

[CONTRIBUTION FROM THE KEDZIE CHEMICAL LABORATORY OF MICHIGAN STATE COLLEGE]

Carbonyl Derivatives of Thiophene. II. The Reformatsky Reaction with Bromine Compounds Other Than α -Bromoesters

BY ROBERT D. SCHUETZ AND WM. H. HOUFF¹

RECEIVED JUNE 16, 1954

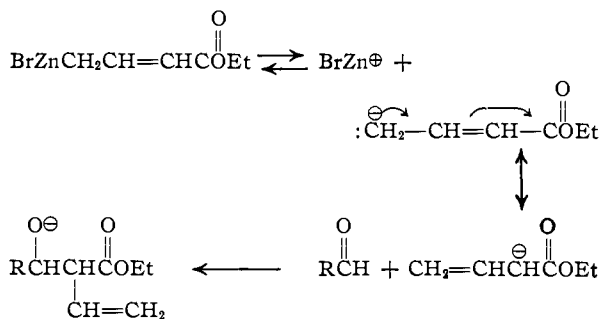
A study of the Reformatsky reaction between thienyl carbonyl derivatives and ethyl γ -bromocrotonate, allyl and propargyl bromide was conducted. The formation of isomeric products with ethyl γ -bromocrotonate was investigated.

In a continuation² of studies dealing with the Reformatsky reaction of ketone and aldehyde derivatives of thiophene, the use of active bromine compounds other than α -bromoesters was investigated. There are three previous reports^{3,4,5} concerning the Reformatsky reaction of 2-thienyl ketones and aldehydes with β -bromoesters, γ -bromocrotonates and propargyl bromide. However, in none of these studies was any investigation conducted upon the more difficultly prepared 3-thienyl carbonyl derivatives nor was any study made of the ethyl or *n*-propyl 2-thienyl ketones.

The reaction of ethyl γ -bromocrotonate with thienyl carbonyl derivatives under Reformatsky conditions yields a variety of products, the origins of which are dependent on the nature of the carbonyl component. A previous report^{3,4} indicated that it was impossible to isolate the resultant esters by distillation and the products were converted to the unsaturated acids. The present investigation points out the possibility of isolation of some of these esters and in the case of the 2- and 3-thenal, the hydroxy esters were isolated in a pure condition from the reaction mixture by vacuum distillation. The products of the 2-acetyl-, 2-propionyl-, 2-*n*-butyryl- and 2-acetyl-3-methylthiophene were contaminated by their corresponding dehydration products. This dehydration of the hydroxy esters is presumed to have occurred during their distillation, since repeated distillation failed to improve the quality of the products, and only resulted in further dehydration. These products were, therefore, converted to the unsaturated compounds by refluxing for eight hours in a 6% oxalic acid solution. The physical properties of the unsaturated esters are listed in Table I.

The interaction of both 2 and 3-thenal with ethyl γ -bromocrotonate resulted in two isomeric hydroxy esters whose boiling points differed by approximately 25°. The lower boiling of the compounds, which was isolated in the larger amount, rapidly adsorbed one mole of bromine. Further, the treatment of the low boiling ester with ozone followed by hydrolysis of the ozonide, resulted in the formation of formaldehyde. This latter observation is indicative of a terminal multiple bond linkage while the rapid reaction with bromine is characteristic of a double bond which is not adjacent to an electronegative group. Consideration of these two

reactions strongly suggest that a rearranged product having a terminal vinyl group was formed. The higher boiling isomeric ester reacted with bromine at a much slower rate, a characteristic of a double bond adjacent to a carboxyl group. Although Miller and Nord³ were unable to isolate any products corresponding to α -vinyl esters, the isolation of such rearranged products have been effected before in Reformatsky reactions employing methyl γ -bromocrotonate.^{6,7} These investigators reported that the α -vinyl isomer boils at a considerably lower temperature than does the normal product. The present investigation confirms this observation. Presumably, the α -vinyl derivative results due to a charge migration in the negative species of the organo zinc halide.



In the case of 2-thenal, the yields of α -vinyl- β -hydroxy ester was 28% of the theoretical while that of the normal product was 16% of the theoretical. With 3-thenal the yields were, respectively, 29 and 17% of the theoretical.

The formation of an α -vinyl isomer was noted to have occurred with 2-acetylthiophene although to a lesser extent than with the aldehydes. The normal hydroxy ester tended to dehydrate upon distillation while the α -vinyl derivative could be isolated and characterized as the hydroxy ester. The normal product was dehydrated and characterized as the alkadienoic ester. The yield of the α -vinyl isomer was 7% while that of the normal product was 26%. There were no isomeric products formed in those reactions where 2-propionyl- and 2-butyrylthiophene served as the carbonyl component. Presumably, the increase in size of the ketonic alkyl group tends to inhibit the attack of the more bulky anionic species bearing the charge on the α -carbon.

Large quantities (52–62%) of unreacted ketones, as well as comparable amounts of reduced ester

(1) Abstracted, in part, from the thesis submitted by Wm. H. Houff in partial fulfillment of the requirements for the degree Doctor of Philosophy at Michigan State College.

(2) R. D. Schuetz and Wm. H. Houff, *THIS JOURNAL*, **77**, 1836 (1955).

(3) R. E. Miller and F. F. Nord, *J. Org. Chem.*, **16**, 1380, 1390 (1951).

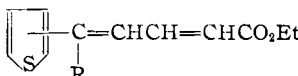
(4) R. E. Miller and F. F. Nord, *ibid.*, **16**, 1270 (1951).

(5) H. Keskin, R. E. Miller and F. F. Nord, *ibid.*, **16**, 199 (1951).

(6) J. English, Jr., and J. D. Gregory, *THIS JOURNAL*, **69**, 2123 (1947).

(7) E. R. H. Jones, D. G. O'Sullivan and M. C. Whiting, *J. Chem. Soc.*, 1415 (1949).

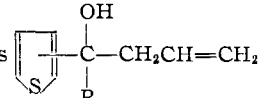
TABLE I
ETHYL 5-THIENYL-5-ALKYL-2,4-PENTADIENOATES



Thienyl deriv.	R	Formula	°C.	B.P.,	Mm.	Yield, %	Carbon, %	Hydrogen, %		
							Calcd.	Found	Calcd.	Found
2	H	C ₁₁ H ₁₂ O ₂ S	148-149		1.0	°	63.5	63.7	5.8	5.9
2	CH ₃	C ₁₂ H ₁₄ O ₂ S	147-148.5		1.0	26	64.8	64.7	6.3	6.4
2	C ₂ H ₅	C ₁₃ H ₁₆ O ₂ S	149-150		1.0	25	66.1	65.9	7.6	7.8
2	<i>n</i> -C ₃ H ₇	C ₁₄ H ₁₈ O ₂ S	162-164		1.0	32	67.9	68.0	7.2	7.4
3	H	C ₁₁ H ₁₂ O ₂ S	149-151		1.0	°	63.5	63.2	5.8	5.6
2-(3-Me)	CH ₃	C ₁₃ H ₁₆ O ₂ S	164-165		1.0	20	66.1	65.9	7.6	6.9

° Prepared as derivatives.

TABLE II



Thienyl deriv.	R	Formula	°C.	B.P.,	Mm.	<i>n</i> _D ²⁰	Yield, %	Carbon, %	Hydrogen, %		
								Calcd.	Found	Calcd.	Found
2	H	C ₉ H ₁₀ OS	89-90.5		1	1.5439	78	62.3	62.1	6.5	5.9
2	CH ₃	C ₉ H ₁₂ OS	82-84		2	1.5512	70	64.3	64.5	7.1	6.7
2	C ₂ H ₅	C ₁₀ H ₁₄ OS	94-96		1.5	1.5260	72.5	65.9	65.7	7.7	7.9
2	<i>n</i> -C ₄ H ₉	C ₁₁ H ₁₆ OS	94-95		0.5	1.5205	73	67.3	66.8	8.2	8.1
3	H	C ₉ H ₁₀ OS	90-91		1	1.5422	80	62.3	62.7	6.5	6.3
3	CH ₃	C ₉ H ₁₂ OS	80-81		1	1.5498	72	64.3	64.5	7.1	7.2
2-(3-Me)	CH ₃	C ₁₀ H ₁₁ OS	97-98.5		0.5	1.5340	70	65.9	65.7	7.7	7.8

resulted from the interaction of thienyl ketones with ethyl γ -bromocrotonate. In those reactions in which thenals were employed a small amount (10-14%) of original aldehyde was found. The presence of unreacted thienyl carbonyl compounds in the Reformatsky reaction has been discussed in a previous paper of this series.²

The condensation of allyl bromide with carbonyl derivatives under the conditions of the Reformatsky reaction has received very little attention.⁸ This active bromine compound was found to react with the thienyl carbonyl derivatives to give excellent yields of the expected 4-hydroxyalkenes. A mixture of equal parts of benzene and tetrahydrofuran was employed as the reaction solvent. Since only very small quantities of unreacted ketone were recovered, it may be speculated that the enolization reaction is of minor importance when allylic bromides were used. There was no indication that the products obtained underwent any degree of dehydration during distillation at low pressures. The yields obtained were of the order 70-80% and very little variation in yields was noted between the thenals and acyl thiophenes nor between the 2-thienyl and 3-thienyl derivatives. Altogether, seven previously unreported 4-thienyl-4-hydroxy-1-alkenes were prepared by this procedure and their physical properties are summarized in Table II.

The function of propargyl bromides as a Reformatsky reagent has received considerable attention.^{3,9-12} One of these reports³ describes the interaction of propargyl bromide with 2-thenal to

yield the expected 1-(2-thienyl)-3-butyne-1-ol. A further study was made of the reaction of propargyl bromide with 2-acetyl-, 2-propionyl- and 2-*n*-butyrylthiophene. Even though the reaction proceeded vigorously, with the zinc being completely consumed, it was impossible to prepare any Reformatsky-type product by the interaction of the 2-thienyl ketones with propargyl bromide. The reaction with 2-thenal was found to proceed as reported³ in a 60% yield. The recovery of unreacted 2-thienyl ketones was for 2-acetylthiophene 84%, 2-propionylthiophene 76% and for 2-*n*-butyrylthiophene 73%. As small quantities of non-distillable material remained in the distillation flask it is possible that small amounts of the expected products may have been formed, but were destroyed by pyrolysis during distillation. However, based upon the large percentages of unreacted ketones recovered, it seems evident that the intermediate propargyl zinc bromide complex promotes considerable enolization in the 2-thienyl ketones.

Experimental

Ethyl γ -Bromocrotonate.—This material was prepared by the treatment of ethyl crotonate with *N*-bromosuccinimide in the presence of benzoyl peroxide according to a previously described procedure.¹³

Propargyl Bromide.—Kirmman's procedure involving the interaction of propargyl alcohol with phosphorus tribromide in the presence of pyridine was utilized for the preparation of propargyl bromide.¹⁴

Thiophene Derivatives.—For reference to the methods of preparation of thiophene derivatives used in this work see the preceding paper in this series.²

Reformatsky Reaction of 2-Thenal with Ethyl γ -Bromocrotonate.—In a typical reaction, 11.2 g. (0.10 mole) of 2-thenal, 19.3 g. (0.10 mole) of ethyl γ -bromocrotonate and 6.5 g. (0.10 mole) of zinc dust were mixed with 100 ml. of dry benzene and placed in a three-necked flask equipped with a stirrer and a reflux condenser to which a calcium chloride

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(9) K. Zeile and A. Meyer, *ibid.*, **75**, 356 (1942).

(10) H. B. Henbest, E. R. H. Jones and I. M. S. Walls, *J. Chem. Soc.*, 2696 (1949).

(11) H. B. Henbest, E. R. H. Jones and I. M. S. Walls, *ibid.*, 3646 (1950).

(12) W. Huber and A. Businger, U. S. Patent 2,540,116 [C. A., **45**, 7584 (1951)].

(13) H. Schmidt and P. Karter, *Helv. Chim. Acta*, **29**, 573 (1946).

(14) A. Kirmman, *Bull. soc. chim.*, [4] **39**, 698 (1926).

tube was attached. A small crystal of iodine was added, stirring was commenced and the bottom of the reaction vessel was heated lightly to initiate the reaction. It was necessary to moderate the vigorous exothermic reaction by temporary immersion of the flask in an ice-bath. After the spontaneous refluxing had subsided, the reaction was continued for one-half hour by the application of heat after which the reaction mixture was allowed to cool to room temperature. Hydrolysis of the reaction mixture was accomplished by the addition, with vigorous stirring, of 75 ml. of ice-cold 10% sulfuric acid. The non-aqueous layer was separated and combined with a subsequent ether extract of the aqueous portion. The combined solutions were extracted successively with 100 ml. of water, 100 ml. of 10% sodium carbonate solution and 100 ml. of water followed by drying over anhydrous sodium sulfate. After removal of the solvents on a steam-bath, the residue was distilled *in vacuo*. The forerun contained 1.3 g. of ethyl crotonate boiling at 30–40° (80 mm.) and 1.2 g. of 2-thenal, b.p. 58–59° (2 mm.). Following the forerun was the first product which amounted to 6.2 g. (28%) of ethyl α -vinyl- β -hydroxy- β -(2-thienyl)-propionate, boiling at 132–134° (1 mm.), n_{25}^D 1.5270.

Anal. Calcd. for $C_{11}H_{14}O_2S$: C, 58.3; H, 6.2. Found: C, 58.0; H, 6.3.

The second product obtained amounted to 3.6 g. (16%) of ethyl 5-(2-thienyl)-5-hydroxy-2-pentenoate and distilled at 160–161° (1 mm.), n_{25}^D 1.5573.

Anal. Calcd. for $C_{11}H_{14}O_2S$: C, 58.3; H, 6.2. Found: C, 58.6; H, 6.0.

Reformatsky Reaction of 3-Thenal with Ethyl γ -Bromocrotonate.—Following the above described procedure, 5.6 g. (0.05 mole) of 3-thenal, 3.25 g. (0.05 mole) of zinc and 9.7 g. (0.05 mole) of ethyl γ -bromocrotonate were allowed to interact in 50 ml. of dry benzene as a solvent to yield two Reformatsky products. The first amounted to 3.3 g. (29%) of ethyl α -vinyl- β -hydroxy- β -(3-thienyl)-propionate, and had the following physical properties: b.p. 134–135° (1 mm.), n_{25}^D 1.5255.

Anal. Calcd. for $C_{11}H_{14}O_2S$: C, 58.3; H, 6.2. Found: C, 57.8; H, 6.4.

The second product, distilling at 158–160° (1 mm.), amounted to 1.9 g. (17%) of ethyl 5-(3-thienyl)-5-hydroxy-2-pentenoate, n_{25}^D 1.5555.

Anal. Calcd. for $C_{11}H_{14}O_2S$: C, 58.3; H, 6.2. Found: C, 58.3; H, 6.4.

Reformatsky Reaction of 2-Acetylthiophene with Ethyl γ -Bromocrotonate.—Employing the usual procedure, 12.6 g. (0.10 mole) of 2-acetylthiophene, 19.3 g. (0.10 mole) of ethyl γ -bromocrotonate and 6.5 g. (0.10 mole) of zinc dust

interacted in 100 ml. of anhydrous benzene. After then carrying out the isolation procedures described above the products were vacuum distilled. The first fraction obtained was 7.1 g. of ethyl crotonate followed by 7.8 g. of 2-acetylthiophene. Following these fractions there was obtained 1.5 g. (7%) of ethyl α -vinyl- β -hydroxy- β -(2-thienyl)-*n*-butyrate boiling at 107–108° (1 mm.), n_{25}^D 1.4959.

Anal. Calcd. for $C_{12}H_{16}O_2S$: C, 59.9; H, 6.7. Found: C, 59.7; H, 6.8.

The next fraction boiling at 155–156° (1 mm.) did not give a correct analysis for the isomeric ester and was refluxed for eight hours in 6% oxalic acid solution to yield 5.8 g. (26%) of ethyl 5-thienyl-5-hydroxy-2,4-hexadienoate boiling at 147–148.5° (1 mm.).

Anal. Calcd. for $C_{12}H_{14}O_2S$: C, 64.8; H, 6.31. Found: C, 64.7; H, 6.5.

4-(2-Thienyl)-4-hydroxy-1-butene.—Into the same apparatus as described above was placed 11.2 g. (0.10 mole) of 2-thenal, 12.1 g. (0.10 mole) of allyl bromide, 6.5 g. (0.10 mole) of zinc, 50 ml. of dry benzene and 50 ml. of anhydrous tetrahydrofuran. The reaction was initiated and carried out in the previously described manner. A quantity of 100 ml. of ice-cold 30% acetic acid being employed to hydrolyze the reaction products. After washing, drying and removal of the solvents, the residue was distilled *in vacuo* to yield 12.0 g. (78%) of a clear colorless liquid boiling at 89–90.5° (1 mm.), n_{25}^D 1.5439.

Anal. Calcd. for $C_8H_{10}OS$: C, 62.3; H, 6.5. Found: C, 62.1; H, 6.9.

1-(2-Thienyl)-3-butyn-1-ol.—The treatment of a solution of 11.2 g. (0.10 mole) of 2-thenal and 11.9 g. (0.10 mole) of propargyl bromide in a mixture of 50 ml. of anhydrous benzene and 50 ml. of dry tetrahydrofuran with 6.5 g. (0.10 mole) of zinc dust according to the preceding procedure yielded 9.1 g. (80%) of the expected product boiling at 84–85° (0.1 mm.), n_{25}^D 1.5220.

Ozonolysis of Ethyl α -Vinyl- β -hydroxy- β -(2-thienyl)-propionate.—Following an already reported procedure,⁷ 0.2 g. of the ester was dissolved in 10 ml. of acetic acid and treated with ozone for one hour. The ozonide was decomposed with zinc dust and water and then distilled until 20 ml. of distillate was collected. The distillate was treated with 0.25 g. of dimedone and set aside overnight in the refrigerator. The resulting crystals were filtered off and recrystallized from a methanol-water mixture of equal parts to yield about 0.1 g. of crystalline material which melted sharply at 187°. The melting point was not depressed when the substance was mixed with the product resulting from the interaction of formaldehyde and dimedone.

EAST LANSING, MICHIGAN

[CONTRIBUTION NO. 139 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TENNESSEE]

The Metalation of Phenoxathiin 10-Oxide and 10,10-Dioxide with *n*-Butyllithium

BY DAVID A. SHIRLEY AND ERWIN A. LEHTO

RECEIVED JUNE 7, 1954

In accord with the known activating influence of the sulfone group, and in contrast to phenoxathiin itself which metalates in the 4-position, the metalation of phenoxathiin 10-oxide and phenoxathiin 10,10-dioxide with *n*-butyllithium occurs at the 1-position (adjacent to sulfur).

The sulfone group has a powerful deactivating effect on adjacent rings undergoing electrophilic substitution, but an opposite effect when these rings undergo metalation by alkyl lithium reagents. Thus Truce and co-workers¹ have metalated a variety of substituted diphenyl sulfones and have observed metalation *ortho* to the sulfone group under relatively mild conditions and in good yields. Gilman and Esmay² have reported the mono- and dimetala-

tion of dibenzothiophene 5,5-dioxide and the metalation (with reduction) of the corresponding sulfoxide, all occurring at the position adjacent to sulfur.

It seemed of interest to examine the metalation of phenoxathiin 10-oxide and -dioxide. Phenoxathiin itself metalates adjacent to the oxygen atom³ (4-position) and this has been related to the fact that dibenzofuran is metalated exclusively when placed in competition with dibenzothiophene.³

(3) H. Gilman, M. W. Van Ess, H. B. Willis and C. G. Stuckwisch, *ibid.*, **62**, 2606 (1940).

(1) (a) W. E. Truce and M. F. Amos, *THIS JOURNAL*, **73**, 3013 (1951); (b) W. E. Truce and O. L. Norman, *ibid.*, **75**, 6023 (1953).

(2) (a) H. Gilman and D. L. Esmay, *ibid.*, **74**, 266 (1952); (b) H. Gilman and D. L. Esmay, *ibid.*, **75**, 278 (1953).