REACTION OF 2,2,6-TRIMETHYL-1,3-DIOXIN-4-ONE WITH SCHIFF BASE

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Abstract —— Heating of 2,2,6-trimethyl-1,3-dioxin-4-one (1) with Schiff bases (2a-f) gave 2,3-disubstituted 6-methyl-1,3-oxazin-4-ones (4a-f). *N*-Benzylidene-*tert*.-butylamine, under the similar condition, gave acetoacetamide derivative (3g) and acetylazetidinone derivative (5).

During the course of the investigation of potential uses of diketene, our interest was focused on the chemistry of a so-called diketene-acetone adduct, 2,2,6-trimethyl-1,3-dioxin-4-one (1), which can be easily made from diketene and acetone in the presence of an acidic catalyst.[1] About this adduct 1, however, only few references are available. Recently, Jäger *et al.*[2] reported that compound 1 reacted with aryl isocyanate to give 3-aryl-6-methyl-1,3-oxazin-2,4-dione, which had been also obtained by the reaction of aryl isocyanate with diketene.[3] This fact suggests that compound 1 has similar activities with those of diketene. On the other hand, we have reported previously the reaction of diketene with Schiff bases to give 2-alkylideneacetoacetamide derivatives 3.[4,5] For instance, refluxing of a solution of diketene and *N*-benzylideneaniline (2a) in chloroform gave 2-benzylideneacetoacetanilide (3a) in 8% yield. Maujean *et al.*[6] reported that the same reaction in the presence of triethylamine afforded the 1,3-oxazine derivatives 4. For instance, a solution of diketene, 2a, and triethylamine in ether was kept at room temperature to give 6-methyl-2,3-diphenyl-1,3-oxazin-4-one (4a) in 22% yield. In view of this point, we investigated the reaction of compound 1 with Schiff bases, about which we wish to report in the present paper.

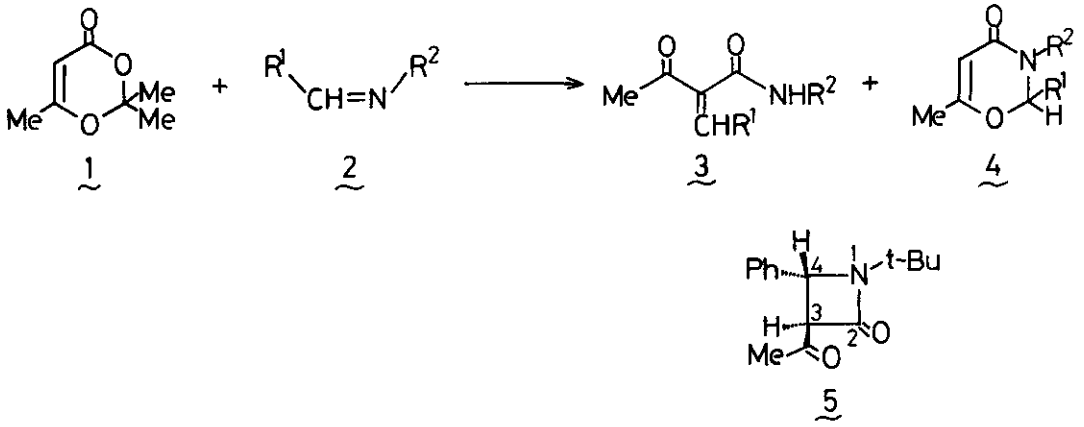
When a solution of compound 1 and an equimolar amount of *N*-benzylidene-

aniline (2a) in xylene was refluxed for 1 hr, 6-methyl-2,3-diphenyl-1,3-oxazin-4-one (4a) was obtained in 36% yield. When the reaction was conducted without solvent at 125 °C for ca. 10 min, the oxazine 4a was obtained in 60% yield. However, the acetoacetanilide 3a could not be detected. The reaction did not proceed at a temperature below 100 °C even in the presence of triethylamine. Similarly, *N*-benzylidene-*p*-anisidine (2b) reacted with compound 1 at 125 °C without solvent to give 3-*p*-methoxyphenyl-6-methyl-2-phenyl-1,3-oxazin-4-one (4b) in 58% yield. The corresponding 1,3-oxazine derivatives 4d and 4f were obtained from *N*-benzylideneethylamine (2d) and *N*-benzylidenecyclohexylamine (2f) in 61 and 62% yields, respectively.

Heating of a mixture of compound 1 and *N*-benzylidenebenzylamine 2c at 125 °C for ca. 30 min gave *N*-benzyl-2-benzylideneacetoacetamide (3c), mp 108 - 109.5 °C, in 3 - 31% yield, and 3-benzyl-6-methyl-2-phenyl-1,3-oxazin-4-one (4c), mp 78.5 - 79 °C, in 47 - 11% yield. Similarly, *N*-benzylidenepropylamine (2e) reacted with compound 1 to give the corresponding acetoacetamide derivative 3e (16 - 11%) and the 1,3-oxazine derivative 4e (27 - 72%). *N*-Benzylidene-*tert*.-butylamine (2g) was allowed to react with compound 1 under the same condition to give a 30% yield of the acetoacetamide derivative 3g and a low yield (8%) of colorless prisms, mp 90 - 92 °C, to which, on the basis of elemental analyses and spectroscopic data, we assigned the β-lactam structure, 3-acetyl-1-*tert*.-butyl-4-phenylazetidin-2-one (5) (Found: C, 73.45; H, 7.75; N, 5.65. $C_{15}H_{19}NO_2$ requires C, 73.45; H, 7.8; N, 5.7%); $\nu_{max.}$ ($CHCl_3$) 1 745 and 1 710 cm^{-1}; δ ($CDCl_3$) 1.25 (9H, s, *tert*.-butyl), 2.28 (3H, s, Me), 3.90 (1H, d, J = 2 Hz, 3-H), 5.01 (1H, d, J = 2 Hz, 4-H), and 7.26 - 7.46 (5H, m, Ph); *m/e* 245 (M^+).

Since methine protons appear at 3.90 ppm and 5.01 ppm as doublet signals with a vicinal coupling constant (J = 2 Hz), the configuration of acetyl and phenyl is assigned to be the *trans*. Interestingly, the β-lactam 5 was not obtained from diketene and 2g.[4] Reaction of *N*-cinnamylidenecyclohexylamine (2h) with compound 1 gave the acetoacetamide derivative 3h in 37% yield.

Results are summarized in Table I.



Scheme 1

Table I. Reaction of 2,2,6-Trimethyl-1,3-dioxin-4-one (1) with Schiff Bases

	Substituent		Reaction Condition				Product			
			1	2	Temp.	Time	3		4	
	R^1	R^2	mmol	mmol	°C	min	mp, °C (lit. mp)	Yield %	mp, °C (lit. mp)	Yield %
a	Ph	Ph	10	10	125	12			94 - 94.5 (90^6)	60
b	Ph	*p*-MeO-Ph	10	10	125	12			88 - 88.5	58
c	Ph	CH_2Ph	6	5	125	30	108 - 109.5	3	78.5 - 79	47
			12	10	120	25		31	(77^6)	11
d	Ph	Et	10	10	130	6			colorless oil	61
e	Ph	Pr	12	10	130	20	80.5 - 83	16	colorless oil	27
			10	10	130	8	(80.5 - 82.5[4])	11		72
f	Ph	(S)	14	10	130	10			125 - 126	62
g	Ph	*tert.*-Bu	14	10	130	10	111 - 111.5 (112 - 113[4])	30		
h	Ph-CH=CH	(S)	12	10	120	20	130.5 - 132 (128 - 130[4])	37		

The results show that the adduct 1 is a good reagent for preparation of 1,3-oxazin-4-one derivatives.

In the previous paper, we proposed that the 2-alkylideneacetoacetamide 3 obtained from diketene and Schiff base was presumably formed *via* the β-lactam intermediate such as 5. However, compound 5 is comparatively stable. Concerning mechanisms of formations of these products 3, 4, and 5, investigation is now in progress.

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References

1. M. F. Carroll and A. R. Bader, *J. Amer. Chem. Soc.*, 1953, 75, 5400.
2. G. Jäger and J. Wenzelburger, *Ann. Chem.*, 1976, 1689.
3. S. Ozaki, Jap. P. 70, 31663 (C. A., 1971, 74, 53811z).
4. T. Kato and Y. Yamamoto, *Chem. Pharm. Bull. (Tokyo)*, 1965, 13, 959.
5. T. Kato, Y. Yamamoto, H. Sekita, and T. Sakamoto, *J. Pharm. Soc. Japan*, 1967, 87, 691.
6. A. Maujean and J. Chuche, *Tetrahedron Letters*, 1976, 2905.

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