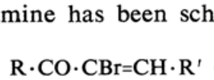
The Reaction Mechanism of α-Bromo-α, β-unsaturated Ketones with Amines

By Hiromi INOKAWA

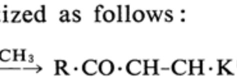
(Received October 19, 1963)

In previous papers,¹⁾ the reaction products of α-bromo-α, β-unsaturated ketones, such as 2-bromo-1-phenyl-2-propen-1-one (I), 2-bromo-1-phenyl-2-buten-1-one (II), 2-bromo-1, 3-diphenyl-2-propen-1-one (III), and 3-bromo-4-phenyl-3-buten-2-one (IV), with methylamine and dimethylamine, were described.



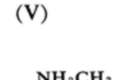
$C_6H_5\cdot CO\cdot \underset{\substack{|\\ Br}}{C}{=}CH_2$

(I)



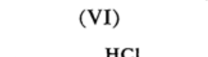
$C_6H_5\cdot CO\cdot \underset{\substack{|\\ Br}}{C}{=}CHCH_3$

(II)



$C_6H_5\cdot CO\cdot \underset{\substack{|\\ Br}}{C}{=}CH\cdot C_6H_5$

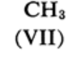
(III)



$CH_3\cdot CO\cdot \underset{\substack{|\\ Br}}{C}{=}CH\cdot C_6H_5$

(IV)

The general course of the reactions of α-bromo-α, β-unsaturated ketones with methylamine has been schematized as follows:

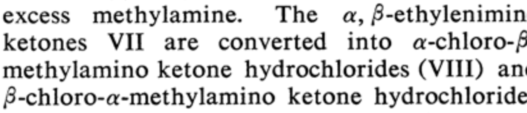


$$R\cdot CO\cdot CBr{=}CH\cdot R' \xrightarrow{NH_2CH_3} R\cdot CO\cdot \underset{\substack{|\\ Br}}{CH}-\underset{\substack{|\\ NHCH_3}}{CH}\cdot K'$$

(V) (VI)

$$\xrightarrow{NH_2CH_3} R\cdot CO\cdot CH-CH\cdot R' \;(\text{bridged by } N\!-\!CH_3) \xrightarrow{HCl}$$

(VII)

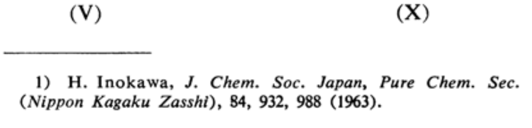


$$\underset{NCl}{R\cdot CO\cdot \underset{\substack{|\\ Cl}}{CH}-\underset{\substack{|\\ NHCH_3}}{CH}\cdot R'} + \underset{HCl}{R\cdot CO\cdot \underset{\substack{|\\ NHCH_3}}{CH}-\underset{\substack{|\\ Cl}}{CH}\cdot R'}$$

(VIII) (IX)

The first step consists of the addition of methylamine to the β-carbon atom of the unsaturated ketones V, followed by the formation of α, β-ethylenimine ketones VII with the excess methylamine. The α, β-ethylenimine ketones VII are converted into α-chloro-β-methylamino ketone hydrochlorides (VIII) and β-chloro-α-methylamino ketone hydrochlorides (IX) by the action of hydrogen choride. However, when R′ is H, only α-chloro-β-methylamino ketone hydrochloride (VIII) is obtained.

The reaction steps of α-bromo-α, β-unsaturated ketones with dimethylamine may be represented as follows:



$$R\cdot CO\cdot \underset{\substack{|\\ Br}}{C}{=}CH\cdot R' \xrightarrow{NH(CH_3)_2} R\cdot CO\cdot \underset{\substack{|\\ Br}}{CH}-\underset{\substack{|\\ N(CH_3)_2}}{CH}\cdot R'$$

(V) (X)

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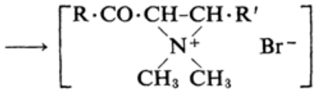
1) H. Inokawa, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), 84, 932, 988 (1963).



(R′=H or CH_3)

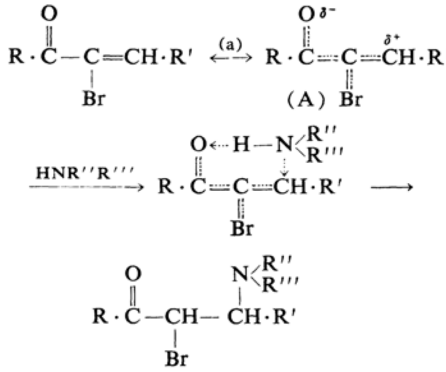
(XI)

The first step is the addition of dimethylamine to the β-carbon atom of the unsaturated ketones. When R′ is H or CH_3, the resulting α-bromo-β-dimethylamino ketones (X) give 1, 1-dimethylaziridinium bromides (XI). When R′ is C_6H_5, however, the α-bromo-β-dimethylamino ketones (X) remain unchanged.

The products and their yields in these reactions are summarized in Table I.

The facts summarized in Table I led the author to conclude (1) that the addition reactions of amines to the β-carbon atom of α-bromo-α, β-unsaturated ketones become difficult in the order of I<II<III<IV, and (2) that the values of the VIII/IX ratio, in which VIII and IX are produced by the ring-opening reactions of α, β-ethylenimine ketones with hydrogen chloride, decrease in the order of I > II > III > IV.

The former conclusion will be discussed first in relation to the reaction mechanism. The first step of the reactions of α-bromo-α, β-unsaturated ketones with amines may be formulated as the following scheme 1:



Scheme 1

When R is C_6H_5 and R′ is turned into H, CH_3, or C_6H_5, the fractional positive charge of the β-carbon atom should decrease as a result of the delocalization caused by the hyperconjugation with a methyl group or by the resonance with a phenyl group. The effect of a phenyl group on the delocalization is larger than that of a methyl group.[2] Consequently, the positive charge of the β-carbon atom should decrease in the order of I > II > III. Comparing III with IV, the formula A in the resonance (a) should contribute more when R is C_6H_5 than CH_3, and thus the addition of amines to the β-carbon atom of III takes place more easily than that of IV. Therefore, the addition of amines becomes difficult in the order of I<II<III<IV.

This conclusion seems to be in agreement with the experimental results obtained by Kohler,[3] who showed that the yields of 1, 4-addition products of phenyl magnesium bromide to 1-phenyl-2-propen-1-one, 1-phenyl-2-buten-1-one, 1, 3-diphenyl-2-propen-1-one, and 4-phenyl-3-buten-2-one are 100, 100, 94, and 12% respectively.

The second conclusion as to the ring-opening reactions of ethylenimine ketones will be discussed in terms of the reaction mechanism. In the reactions of ethylenimine ketones with hydrogen chloride, the intermediate VII′ must be produced first* by the addition of a proton, the resulting positive charge facilitates the fission of an ethylenimine ring. Therefore, the reaction proceeds according to two paths, b and c, in Scheme 2.

In the path b, the fractional positive charge on the α-carbon atom is important. The fractional positive charge is caused by the strong electron-attracting force of –CO– and facilitates the attack of Cl^- on the α-carbon atom. The electron-attracting force of a benzoyl group is larger than that of an acethyl group. Accordingly, the path b proceeds more easily when R is C_6H_5 (in VII′) than when it is CH_3. In the path c, on the other hand, the stability of

TABLE I. YIELDS OF REACTION PRODUCTS

No.	V		With methylamine			VIII/IX	With dimethylamine	
	R	R′	VII %	VIII X	IX %		X %	XI %
I	C_6H_5	H	30*	30	0	∞	75	42
II	C_6H_5	CH_3	68	48	20	2.4	73	24
III	C_6H_5	C_6H_5	57	19	38	0.5	56	—
IV	CH_3	C_6H_5	36	6	30	0.2	11	—

* A by-product, $C_{19}H_{18}O_2NBr$, was formed in a 35% yield by the addition of 1 mol. methylamine to 2 mol. of I.

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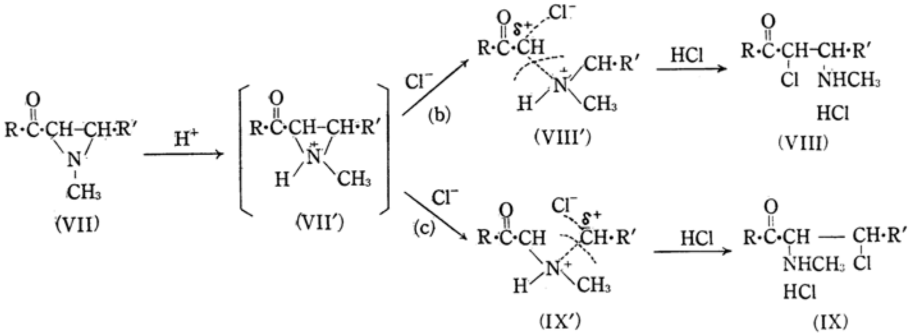
[2] W. R. R. Parl and G. F. Wright, *J. Am. Chem. Soc.*, **76**, 3036 (1954).

[3] E. P. Kohler, *Am. Chem. J.*, **38**, 511 (1907).

* The ionization constants (k_b) of the ethylenimines much are greater than 3.8×10^{-10}. H. C. Brown and M. Gerstein, *J. Am. Chem. Soc.*, **72**, 2926 (1950).



Scheme 2

the transition state IX′ seems to be of importance. As has been mentioned in the discussion of the addition reaction, the delocalization of the fractional positive charge on the β-carbon atom is caused by the resonance with a methyl or phenyl group, and the stability of IX′ increases by the delocalization energy in the order of I<II<III, the reactions through the path c becoming easier in the order of I<II<III. Consequently, the values of VIII/IX become smaller in the order of I>II>III>IV.

Summary

It has been considered that, in the reaction of α-bromo-α, β-unsaturated ketones with amines, α-bromo-β-amino ketones are produced first by the 1, 4-addition of amines and converted to ethylenimine ketones in the presence of excess amines. The ethylenimine ketones react with hydrogen chloride to give α-chloro-β-amino and β-chloro-α-amino ketones, the yields of these ketones depending on the variation of the fractional positive charge at the α-carbon atom and on the delocalization energy on the β-carbon atom by R′.

The author wishes to express her hearty thanks to Professor Ryozo Goto of kyoto University for his invaluable advice and encouragement throughout this work.

Department of Chemistry
Faculty of Science
Kyoto University
Sakyo-ku, Kyoto