A FACILE SYNTHESIS OF THIAZOLIDIN-5-ONES AND THEIR STRUCTURAL ASSIGNMENT

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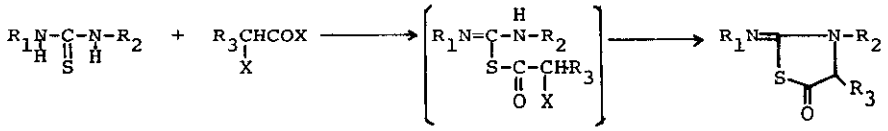
Abstract——The reaction of 1,3-disubstituted thioureas(I) with α-haloacyl halides(II) was found to afford thiazolidin-5-ones(IV) in 5% sodium hydroxide-dichloromethane in the yields of 34-89%. The structures of IV were discussed in details.

Due to the wide variety of physiological activity, numerous studies[1] on the chemistry of thiazolidin-4-ones have hitherto been made. However, surprisingly little is known concerning the isomeric thiazolidin-5-ones. We found that thiazolidin-5-ones were readily formed by the reaction of 1,3-disubstituted thioureas with α-haloacyl halides. This paper deals with the facile synthesis of thiazolidin-5-ones and their structural assignment.



Ia-h II IIIa-h IVa-h

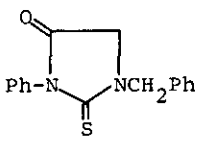
A typical procedure is as follows: To a stirred mixture of the thiourea(I, 5mM), CH_2Cl_2(20 ml) and aqueous 5% NaOH(5 ml) was gradually added the α-haloacyl halide (II, 5 mM) under chilling with ice-water, and then additional 5% NaOH(10 ml) was added, and the reaction mixture was stirred for 12 hr at room temperature. Then the CH_2Cl_2 layer was separated, dried, and evaporated. The residue was purified by recrystallization or by silica-gel column chromatography. The results are summarized in Table I.

Table I Preparation of Thiazolidin-5-ones(IV)

IV	R_1	R_2	R_3	mp(°C)	Yield(%)	IR(cm^{-1}) νC=O	νC=N	Mass(M^+)
a	$PhCH_2$	Ph	H	168-169	89	1735,	1630	282
b	$PhCH_2$	Ph	CH_3	79-80	72	1720,	1630	296
c	CH_3	$PhCH_2$	H	59-60	34	1728,	1635	220
d	CH_3	$PhCH_2$	CH_3	oil	56	1727,	1640	234
e	CH_3	Ph	H	oil	40	1735,	1630	206
f	CH_3	Ph	CH_3	oil	55	1734,	1630	220
g	Ph	Ph	H	172-173	52	1730,	1628	268
h	$PhCH_2$	$PhCH_2$	H	68-69	65	1720,	1640	296

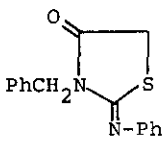
All products gave satisfactory ir, nmr, and mass spectral data, and elemental analyses.

In the reaction of I (R_1=$PhCH_2$,R_2=Ph) with II, it is possible to form the following three different compounds: the thiazolidin-5-one(IV), the pseudothiohydantoin(V), and the thiazolidin-4-one(VI). In order to clarify the structure of the product, the compounds(V and VI) were synthesized by other routes.



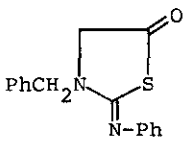
V

mp 175-176°



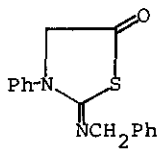
VI

mp 68-69°



IVa

mp 168-169°



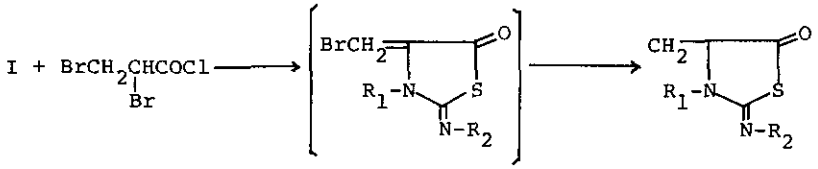
VII

The pseudothiohydantoin(V) was prepared by the reaction of phenyl isothiocyanate with N-benzylaminoacetonitrile and then by hydrolysis with 6 N HCl. The ir spectra of V showed the carbonyl and ureido absorptions at 1760 and 1485 cm^{-1}, respectively. The thiazolidin-4-one(VI) was synthesized from 1-benzyl-3-phenylthiourea and ethyl chloroacetate.[2] The compound VI exhibited ir absorptions at 1715 and 1620 cm^{-1} assignable to the carbonyl and imino groups, respectively. On the other hand, the ir spectra of the product indicated absorptions of the carbonyl and imino groups at 1735 and 1630 cm^{-1}, respectively. From these ir data, the structure of the product is

apparently different from V and VI. Therefore, the structures of IVa and VII seem to be suitable for the product and its isomer. For the purpose of the discrimination of IVa and VII, hydrolysis of the product was carried out in 2 N NaOH-EtOH under reflux to afford N-benzylglycine and aniline. This result denied the possible formation of the isomer(VII). Consequently, it seems reasonable to conclude that IVa is suitable for the structure of the product. The data of nmr and mass spectra also supported this assigned structure.

The reaction course is assumed as follows: the thiol sulfur atom of I initially attacks the carbonyl group of α-haloacyl halides(II) to give the intermediately formed thiol esters(III), followed by intramolecular cyclization to IVa.

Analogously, the reaction of I with α,β-dibromopropionyl chloride(VIII) was carried out under the same conditions to give 4-methylenethiazolidin-5-ones(X) in 75-83% yields.



VIII IX X

The reaction is presumed to proceed via IX, which is immediately subjected to β-elimination to yield X. The results are summarized in Table II.

Table II Preparation of 4-Methylenethiazolidin-5-ones(X)

R_1	R_2	mp(°C)	Yield(%)	IR(cm^{-1}) ν C=O	ν C=N	Mass(M^+)
$PhCH_2$	Ph	208-209	82	1720,	1620	294
Ph	Ph	276-277	83	1720,	1620	280
CH_3	Ph	256-258	75	1730,	1640	218
CH_3	$PhCH_2$	265-268	81	1725,	1650	232

Further applications to other heterocyclic compounds are being investigated.

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