CHEMISTRY LETTERS, pp. 631-634, 1993.

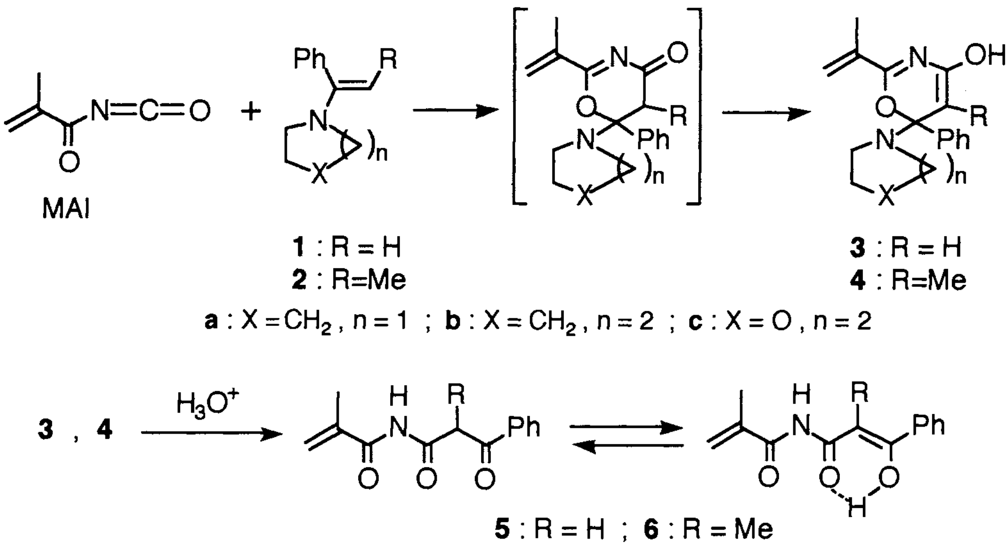
Novel Cycloaddition Reactions of Methacryloyl Isocyanate with Enamines

Otohiko TSUGE,* Taizo HATTA, Ryuzo MIZUGUCHI, and Hisayoshi KATO
Graduate Course of Applied Chemistry, Kumamoto Institute of Technology, Ikeda-machi, Kumamoto 860

Methacryloyl isocyanate (MAI) functioned as an ambident heterodiene in the cycloaddition reactions. Thus, enamines added not only to the acyl isocyanato moiety, but also to the enone moiety in MAI. Regiochemistry of this cycloaddition markedly depended on the reaction conditions. The pathways for the formation of products are also described.

Methacryloyl isocyanate (MAI) is a new polyfunctional reagent bearing an enone moiety as well as a highly reactive acyl isocyanato group. Acyl isocyanates[1)] and α,β-unsaturated carbonyl compounds[2)] have been known to behave as heterodienes in the Diels-Alder type reaction. Thus, MAI may be regarded as an ambident heterodiene for the Diels-Alder reaction. We report here that in the cycloaddition reaction with enamines MAI functions not only as an acyl isocyanate, but also as an enone, depending on the reaction conditions.

The reaction of MAI with enamines **1** or **2**, derived from acetophenone or propiophenone, proceeded readily at room temperature to furnish the corresponding tautomers of initial [4 + 2] cycloadducts, **3** or **4**, in good yields, respectively[3)] (Table 1). Hydrolysis of **3** and **4** gave the corresponding phenacylcarbonylmethacrylamides **5** and **6**[4)] (Scheme 1).



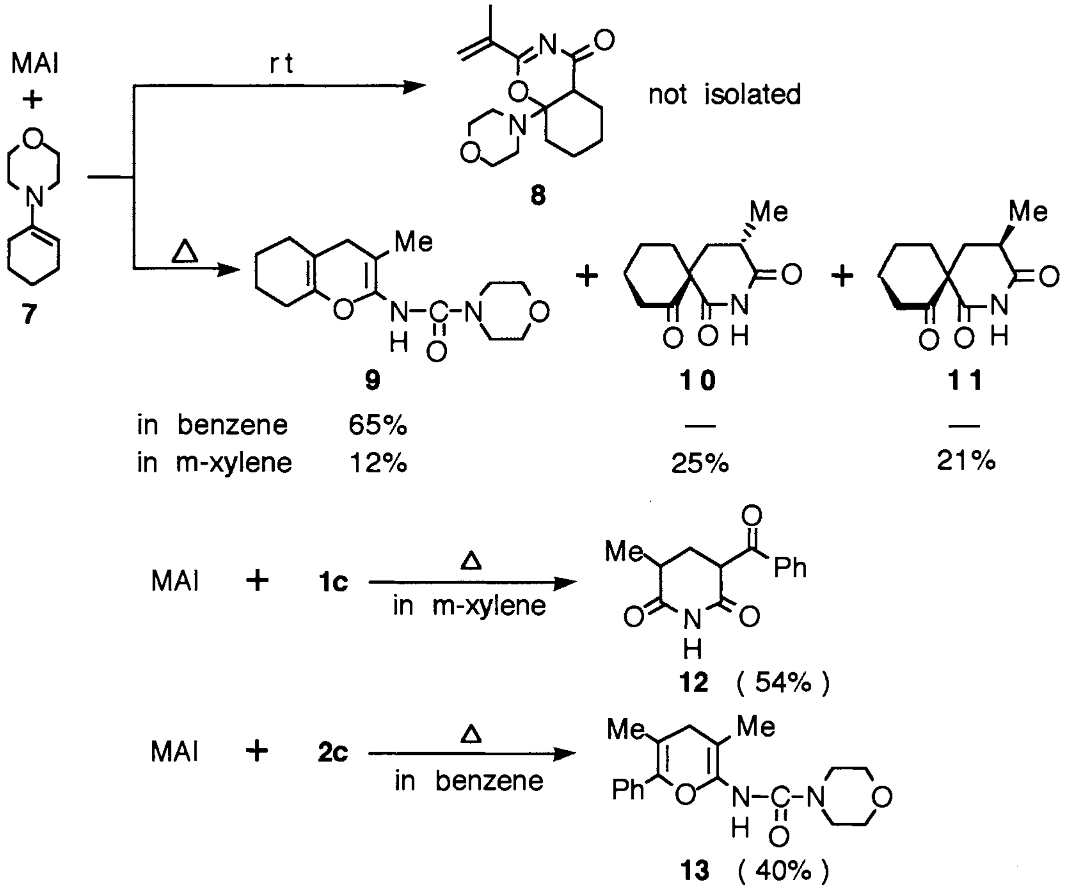
Scheme 1.

Table 1. Cycloaddition of MAI to Enamines **1** and **2**

Enamine	Solvent	Adduct	Yield / %	Enamine	Solvent	Adduct	Yield / %
1a	Et_2O	**3a**	90	**1c**	C_6H_6	**3c**	95
1a	C_6H_6	**3a**	89	**2a**	Et_2O	**4a**	83
1b	Et_2O	**3b**	94	**2b**	Et_2O	**4b**	84
1b	C_6H_6	**3b**	99	**2c**	Et_2O	**4c**	88
1c	Et_2O	**3c**	99				

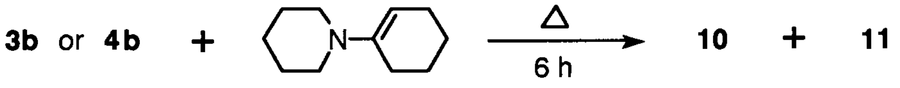
Although attempts to isolate the [4 + 2] cycloadduct **8** from the reaction of MAI with 1-morpholinocyclohexene **7** in benzene at room temperature were unsuccessful, inspection of the VT-NMR spectra of an equimolar mixture of MAI and **7** in C_6D_6 indicated that the initial cycloadduct **8** formed at room temperature gradually disappeared with a rise in temperature, and eventually transformed into a new compound **9** at 75 °C after 23 h.5)

The reaction of MAI with **7** was thus conducted under more severe conditions: In the reaction in refluxing benzene for 24 h 3-methyl-2-ureido-4H-5,6,7,8-tetrahydrochromene **9** was obtained, while the same reaction in m-xylene under reflux for 7 h gave a mixture (ca. 1:1) of two stereoisomeric 4-methyl-2-azaspiro[5.5]-undecane-1,3,7-triones **10** and **11**,6) along with a low yield of **9** (Scheme 2). We wish to emphasize that the products **9**-**11** correspond to those derived from a [4 + 2] cycloadduct of **7** to the enone moiety in MAI.



Scheme 2.

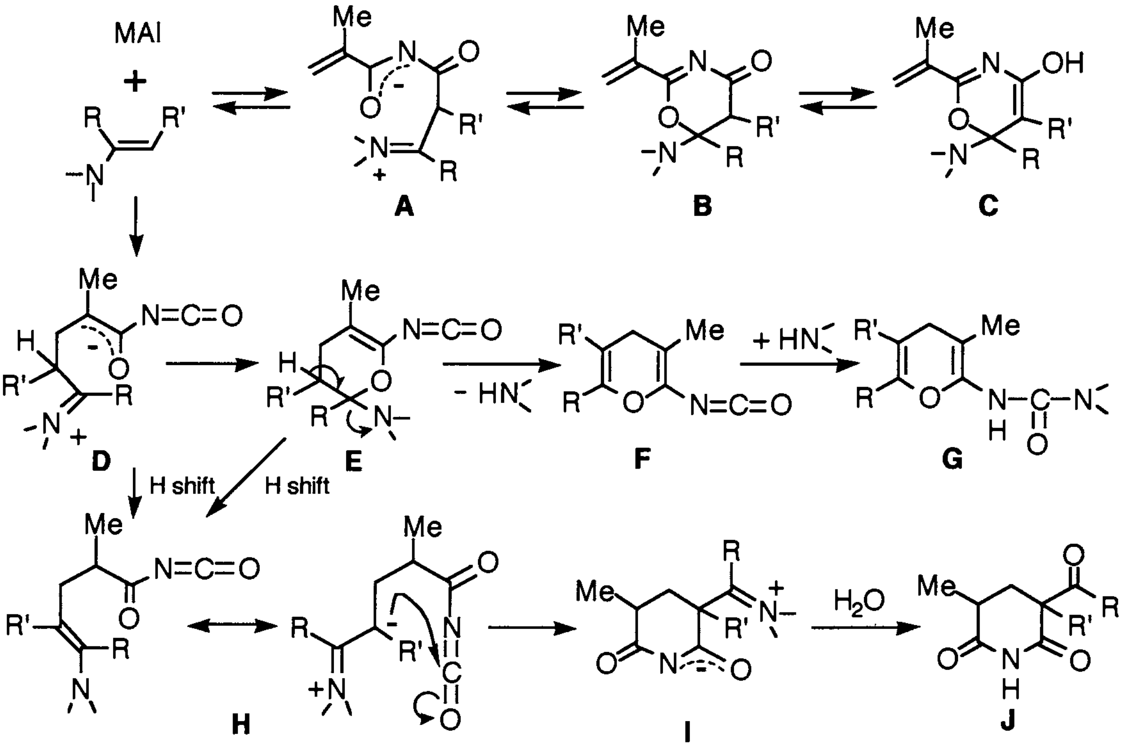
We have also found that MAI reacted with acyclic enamines **1** and **2** under more severe conditions to form the products corresponded to **9**-**11**. For example, the reaction of MAI with **1c** in refluxing m-xylene for 7 h gave 3-benzoyl-5-methylpiperidine-2,6-dione **12**, whereas MAI reacted with **2c** in benzene under reflux for 24 h afforded 4H-pyran derivative **13**[7] (Scheme 2).



Scheme 3.

Furthermore, it has been found that on heating the [4 + 2] cycloadduct **3b** with excess of 1-(1-piperidinyl)cyclohexene in m-xylene under reflux a mixture of **10** and **11** (ca. 1:1) was obtained in 62% yield, while a similar reaction of cycloadduct **4b** furnished again a mixture of **10** and **11** (ca. 1:1) in a good yield (88%) even in refluxing benzene (Scheme 3). The **10**/**11** ratios were determined by NMR spectra. The above fact strongly suggests that the [4 + 2] cycloadducts **3**, particularly **4**, undergo a thermal dissociation into the original components, MAI and the enamine, followed by addition of the enamine to the enone moiety in MAI.

On the basis of the above observations, the reaction pathways for the formation of products can be illustrated as shown in Scheme 4. Under mild conditions MAI reacts with enamine to form [4 + 2] cycloadduct **B** or **C** via a betaine **A**. These processes are reversible, and the equilibrium lies so far to the left with a rise in temperature: Eventually complete dissociation to two original components occurs. At higher reaction temperature the regenerated enamine adds to the enone moiety in MAI to generate cycloadduct, 2-isocyanato-4H-5,6-dihydropyran **E**, via a betaine **D**. The cycloadduct **E** decomposes to stable compounds through two paths,



Scheme 4.

depending on the nature of enamine as well as on the reaction conditions. Elimination of amine from **E**, followed by the addition of the amine to isocyanato group gives 2-ureido-4H-pyran (**E**→**F**→**G**). On the other hand, hydrogen shift in **D** and/or **E** generates 5-amino substituted 4-pentenoyl isocyanate **H** which undergoes intramolecular cyclization to a betaine **I**. On work up **I** is hydrolyzed to stable piperidinedione **J.**

We are grateful to Nippon Paint Co. Ltd. for supplying MAI.

References

1) O. Tsuge, "Acyl and Thioacyl Derivatives of Isocyanates, Thiocyanates, and Isocyanates," in "The Chemistry of Cyanates and Their Thio Derivatives," Part 1, ed by S. Patai, John Wiley & Sons, New York (1977), Chap. 13.

2) D. L. Boger and S. M. Weinreb, "Hetero Dield-Alder Methodology in Organic Synthesis," Academic Press, Inc., New York (1987), Chap 7.

3) After a solution of MAI (1.1 g, 10 mmol) in a given solvent (3 mL) was added dropwise to a solution of enamine (9 mmol) in the same solvent (3 mL) at 20 °C under nitrogen, the reaction mixture was stirred for 30 min under the same conditions. In contrast with **3**, the cycloadducts **4** were found to be partially dissociated into betaines like **A** (R=Ph, R'=Me in Scheme 4) in solution at room temperature.

4) All new compounds in this paper gave satisfactory spectral and analytical data. For example, **3b**: Colorless plates, mp 157-158 °C. IR (KBr) 3232, 1690, 1620 $\mathrm{cm^{-1}}$; ^{1}H-NMR ($\mathrm{CDCl_3}$) δ=1.60 (6H, brs, β,γ-$\mathrm{CH_2}$ of piperidine ring), 1.89 (3H, d, J=1.5 Hz,$\mathrm{CH_3}$), 3.21 (4H, brs, α-$\mathrm{CH_2}$ of piperidine ring), 5.32 (1H, d, J=1.5 Hz, =**CH**), 5.58 (1H, s, =**CH**), 6.35 (1H, s, 5-**CH**=), 7.19-7.45 (5H, m, Ar**H**), 8.05 (1H, brs, **OH**). MS m/z 298 ($\mathrm{M^+}$). Anal. Found: C, 72.44; H, 7.45; N, 9.33%. Calcd for $\mathrm{C_{18}H_{22}N_2O_2}$: C. 72.45; H, 7.43; N, 9.39%. ^{1}H-NMR spectra indicated that **5** and **6** partially exist in the corresponding enol form in solution. For example, **5**: Mp 95-96 °C. IR (KBr) 3254, 1709 $\mathrm{cm^{-1}}$; ^{1}H-NMR ($\mathrm{CDCl_3}$) δ=1.94 (1.5H, d, J=1.5 Hz, $\mathrm{CH_3}$), 4.53 (1.5H, d, J=1.5 Hz, $\mathrm{CH_3}$), 4.53 (1H, s, $\mathrm{CH_2}$), 5.63 (1H, d, J=1.5 Hz, =**CH**), 5.92 (1H, s, =**CH**), 7.23 (0.5H, s, =**CH**), 7.30-7.84 (3H, m), 7.91-8.09 (2H, m), 8.79, 9.43 (each 0.5H, brs, **NH**), 14.24 (0.5H, s, **OH**).

5) In the NMR spectrum at 27.5 °C the signals assigned to the structure **8** appeared at δ=1.86 (3H, d, J=1.43 Hz, $\mathrm{CH_3}$), 1.23-3.63 (16H, m, $\mathrm{CH_2}$), 4.82 (1H, t, J=3.38 Hz, CH), 5.21 (1H, q, J=1.43 Hz, =**CH**), and 5.66 (1H, s, =**CH**). The NMR spectrum at 75 °C after 23 h exhibited signals assigned to **9** at δ=1.11 (3H, s, $\mathrm{CH_3}$), 0.99-3.65 (18H, m, $\mathrm{CH_2}$) and 8.78 (1H, brs, NH). Pure **9**: Mp 205-207 °C. IR (KBr) 3222, 1709 $\mathrm{cm^{-1}}$; ^{1}H-NMR ($\mathrm{CDCl_3}$) δ=1.25 (3H, s, $\mathrm{CH_3}$), 2.00 (2H, s, 4-**H**), 0.83-2.20 (8H, m, $\mathrm{CH_2}$), 2.20-2.80, 3.17-4.00 (each 4H, m, $\mathrm{CH_2}$), 8.18 (1H, brs, NH).

6) Pure **10**, mp 170 °C, could be isolated. The structure of **10** was confirmed by its X-ray structural analysis, which will be reported elsewhere..

7) The reaction of MAI with **1c** in refluxing benzene gave only **3c**, since **3c** was stable under the conditions. On the other hand, a complex mixture was obtained in the reaction of MAI with **2c** in m-xylene under reflux.

(Received January 13, 1993)