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STUDIES ON THE CHEMISTRY OF HETEROCYCLICS. XXI.[1, 2, 3] THE DARZENS REACTION

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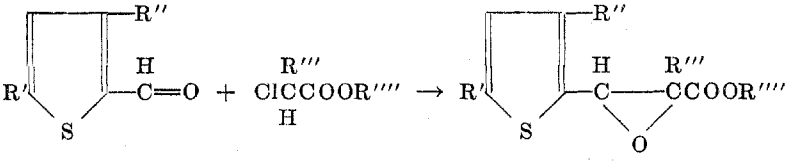
Although the Darzens reaction has been in use since its discovery by Erlenmeyer in 1892 (1), its application to heterocyclic aldehydes has been scanty (2, 3). In view of the simple one-step synthesis of 2-thenaldehyde and substituted aldehydes (4) and the wide synthetic applicability of glycidic esters, it was desired to test the feasibility of the Darzens reaction with these compounds.

The Darzens glycidic ester condensation involves the interaction of an aldehyde or a ketone with an α-halo ester to give rise to an α,β-epoxy ester (glycidic ester). The reaction between 2-thenaldehyde and substituted 2-thenaldehydes with either methyl chloroacetate or ethyl α-chloropropionate can be formulated as follows:



When R′ is C_2H_5 or Cl, R″ is H; R‴ is either H or CH_3, and R⁗ either CH_3 or C_2H_5. When R″ is CH_3, R′ is H, R‴ is either H or CH_3, and R⁗ either CH_3 or C_2H_5.

The Darzens reaction offers a convenient method for the production of aldehydes or ketones in which the carbon chain has been lengthened by one or two carbon atoms respectively. This may be carried out by decarboxylation of the glycidic acid which has been obtained from the glycidic ester by saponification.

This condensation can be effected with either sodium alkoxides, in which the latter corresponds to the alcohol portion of the halo ester, sodium amide, or the (usually powdered) metal itself. The advantage of higher yields and milder reaction conditions afforded by the use of the alkoxide may be offset by either its unavailability or the difficulty of obtaining it in the alcohol-free state necessary for the reaction. We have found that the reactivity of 2-thenaldehyde and the substituted 2-thenaldehydes is similar to that of benzaldehyde when the same condensing agent is used. When powdered sodium was chosen the yield of ester averaged 35 to 40%. However, when a sodium alkoxide was the reagent, the yields of the esters were approximately 65 to 70%. Applying the commercially

[1] This investigation was carried out under the aegis of the Office of Naval Research.

[2] The contents of this paper were presented before the Division of Organic Chemistry of the American Chemical Society, Boston, Mass., April, 1951.

[3] For paper XX in this series see *J. Org. Chem.*, **17**, 778 (1952).

available alcohol-free sodium methoxide, we have found that no transesterification occurs when an ethyl ester is used. The product from the condensation of 2-thenaldehyde with ethyl α-chloropropionate in the presence of this sodium methoxide was the expected ethyl β-(2-thienyl)glycidate.

To evaluate the influence of different solvents on this reaction, we have carried out our condensations in absolute ether, anhydrous toluene, benzene, and xylene as well as in the absence of any solvent. In the latter case, the alkoxide, in powder form, was added to a stirred mixture of the carboxyl component and the halo ester, while in all other cases, a suspension of the alkoxide in the solvent under investigation was added to a solution of the carbonyl compound and the halo ester in the same solvent. We have found that the solvent does not have any direct effect on the yield of the reactions nor on the conditions of this reaction. However, there are some indirect effects which have to be taken into consideration when a solvent is chosen. One of the products of this reaction is sodium halide. When powdered sodium serves as the condensing agent, the sodium halide formed tends to plate out on the surface of the sodium particles, impeding the reaction. To avoid this, an aromatic solvent is suggested, since in the presence of such solvents, the sodium halide separates as a colloidal suspension and does not coat the sodium. This type of condensation seems to be preceded by an induction period and then, in some cases, proceeds with surprising vigor and with the liberation of a large amount of heat. Since most of the aromatic solvents used are rather high-boiling, this heat cannot be dissipated by reflux until the reaction temperature has risen well over 100°. Since the temperature is important in this reaction, this presents a serious difficulty. Another factor is the ease of removal of the solvent before distillaton *in vacuo* of the product. Obviously, ether can be removed at room temperature *in vacuo* while it is necessary to warm the mixture in order to facilitate the removal of toluene or xylene. These difficulties were obviated by using ether as a solvent, dropping the mixture of the carboxyl compound and halo ester onto a well-stirred suspension of powdered sodium in absolute ether, to destroy the coating of colloidal sodium halide as much as possible, at such a rate that the reaction is kept at a gentle reflux. When the alkoxide is used as the reagent, these difficulties do not prevail; therefore ether is the solvent of choice.

Most of the reports in the literature agree that the reaction should be kept cold, at least in the initial steps. While in one (5) a reaction temperature as low as −80° was recommended, none suggest temperatures above 0°. It is to be mentioned, therefore, that in the condensation of 2-thenaldehyde with ethyl α-bromopropionate in the presence of powdered sodium, it was necessary to raise the temperature to that of refluxing ether before the reaction could be initiated.

Our data are in agreement with those of Haller and co-workers (6) regarding the choice of the halo ester. When an α-bromo ester is used, the amount of higher-boiling residue is greater than in the case of the α-chloro ester.

Using these reaction conditions, eight glycidic esters were prepared, the physical constants and analytical data of which are listed in Table I.

EXPERIMENTAL[4, 5]

Since the method of preparation of the glycidates is the same using either methyl chloroacetate or ethyl α-chloropropionate providing the same condensing agent is used, the condensation of 2-thenaldehyde with methyl chloroacetate will exemplify the procedures.

Condensation using sodium shot. A mixture of 2-thenaldehyde (16.8 g., 0.15 mole) and methyl chloroacetate (16.3 g., 0.15 mole) was added dropwise to 3.5 g. (0.15 mole) of sodium shot that had been covered with 200 cc. of absolute ether in a three-necked flask. The flask was fitted with a reflux condenser and a mercury-sealed stirrer and immersed in an ice-salt bath. The mixture of the carbonyl component and the halo ester was added at such a rate that the evolution of hydrogen did not become violent but that a gentle reflux was maintained. After all the mixture had been added and the evolution of hydrogen had moderated,

TABLE I

GLYCIDIC ESTERS PREPARED BY THE DARZENS REACTION

GLYCIDIC ESTER	YIELD, %	M.P., °C.	B.P., °C.	MM.	ANALYSES			
					Calc'd		Found	
					C	H	C	H
Methyl β-(2-thienyl)glycidate	39[a]							
	64[b]	[c]	119	3	52.17	4.29	52.40	4.34
Ethyl α-methyl-β-(2-thienyl)glycidate	39[a]							
	66[b]	[c]	122[d]	4	56.60	5.66	56.28	5.36
Methyl β-(3-methyl-2-thienyl)glycidate	40[a]	112	131	3	54.52	5.05	55.10	4.88
Ethyl α-methyl-β-3-methyl-2-thienyl)glycidate	10[a]	[c]	123	5	58.40	6.19	58.60	6.07
Methyl β-(5-ethyl-2-thienyl)glycidate	69[b]	85	157	7	56.60	5.66	56.72	5.40
Ethyl α-methyl-β-(5-ethyl-2-thienyl)glycidate	70[b]	[c]	142	5	60.00	6.66	59.23	6.27
Methyl β-(5-chloro-2-thienyl)glycidate	37[a]	72–73	158	8	43.93	3.20	44.24	3.25
Ethyl α-methyl-β-(5-chloro-2-thienyl) glycidate	60[b]	[c]	147	3	48.68	4.46	48.49	4.37

[a] Condensation using sodium shot. [b] Condensation using sodium methoxide. [c] Liquid at room temperature. [d] Reference (3) gives 144° at 20 mm.

the flask was removed from the ice-bath and placed on a hot-water bath. Gentle reflux was maintained for one-half hour to complete the reaction. The mixture was then hydrolyzed by the cautious addition of ice-water followed by glacial acetic acid until the water layer was acid to litmus. The ether layer was then separated and the aqueous layer extracted twice more with ether. The ether portions were combined, dried over sodium sulfate, the ether removed *in vacuo*, and the product fractionated. After the unreacted aldehyde had been removed from the mixture, there was a break in vaporization and a drop in temperature until the glycidic ester began to distill.

[4] The analyses were carried out by A. A. Sirotenko of this Department.

[5] The thiophene and 3-methylthiophene used in these studies were obtained through the courtesy of Drs. O. J. Weinkauff and C. A. Hochwalt, Monsanto Chemical Company, St. Louis, Mo.

Condensation with the aid of sodium alkoxide. A solution was prepared of 2-thenaldehyde (15.8 g., 0.15 mole) and methyl chloroacetate (16.3 g., 0.15 mole) in absolute ether in the usual apparatus. A suspension of the alkoxide (0.15 mole) in absolute ether was added over a period of an hour to the well-stirred mixture. There was usually a gradual darkening of the solution from a yellow to a deep red as the reaction progressed. After all of the alkoxide was added, the mixture was allowed to stand at room temperature overnight. It was hydrolyzed by pouring onto ice and acidified with glacial acetic acid. The ether layer was separated and the aqueous portion washed twice with ether. The ether extracts were combined, dried over sodium sulfate, the ether was removed, and the product rectified.

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