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REACTION OF α-BROMO-α,β-UNSATURATED ESTERS AND BUTENOLIDES WITH MALONAMIC ESTERS

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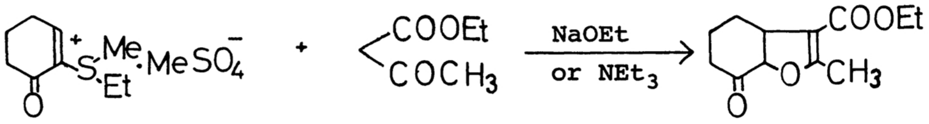
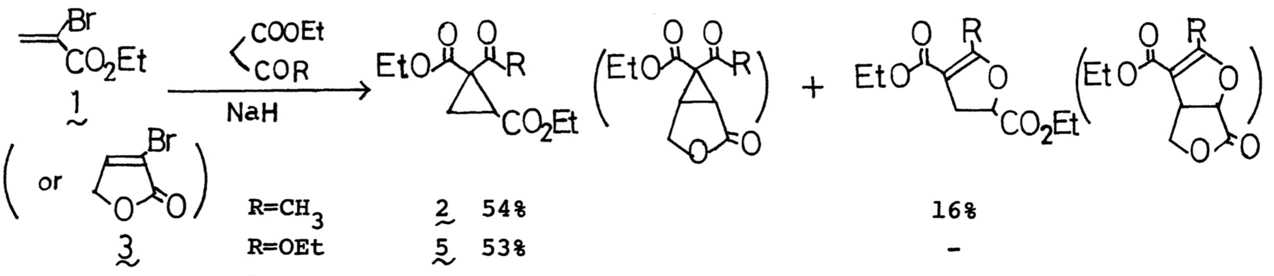
α-Bromo-α,β-unsaturated esters and α-bromobutenolides reacted with sodium salts of methyl malonamates to afford cyclopropanes, α-methoxycarbonyllactams and 5-amino-4-methoxycarbonyl-2,3-dihydrofurans. The last compounds could be easily converted into α-methoxycarbonyl-γ-lactones. The ratio of these compounds formed is influenced by the structures of both malonamates and unsaturated compounds, especially by the substituents at nitrogen of the malonamates, and by the reaction conditions.

Previously Mukaiyama et al. reported that unsaturated sulfonium salts reacted with active methylene compounds to give dihydrofuran derivatives in high yields.1) This reaction seems to be very useful for the preparation of the furan derivatives,

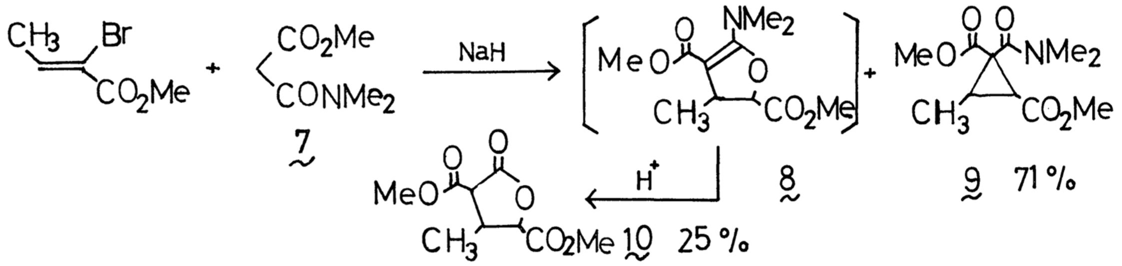


but the preparation of the sulfonium salts requires elabolate routes. On the other hand, halogen is a good leaving group as well as dialkylsulfonio group. Therefore, α-bromo-α,β-unsaturated carbonyl compounds, which can be more easily obtained than α-dialkylsulfonio-α,β-unsaturated ones, are expected to react with active methylene compounds in a similar fashion, we first examined the reaction of α-bromoacrylate (1) and α-bromobutenolide (3) with sodium salt of ethyl acetoacetate. As expected, cyclization took place and dihydrofuran derivative (4) was



R=CH_3	2 54%		16%	
R=OEt	5 53%		-	
R=CH_3		-		4 55%
R=OEt		6 70%		-

obtained from the butenolide (3) in 55% yield. On the contrary, the acrylate gave cyclopropane derivative (2) as a major product. Similar reaction of 1 or 3 with diethyl malonate afforded cyclopropane derivative (5 or 6), respectively. Although this reaction did not give dihydrofuran derivatives, it seemed of great value if α-alkoxycarbonyl-γ-lactones or their equivalents, known as important intermediates of α-methylenelactones2), can be prepared by the similar reactions. Then we examined the reaction with malonamic esters with the consideration that the nucleophilicity of carbonyl oxygen atom of carboxyamide is higher than that of carboxylic ester and, therefore, the oxygen atom of the carboxyamide group will attack more favorably on carbon atom to give 5-aminodihydrofurans. As expected, the reaction of methyl α-bromocrotonate with sodium salt of methyl N,N-dimethylmalonamate (7) afforded the corresponding 5-aminodihydrofuran (8) and cyclopropane (9) derivatives, though the former was isolated as lactone derivative (10) by quenching the reaction with aqueous acid. As the proportion of the lactone was not satisfactory, the influence of the substituents at nitrogen atom of malonamates on the ratio of the products was then examined using various methyl malonamates.



The reaction of α-bromo-α,β-unsaturated esters (12) with sodium salt of methyl N,N-disubstituted malonamates (11) gave lactone (13) and cyclopropane (14) derivatives. The alkyl substituents at nitrogen atom of the malonamates influenced the ratio of these compounds slightly, but the ratio rather depended upon the reaction conditions, especially on solvent. In aprotic polar solvents such as DME-HMPA or DMF the yield of the desired lactone increased, though the cyclopropane derivative was a main product in THF or DME alone. Futhermore, bromine atom is more suitable leaving group than chlorine atom. Unfortunately, when butenolide (15) was used in place of 12, the main product was cyclopropane derivative (16) even under the conditions favorable for the formation of 5-aminodihydrofurans in the case of 12. Some results were summarized in Table 1.

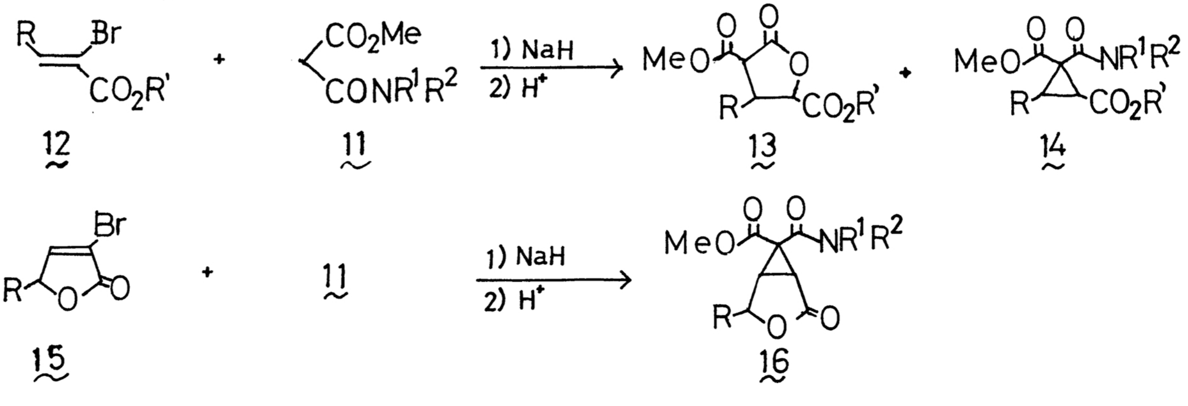


Table 1. Reaction of α-Bromo-α,β-unsaturated Esters (12) or Butenolides (15) with Sodium Salts of Methyl N,N-Dialkylmalonamates (11)

12 or 15			Malonamates (11)		Reaction Conditions			Products (Yield%)3)		
	R	R'	R^1	R^2	Solv.	Temp.	Time(h)	13	14	16
12	CH_3	CH_3	CH_3	CH_3	DME-HMPA	0°C	5	57	21	--
	CH_3	CH_3	CH_3	CH_3	DME	0°C	5	25	71	--
	CH_3	CH_3	$-(CH_2)_4-$		THF-HMPA	0°C	5	44	35	--
	C_6H_5	CH_3	CH_3	CH_3	DMF	rt	5	56	35	--
15	H	--	CH_3	CH_3	DME	0°C	4.5	--	--	42
	CH_3	--	CH_3	CH_3	THF	0°C	5	--	--	62
	C_8H_{17}	--	CH_3	CH_3	THF-HMPA	rt	3	--	--	49

On the other hand, lactam derivatives (17 or 18) were obtained almost exclucively by the reaction of 12 or 15 with sodium salts of N-monosubstituted malonamates (19) as shown in Table 2.

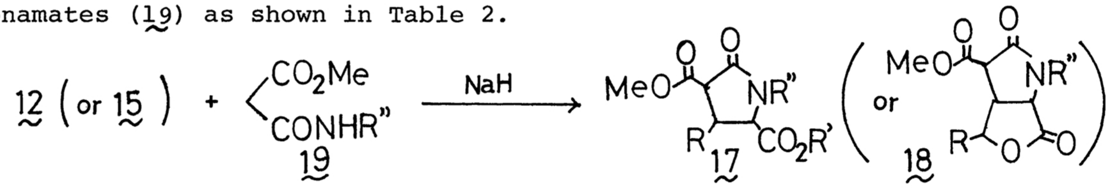


Table 2. Reaction of α-Bromo-α,β-unsaturated Esters (12) or Butenolides (15) with Sodium Salts of Methyl N-Monosubstituted Malonamates (19)

12 or 15			Malonamates (11)	Reaction Conditions			Products (Yield%)3)	
	R	R'	R''	Solv.	Temp.	Time(h)	17	18
12	H	C_2H_5	C_6H_5	C_6H_6	0°C	3	61	--
	CH_3	C_2H_5	CH_3	THF	-40°C	5	58	--
	CH_3	CH_3	t-C_4H_9	THF	rt	2	65	--
	CH_3	CH_3	C_6H_5	C_6H_6	rt	24	95	--
15	H	--	t-C_4H_9	THF	0°C	3	--	50
	H	--	C_6H_5	THF	-25°C	5	--	60

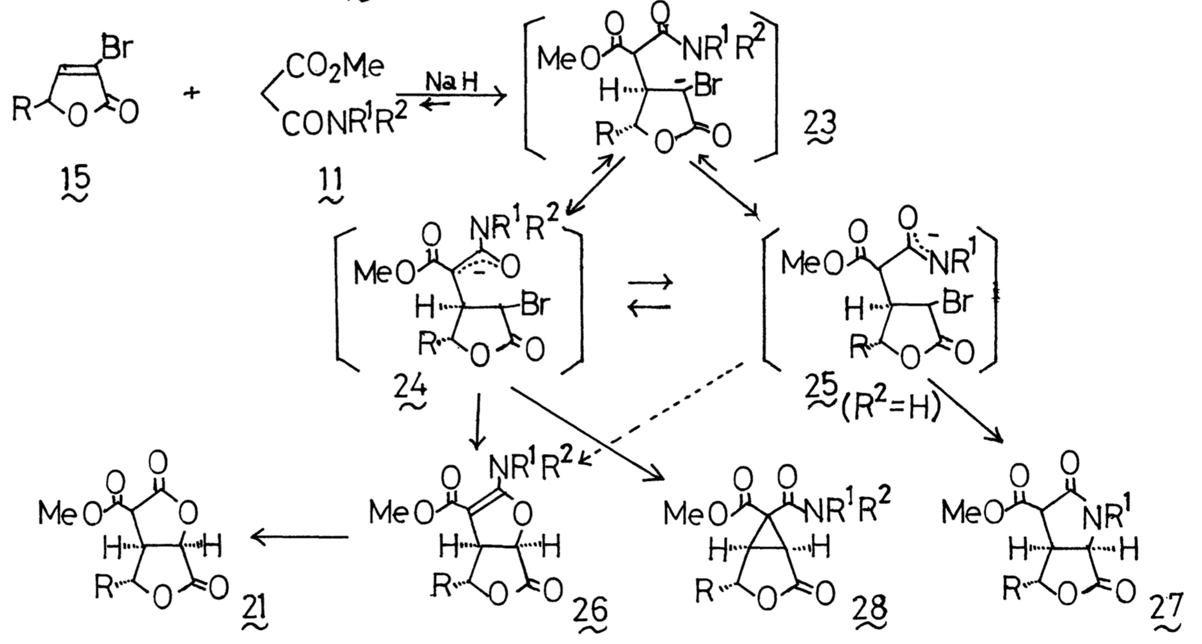
Then we examined the reaction of butenolides (15) with sodium salt of unsubstituted malonamate (22) and it was found that this reaction afforded mainly 5-aminodihydrofurans (20) in fairly good yields, which could be converted to the desired di-γ-lactone (21) quantitatively after the treatment with dil-HCl solution (Table 3). Futhermore, it was confirmed that this reaction proceeds stereoselectively so that the ring junction is cis and the stereochemical relations between the alkyl substituent R and the introduced lactone ring is trans based on the NMR data of the aminodihydrofuran (20), di-γ-lactone (21) and the corresponding α-methylene derivative derived from (21), which is discussed in the following paper.5)

Table 3. Reaction of α-Bromobutenolides (15) with Sodium Salt of Methyl Malonamate (22)

15	Reaction Conditions			Products[3)]		
R	Solv.	Temp.	Time(h)	Yield(%) of 20	Mp(°C) 20	21
CH_3	THF	0°C	4	40	147-149	123.5-125
C_2H_5	THF	0°C	4	36	180.5-181	78-80
n-C_8H_{17}	THF-HMPA	0°C	2	60[a)]	139-140	58-59

a) Accompanied by the corresponding lactam (27, R=C_8H_{17}, R^1=H) in 8% yield.

The mechanism of the above mentioned reactions may be explained as follows. The intermediate (23) produced from methyl malonamate (11) and butenolide (15) by the Michael addition, changes into either 24 or 25 by prototropy. Then, intramolecular nucleophilic substitution occurs. That is, when the enolate oxygen of 24 attacks, 5-aminodihydrofuran (26) is produced. In the case of at least one of the substituent at nitrogen atom of malonamate being hydrogen, the lactam derivative (27) is formed via 25 by the attack of the nitrogen anion. In the case of straight-chain ester (12) a similar mechanism is, of course, possible.



References and Notes

1) T. Mukaiyama, T. Adachi, and T. Kumamoto, Bull. Chem. Soc. Jpn., 44, 3155 (1971).
2) As for the synthesis of α-methylene lactones, see review; P. A. Grieco, Synthesis, 1975, 67; R. B. Gammill, C. A. Wilson, and T. A. Bryson, Synth. Commun., 5, 245 (1975); H. Takei, Kagaku no Ryoiki, 33, 680 (1979).
3) The structures of the products were confirmed by elemental analysis and NMR and IR spectra, though the stereochemistry of them could not be completely ascertained except for some compounds.
4) A typical experiment was carried out as follows. To a suspension of NaH (0.96 g, 50% in mineral oil) in dry benzene, methyl N-phenylmalonamate (3.85 g) was added and the mixture was stirred for 30 min. Then methyl α-bromocinnamate (4.82 g) in benzene was added to the solution at 0°C and the mixture was stirred for 24 h at room temperature. The usual work-up afforded N-phenyl-α,γ-dimethoxycarbonyl-β-phenyl-γ-butyrolactam. The yield was 6.68 g (95%). mp 149°C.
5) H. Takei, Y. Fukuda, T. Taguchi, T. Kawara, H. Mizutani, and T. Mukuta, Chem. Lett., 1980, 1311.

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