$, R = *n*-Bu; **b** : Ar = Ph, R = *n*-Bu
c : Ar = Ph, R = CH$_2$Ph; **d** : Ar = Ph, R = cyclohexyl

Scheme 2

In a certain reaction of **MAI** with **5d** a 1:2 adduct (**9d**) was incidentally isolated in a trace amount: The 1:1 adduct (**7d**) was allowed to react with an equivalent of **MAI** in benzene at room temperature for 3 h, giving the 1:2 adduct, *N*-methacryloyl-5-oxazinecarboxamide (**9d**) in 89% yield.[9] Under similar conditions the reaction of 1:1 adduct (**7b**) or (**7c**) with **MAI** gave the corresponding 5-carboxamide (**9b**), mp 162-163 °C, or (**9c**), mp 183-184 °C, in 81 or 51% yield, respectively. In the reaction of **7d** with phenyl isocyanate in refluxing benzene for 8 h a similar *N*-phenyl-5-oxazinecarboxamide (**10**) as colorless prisms, mp 164-165 °C, was obtained in 22% yield. Although electron-deficient alkenes such as acrylonitrile and fumaronitrile did not react with **7**, in benzene at 50 °C for 10 h dimethyl acetylenedicarboxylate attacked position 5 in **7d** to give a 70% yield of a 1:1 mixture of (E)- and (Z)-alkenes (**11**) as orange oil (Scheme 3). It has also been found that **7d** isomerized into 3-(1-cyclohexylamino-1-phenylmethylene)-5-methyl-piperidine-2,6-dione (**12**)[10] in 58% yield when heated in refluxing *m*-xylene for 33.5 h. The same compound (**12**) was directly obtained in 32% yield from the reaction of **5d** with **MAI** in *m*-xylene under

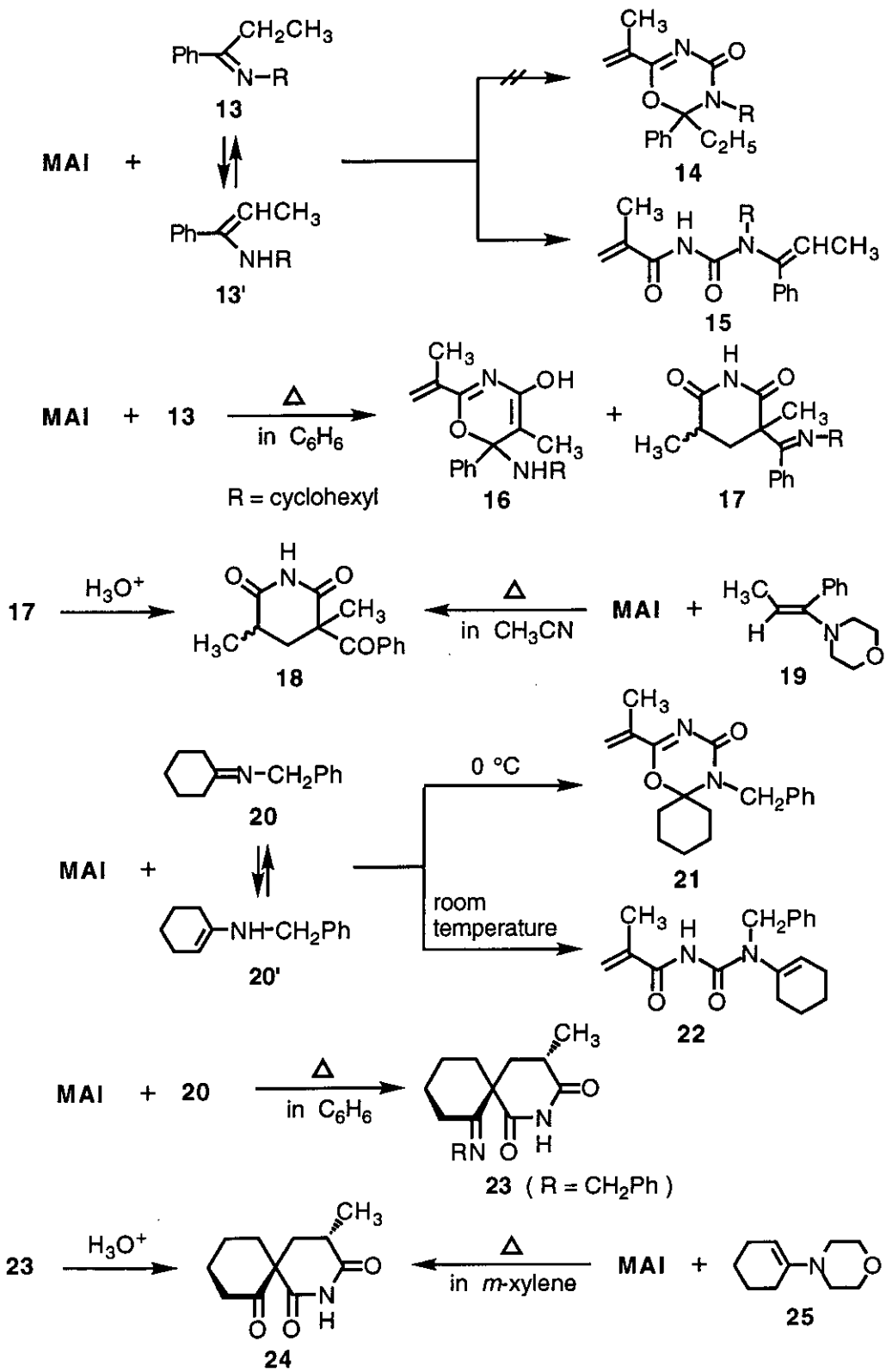
reflux for 6.5 h. The formation of **12** will be described below.



Scheme 3

Reaction of Imines Derived from Propiophenone and Cyclohexanone. In the reaction of **MAI** with α-ethylbenzylidenecyclohexylamine (**13**) in CCl_4 at 0 °C for 20 h or in Et_2O at room temperature for 3 h, no 1,3,5-oxadiazinone compound (**14**) was detected, but instead a mixture of (Z)- and (E)-1-cyclohexyl-1-(1-phenylpropenyl)-3-methacryloylureas (**15**) (Z/E=1.5),[11] in an excellent yield, respectively. The urea (**15**) corresponds to the addition product of **MAI** to the NH group in enamine tautomer (**13'**). The same reaction in benzene under reflux for 4 h gave piperidinedione (**17**)[12] in 62% yield, together with a trace amount of 1,3-oxazine (**16**), mp 134-135 °C (decomp.); **15** was converted into **16** (2%) and **17** (76%) in refluxing benzene for 4 h. Hydrolysis of **17** with a 5% ethanolic hydrochloric acid at room temperature gave a 76% yield of 3-benzoyl derivative (**18**) as colorless needles, mp 117-118 °C, which was obtained in a 7% yield by the reaction of **MAI** with propiophenone enamine (**19**) in CH_3CN under reflux for 20 h as shown in Scheme 4.

On the other hand, **MAI** reacted with cyclohexylidenebenzylamine (**20**) in Et_2O at 0 °C for 1 h to give a comparatively stable 1,3,5-oxadiazinone (**21**) as white crystals, mp 57-58 °C, in 65% yield; hydrolysis of **21** gave urea (**3**). The same reaction at room temperature for 3 h, however, afforded a 60% of the urea (**22**), mp 91-92.5 °C, like **15**. When **MAI** was allowed to react with **20** in benzene under reflux for 5 h, spiro-piperidinedione (**23**), mp 146.5-147.5 °C, was isolated as a single stereoisomer in 23% yield. Hydrolysis of **23** with a 5% ethanolic hydrochloric acid at 50 °C gave 4-methyl-2-azaspiro[5.5]undecane-1,3,7-trione (**24**) as colorless prisms, mp 170 °C, which is identical with one of two stereoisomer [1a] from the reaction of **MAI** with cyclohexanone enamine (**25**) (Scheme 4).


MAI +
13
13'
14
15
MAI + 13
Δ
in C6H6
R = cyclohexyl
16
17
17
H3O+
18
Δ
in CH3CN
MAI +
19
20
20'
0 °C
room temperature
21
22
MAI + 20
Δ
in C6H6
23 (R = CH2Ph)
23
H3O+
24
Δ
in m-xylene
MAI +
25

Scheme 4

The structure of **24** was confirmed by its X-ray crystallographic analysis and ORTEP drawing is shown in Figure 1.[13]

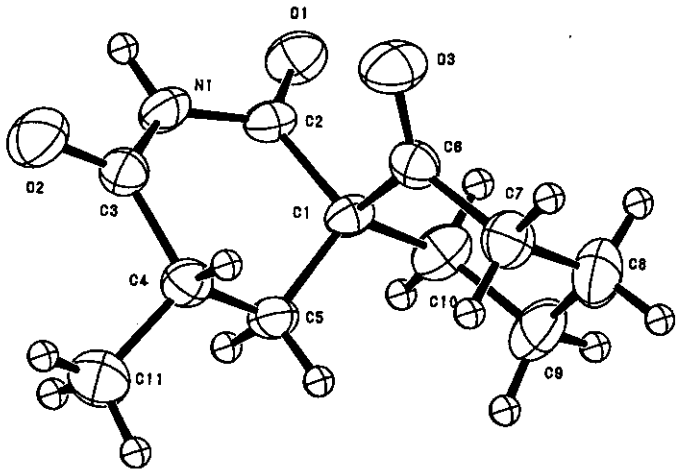
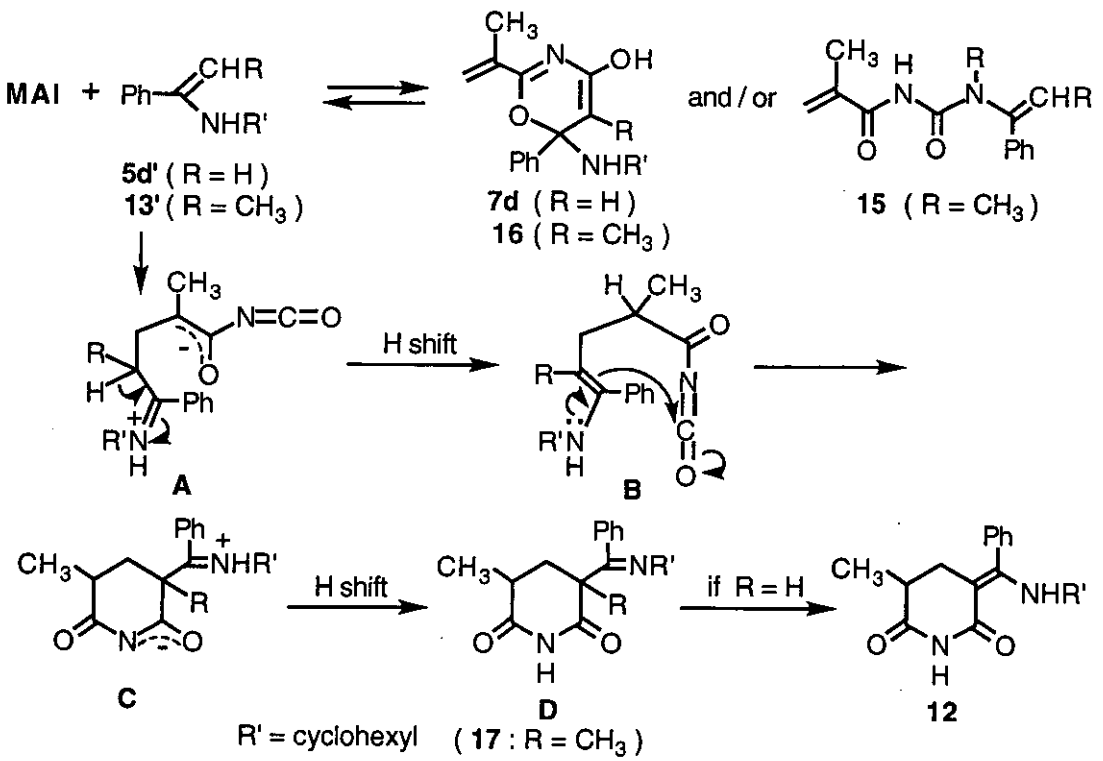


Figure 1. ORTEP drawing of **24**

The pathways for the formation of products, particularly piperidinediones, derived from the reaction of enamine tautomers of imines, are illustrated by representative reactions of **MAI** with enamine tautomers (**5d'**) and (**13'**) of imines (**5d**) and (**13**) shown in Scheme 5.



Scheme 5

Under rather mild conditions **MAI** reacts with enamine tautomer (**5d'**) or (**13'**) to form 1,3-oxazine (**7d**) or (**16**), and/or urea (**15**), respectively. On the basis of the above observations (Schemes 2, 3 and 4), this process is reversible, and the equilibrium lies as far to the left with a rise in temperature: Eventually complete dissociation to **MAI** and enamine tautomer occurs. At higher reaction temperature the regenerated enamine tautomer (**5d'**) or (**13'**) adds to the enone moiety in **MAI** to generate a betaine (**A**). Hydrogen shift in **A** generates 5-amino-substituted 4-pentenoyl isocyanate (**B**) which undergoes intramolecular cyclization to a betaine (**C**). Hydrogen shift in **C** gives rise to stable piperidinedione (**D**) which is **17** if R is CH_3. Piperidinedione (**D**) isomerizes into a more stable enamine tautomer (**12**) if R is hydrogen.

Thanks are due to Nippon Paint Co. Ltd.for supplying **MAI**.

REFERENCES AND NOTES

1. a) O. Tsuge, T. Hatta, R. Mizuguchi, and H. Kato, *Chem. Lett.*, **1993**, 631; b) O. Tsuge, T. Hatta, R. Mizuguchi, T. Kobayashi, and R. Kanzaki, *Heterocycles*, 1996, **42**, 533; c) O. Tsuge, T. Hatta, and R. Mizuguch, *Heterocycles*, 1994, **38**, 235; d) S. Urano, K. Aoki, N. Tsuboniwa, R. Mizuguchi, and O. Tsuge, *Prog. Org. Coat.*, 1992, **20**, 471.
2. R. Nehring and W. Seeliger, *Liebigs Ann. Chem.*, 1966, **698**, 167.
3. O. Tsuge and S. Kanemasa, *Tetrahedron*, 1972, **28**, 4737.
4. All the reactions using **MAI** were conducted in dry solvent under nitrogen.
5. All the new products gave satisfactory spectral and analytical data.
6. 2*H*-1,3,5-oxadiazin-4(3*H*)-ones shows the characteristic bands due to $\nu_{C=O}$ and $\nu_{C=N}$ around 1670 and 1640 cm^{-1} in ir spectra, respectively (O. Tsuge and S. Kanemasa, *Bull. Chem. Soc. Jpn.*, 1972, **45**, 2877, and ref. 1b).
7. The characteristic absorption bands due to two cycloadducts appeared at 1663 and 1636 cm^{-1} for **6a**, and 3430 and 1702 cm^{-1} for **7a**, respectively.
8. Various imines **5** in which Ar are p-tolyl, p-nitrophenyl-, 2- and 4-pyridyl reacted with **MAI** in similar conditions to give the corresponding 1,3-oxazines in excellent yields, respectively.
   As representative spectral data for 1,3-oxazines are shown those of **7d** as colorless needles. Ir (KBr) 3272, 1690 cm^{-1}; ^1H nmr ($CDCl_3$) δ=0.90-1.90 (10H, m), 1.98 (3H, br s), 3.00-3.40 (1H, m, C**H**), 5.48 (1H, br d, =CH_2), 5.82 (1H, br s, =CH_2), 6.01 (1H, s, 5-**H**), 7.35 (5H, s), 8.59 (1H, br s, O**H**), 9.94 (1H, br d, N**H**); ^{13}C nmr ($CDCl_3$) δ=18.65, 24.47, 25.29, 34.46, 52.85, 87.94 (5-**C**), 120.91, 127.56, 128.38, 129.28, 136.26, 140.60, 166.67 (6-**C**), 166.97 (2-**C**), 168.73 (4-**C**); ms m/z 312 (M^+).
9. **9d**: Colorless prisms; mp 176-177 °C; ir (KBr) 3256, 1715, 1657 cm^{-1}; ^1H nmr ($CDCl_3$) δ=0.70-1.85 (10H, m), 1.66, 2.06 (each 3H, br s), 2.60-3.65 (1H, m), 5.27 (2H, br d, J=5.3 Hz, =CH_2), 5.58, 6.03 (each 1H, br s, =CH_2), 7.43 (5H, s), 7.99 (1H, br s, O**H**), 11.61 (1H, br d, J=9.2 Hz, N**H**), 11.95 (1H, br s, N**H**); ^{13}C nmr ($CDCl_3$) δ=18.18, 18.30, 24.18, 24.93, 33.65, 54.12, 97.26 (5-**C**), 121.26, 122.38, 128.22, 129.26, 130.74, 133.80, 139.63, 140.28, 165.70 (6-**C**), 166.02, 167.11 (2-C), 169.03, 169.90 (4-**C**); ms m/z 423 (M^+).

10. **12**: Colorless prisms; mp 194-194.5 °C; ir (KBr) 3162, 3114, 1707, 1624 cm^{-1}; ^1H nmr ($CDCl_3$) δ=1.09 (3H, d, J=6.7 Hz), 1.20-1.95 (10H, m), 2.04 (2H, d, J=2.6 Hz), 2.15-2.60 (1H, m), 2.60-3.20 (1H, m), 7.10-7.35 (2H, m), 7.35-7.55 (3H, m), 8.30 (1H, br s, N**H**), 10.10 (1H, br d, N**H**); ^{13}C nmr ($CDCl_3$) δ=14.99. 24.32, 25.18, 30.27 (4-**C**), 34.25, 36.50 (5-**C**), 52.69, 87.49 (3-**C**), 127.22, 127.41, 128.84, 134.36, 162.85, 168.72 (2-**C**), 175.92 (6-**C**); ms m/z 312 (M^+).
11. **15**: Colorless prisms; mp 131-132 °C; ir (KBr) 3432, 1744, 1678 cm-1; ^1H nmr ($CDCl_3$) δ=0.60-2.20 (16H, m), 3.90-4.40 (1H, m), 5.20-5.40 (1.4 H, m, =C**H**$_2$), 5.45 (0.6 H, s, =C**H**$_2$), 5.94 (0.6 H, q, J=7.4 Hz, =C**H** in (Z) isomer), 6.34 (0.4 H, q, J=7.0 Hz, =C**H** in (E) isomer), 7.37 (5H, s), 8.08 (0.4H, br s, N**H**), 8.29 (0.6H, br s, N**H**); ms m/z 326 (M^+).
12. The stereochemistry of **17** isolated as a single product is not clear yet : colorless needles; mp 146 °C; ir (KBr) 3230, 1725, 1702, 1638 cm^{-1}; ^1H nmr ($CDCl_3$) δ=0.70-1.90 (17H, m), 2.28 (1H, dd, J=14.0, 5.0 Hz), 2.60-3.10 (2H, m), 6.65-7.20 (2H, m), 7.30-7.60 (3H, m), 7.96 (1H, br s, NH); ^{13}C nmr ($CDCl_3$) δ=15.35, 22.45, 23.78, 25.57, 33.21 (4-**C**), 33.82 (5-**C**), 38.00, 53.24 (3-**C**), 60.57, 126.80, 128.40, 128.45, 134.48, 167.55 (**C**=N), 175.18 (**C**=O), 175.68 (**C**=O); ms m/z 326 (M^+).
13. X-Ray crystallographic analysis was carried out on a Rigaku AFC5S diffractometer. The diffraction data were collected with the use of MoKα radiation and 2163 independent reflactions were used for solving the structure by the TEXSAN program (TEXSAN TEXRAY, Structure Analysis Package, Molecular Structure Corporation). Crystal data for **22**: $C_{11}H_{15}NO_3$, F.W.=209.24, monoclinic, space group $P2_1/n$ (# 14), a=9.471(8) Å, b=11.449(3) Å, c=10.300(2) Å, β=104.99(3)°, V=1078.9(8) $Å^3$, Z=4, Dcal=1.288 g/cm^3; R=0.044, Rw=0.048.

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