[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, HOPE COLLEGE]

Condensations of Epoxides with 2-Thienylsodium and 2-Thienylmagnesium Bromide

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2-Thienylsodium and 2-thienylmagnesium bromide are condensed with propylene oxide, styrene oxide and epichlorohydrin to yield 1-(2-thienyl)-2-propanol, 1-(2-thienyl)-2-phenyl-2-ethanol and 1-(2-thienyl)-3-chloro-2-propanol, respectively. Yields of 60, 63 and 60.5%, respectively, were obtained *via* the Grignard reagent, whereas yields were 32.4, 50.5 and 32.5% by the 2-thienylsodium route. The dehydration products were prepared and studied. Phenylacetaldehyde with 2-thienylmagnesium bromide produced an 86% yield of 1-(2-thienyl)-2-phenyl-1-ethanol.

Previous workers have studied the application of organometallic reagents to the synthesis of thiophene derivatives.

Schick and Hartough[1] have developed the metalation of thiophene by the present method. They prepared 2-thienylsodium in an inert solvent above 50°. They further demonstrated that thiophene could not be metalated directly and that mercury is essential to the metalation. The metalation of thiophene had been previously accomplished by Schorigin,[2] who had utilized diethylmercury and sodium. Gilman and Brewer[3] metalated thiophene by essentially the same method with 2,2-difurylmercury and sodium to obtain a 16% yield of 2-thiophenecarboxylic acid after carbonation.

The literature contains two references to the addition of 2-thienylsodium to epoxides. Schick and Hartough[4] undertook the study of the reaction of ethylene oxide with thienyl-, halothienyl- and alkylthienylsodium compounds. They isolated the corresponding thienylethanols, and accomplished their dehydration to vinylthiophenes. Gmitter and Benton[5] studied the reaction of butadiene monoxide with 2-thienylsodium and 2-thienylmagnesium bromide. They isolated the resulting alcohol in both cases, dehydrated and converted them to the same maleic anhydride addition compound by the Diels–Alder method. They demonstrated that 1-(2-thienyl)-3-butene-2-ol resulted from the condensation of 2-thienylsodium with butadiene monoxide.

For our studies we selected three additional epoxides; styrene oxide, propylene oxide and epichlorohydrin. Work carried out by this group, simultaneously with that of Gmitter and Benton,[5] produced identical results in the reaction between butadiene monoxide and 2-thienylsodium. We did not attempt the condensation with the Grignard reagent.

Styrene oxide was found to add to 2-thienylsodium to yield 1-(2-thienyl)-2-phenyl-2-ethanol (I). The alcohol was found to dehydrate with extreme ease. It was dehydrated by distillation from potassium acid sulfate to 1-(2-thienyl)-2-phenylethylene (II), a pale yellow crystalline compound with a melting point of 109–110°. Evidence for the structure of II is based in part upon the extreme ease with which I dehydrated, suggesting the presence of a secondary rather than a primary alcohol. Final proof was obtained by the synthesis of II by an alternate route which utilized the condensation of phenylacetaldehyde with 2-thienylmagnesium bromide to produce 1-(2-thienyl)-2-phenyl-1-ethanol (III), which was dehydrated by distillation from potassium acid sulfate to pale yellow crystals which melted at 109–110° and which failed to depress the melting point when mixed with II.

2-Thienylmagnesium bromide has been condensed with epoxides in three instances. Blicke and Burckhalter[6] obtained 1-(2-thienyl)-2-ethanol (53%) and 1-(2-thienyl)-2-propanol (60%) by the interaction of 2-thienylmagnesium bromide with ethylene oxide and propylene oxide, respectively. Gmitter and Benton[5] showed that butadiene monoxide reacted with this Grignard reagent to form 4-(2-thienyl)-2-butene-1-ol by 1,4-addition (26%). Styrene oxide was found to add to 2-thienylmagnesium bromide to yield I, which was then dehydrated by distillation from potassium acid sulfate to yield yellowish-white crystals melting at 109–110° which failed to depress the melting point when mixed with II.

2-Thienylsodium was added to propylene oxide to yield 1-(2-thienyl)-2-propanol (IV). This compound was previously prepared by Blicke and Burckhalter,[6] from 2-thienylmagnesium bromide, and was dehydrated by refluxing with potassium acid sulfate to 1-(2-thienyl)-1-propylene (V). The reaction described by Blicke and Burckhalter was repeated in order to compare the physical constants and ultraviolet absorption data of the alcohol and the dehydration product with those of the compounds obtained by the 2-thienylsodium reaction and dehydration. The physical constants were found to be the same for the compounds prepared by the two methods. The ultraviolet absorption spectra showed the same maximum in absorption for the alcohols obtained by the two methods, and the same bathochromic shift in the dehydration products indicating that dehydration occurred and that the new double bond was in conjugation with the thiophene system.

2-Thienylmagnesium bromide was treated with epichlorohydrin to yield 1-(2-thienyl)-3-chloro-2-propanol (VI). All attempts to dehydrate this alcohol led either to a polymeric mass in the still pot or to the original alcohol.

When 2-thienylsodium was added to epichlorohydrin and the resulting mixture acidified with dry hydrogen chloride, the same alcohol VI was obtained.

The above experimental work when considered with the instances cited in recent literature points

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[1] J. W. Schick and H. D. Hartough, THIS JOURNAL, **70**, 286 (1948).

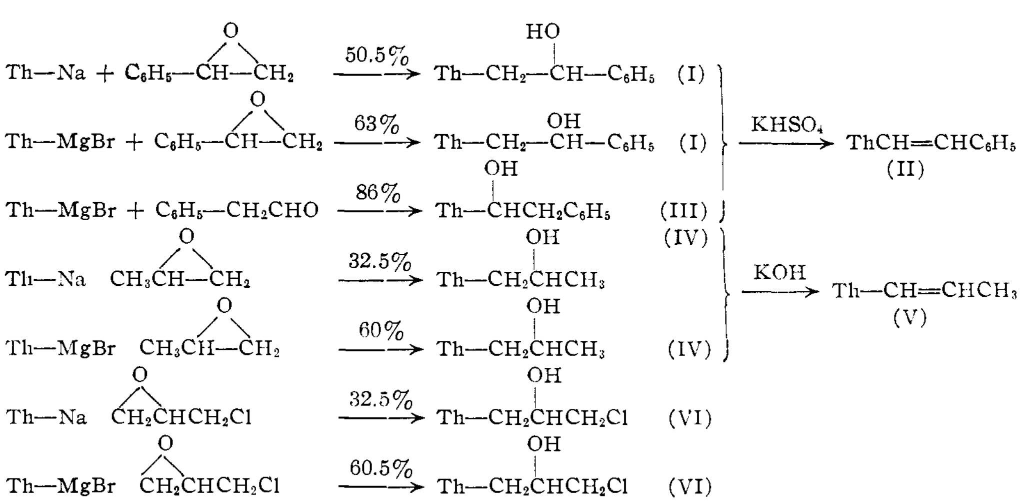
[2] P. Schorigin, *Ber.*, **43**, 1938 (1910).

[3] H. Gilman and F. Brewer, THIS JOURNAL, **56**, 1123 (1934).

[4] J. W. Schick and H. D. Hartough, *ibid.*, **70**, 1646 (1948).

[5] G. T. Gmitter and F. L. Benton, *ibid.*, **72**, 4586 (1950).

[6] F. F. Blicke and J. H. Burckhalter, *ibid.*, **64**, 478 (1942).



up some interesting comparisons between the reactions of these two organometallic reagents with epoxides. In every instance, the yields with the Grignard reagent were found to be superior to those obtained with 2-thienylsodium. Reactions using the Grignard reagent were also noted to be simpler to carry out, and it was our experience that the products were more easily isolated. Therefore, except for the special case of 1,4-addition of butadiene monoxide to the Grignard reagent,[5] this reagent was found to be superior for the preparation of these thiophene derivatives. The Grignard compounds, however, require the use of either bromo- or iodothiophene since 2-chlorothiophene does not form a Grignard reagent with magnesium. Thienylsodium forms easily from 2-chlorothiophene and therefore may prove a more economical reagent for this type of reaction in spite of the lower yields.

Table I

Epoxide	With Th-Na Product	Yield,[a] %	With Th-MgBr Product	Yield, %
Ethylene oxide	2-(2-Thienyl)-1-ethanol	47	2-(2-Thienyl)-1-ethanol	53
Butadiene monoxide	1-(2-Thienyl)-3-butene-2-ol	16.2	4-(2-Thienyl)-2-butene-1-ol	26
Propylene oxide	1-(2-Thienyl)-2-propanol	32.4	1-(2-Thienyl)-2-propanol	60
Styrene oxide	1-(2-Thienyl)-2-phenyl-2-ethanol	50.5	1-(2-Thienyl)-2-phenyl-2-ethanol	63
Epichlorohydrin	1-(2-Thienyl)-3-chloro-2-propanol	32.5	1-(2-Thienyl)-3-chloro-2-propanol	60.5

[a] The yields reported are based on the amount of halothiophenes used. Schick and Hartough[1] report that the metalation of 2-chlorothiophene with sodium results in only 84% conversion to 2-thienylsodium. We were not able to increase this yield. This fact may explain in part the lower yields obtained when using 2-thienylsodium.

Experimental

All reactions were carried out in a nitrogen atmosphere.

1-(2-Thienyl)-2-propanol (IV) from 2-Thienylsodium.—One mole (118 g.) of 2-chlorothiophene was added to freshly prepared sodium amalgam sand containing 50 g. (2.17 moles) of sodium and 20 g. (0.10 mole) of mercury in 500 ml. of benzene. The reaction mixture was stirred and refluxed for three hours in a nitrogen atmosphere. The mixture was cooled to 0–10° in an ice-bath and 59 g. (1 mole) of propylene oxide was added dropwise with stirring. When the addition was complete, the mixture was allowed to stand overnight. A saturated solution of ammonium chloride was cautiously added with stirring and cooling until no further temperature rise was evident. The resulting sludge was filtered out of the mixture. The benzene layer was separated, and dried over anhydrous sodium sulfate. The benzene was removed by distillation and the residue distilled under reduced pressure. Forty-two grams of pure material was obtained; yield 32.4%, b.p. 87° (7 mm.), n^{22}D 1.530. The phenylurethan melted at 65–66°. *Anal.* Calcd. for $C_{14}H_{15}O_2NS$: N, 5.36; S, 12.96. Found: N, 5.46; S, 12.57.

1-(2-Thienyl)-1-propylene (V).—Five grams of the alcohol obtained above was mixed with 10.5 g. of potassium hydroxide and distilled under reduced pressure. A mixture of water and the olefin was collected. Five ml. of ether was added to the mixture and the ether layer decanted, dried and distilled. Yields of 60–70% of the dehydration product were obtained distilling at 63–64° (14 mm.), n^{23}D 1.5645. *Anal.* Calcd. for C_7H_8S: S, 25.82. Found: S, 25.82.

1-(2-Thienyl)-2-phenyl-2-ethanol (I) and 1-(2-Thienyl)-2-phenylethylene (II) from 2-Thienylsodium.—To one mole of 2-thienylsodium was added 120 g. (1.0 mole) of styrene oxide, and the reaction carried out as described above. The product upon distillation was a pale straw colored liquid. The yield of I was 100.8 g., 50.5%, b.p. 169–170° (8 mm.). The phenylurethan melted at 106.5–107° and failed to depress the melting point of the phenylurethan obtained by the Grignard route. A good yield of II was obtained by distilling a mixture of equal weights of the alcohol with potassium bisulfate. The product was recrystallized from absolute ethanol to give pale yellowish-white crystals melting at 109–110°. *Anal.* Calcd. for $C_{12}H_{10}S$: C, 77.40; H, 5.41; S, 17.22. Found: C, 77.43; H, 5.22; S, 16.96.

1-(2-Thienyl)-2-phenyl-1-ethanol (III) and Dehydration to II.—To 0.5 mole of 2-thienylmagnesium bromide in 400 ml. of absolute ether cooled in an ice-bath, was added 60.5 g. (0.5 mole) of phenylacetaldehyde. The addition was carried out dropwise with stirring and the reaction carefully controlled by external cooling. The mixture was allowed to stand overnight, and was then hydrolyzed with a saturated solution of ammonium chloride. The product III was distilled under reduced pressure to give 88 g. of product; b.p. 132–134° (1–2 mm.), yield 86%. This product contained a small amount of dehydration product II which could be removed by filtration. The phenylurethan of III melted at 118°. *Anal.* Calcd. for $C_{19}H_{17}O_2NS$: N, 4.33; S, 9.91. Found: N, 4.51; S, 10.05. The alcohol was converted to the dehydration product II by distillation from an equal weight of potassium hydrogen sulfate. Recrystallization from absolute ethanol yielded pale yellowish-white crystals melting at 109–110°. A mixed melting point of the purified material failed to depress the melting point of II.

1-(2-Thienyl)-2-phenyl-2-ethanol (VI) from 2-Thienylmagnesium Bromide.—To a solution of 0.83 mole of 2-

thienylmagnesium bromide in 200 mg. of absolute ether cooled in an ice-bath, was added 90 g. (0.75 mole) of styrene oxide in an equal volume of ether. The mixture solidified upon standing overnight. The Grignard addition product was decomposed with a saturated solution of ammonium chloride as described above. The ether was removed under reduced pressure and the product I was collected at 169–170° (8 mm.), and fractionated to yield 96.1 g., b.p. 155–160° (4 mm.), yield 63%. *Anal.* Calcd. for $C_{12}H_{12}OS$; C, 71.02; H, 5.92; S, 15.77. Found: C, 71.30; H, 5.86; S, 15.57; phenylurethan, m.p. 106.5–107°. *Anal.* Calcd. for $C_{19}H_{17}O_2NS$: N, 4.33; S, 9.91. Found: N, 4.37; S, 9.71.

1-(2-Thienyl)-3-chloro-2-propanol (VI) from 2-Thienylmagnesium Bromide.—One mole of epichlorohydrin was added to 0.5 mole of 2-thienylmagnesium bromide in 400 ml. of absolute ether at 0–10°. The resulting mixture was hydrolyzed with a saturated solution of ammonium chloride and distilled to give 62.2 g. (0.485 mole) of 1,3-dichloro-2-propanol (b.p. 84° (16 mm.)) which results from the excess of epichlorohydrin. Fifty-three grams of VI was then collected; b.p. 119–122° (8 mm.), yield 60.5%. *Anal.* Calcd. for C_7H_9OSCl: S, 18.15; Cl, 20.07. Found: S, 17.93; Cl, 19.87. The phenylurethan melted at 87°. *Anal.* Calcd. for $C_{14}H_{14}O_2NSCl$: N, 4.74; S, 10.84. Found: N, 4.61; S, 10.94.

1-(2-Thienyl)-3-chloro-2-propanol (VI) from 2-Thienylsodium.—To 0.25 mole of 2-thienylsodium in 125 ml. of benzene was added 0.35 mole of epichlorohydrin with cooling. After stirring overnight the mixture was acidified by passing dry hydrogen chloride into the mixture cautiously while cooling the flask. The benzene was distilled under reduced pressure after the sludge was filtered out and 11.7 g. of 1,3-dichloro-2-propanol was obtained. Fourteen and eight-tenths grams of 1-(2-thienyl)-3-chloro-2-propanol (VI) was obtained; b.p. 120–121° (7 mm.), yield 32.5%. The phenylurethan melted at 86–87° and the melting point was not depressed when mixed with a sample obtained by the Grignard method.

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Some Nucleophilic Displacements on 3-Bromo-1,2-epoxybutane and 1-Bromo-2,3-epoxybutane

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Reaction of 3-bromo-1,2-epoxybutane (I) and of 1-bromo-2,3-epoxybutane (II) with a molar quantity of sodium methoxide in methanol and of sodium ethoxide in ethanol has been shown in each case to yield mainly the corresponding 1-alkoxy-2,3-epoxybutane, indicating that the nucleophilic displacements involved occur preferentially at the primary carbon, without regard for the nature of the substituent at the primary position. The only other and minor product in every case was the corresponding 1,2-dialkoxy-3-butanol, probably formed by further reaction of the major product with alkoxide. Reduction of the 1-alkoxy-2,3-epoxybutanes with lithium aluminum hydride yielded the corresponding 1-alkoxy-2-butanols. With the quantity of lithium aluminum hydride theoretically required to reduce only one of the two functional groups, I gave a mixture of *threo*-3-bromo-2-butanol and 2-butanol and II only 2-butanol and recovered II. Heated with 50% sulfuric acid, 1,2-dimethoxy-3-butanol (IV) was converted to 1-methoxy-2-butanone (VII). The theoretical implications of these results are discussed.

Surprisingly little is known about the relative reactivities toward nucleophilic agents of the halogen-bearing *vs.* the epoxide-ring carbon atoms in α-halogenated epoxides. Many nucleophilic displacements on epichlorohydrin, under typical SN2 conditions, in which the nature of the products clearly indicates preferential attack at the primary carbon of the epoxide ring, are, of course, reported.[2] Trevoy and Brown[3] have commented specifically on the fact that in the reaction of epichlorohydrin with lithium aluminum hydride, the replacement of chlorine by hydrogen proceeds at a slower rate than the reduction of the epoxide ring. Gilman, *et al.*,[4] likewise accept the interpretation[5] that the first step in the synthesis of 1-diethylamino-2,3-epoxypropane from epichlorohydrin and diethylamine is fission of the epoxide ring. In fact all of the reactions of epichlorohydrin which ostensibly consist merely of a displacement of the chlorine by a nucleophilic agent under typical SN2 conditions may possibly proceed *via* initial attack with ring opening at the primary carbon atom of the epoxide-ring to form an intermediate chlorine-containing alkoxide ion, followed by intramolecular displacement of the chloride ion by the alkoxide oxygen with epoxide ring formation in the new position.

Haynes and co-workers[6] have quite recently reported an interesting reaction between epichlorohydrin and sodium acetylide in which pent-2-en-4-yn-1-ol, $HC\equiv C-CH=CH-CH_2OH$, is the major product. The conclusion of these workers that the first step in the reaction is the substitution of the chlorine atom of epichlorohydrin was based in part upon analogy with the reaction between 1-bromo-2,3-epoxybutane (II) and sodium acetylide, wherein hex-3-en-5-yn-2-ol, $HC\equiv C-CH=CH-CH(OH)-CH_3$, was the principal product. The two cases are not entirely comparable, however, inasmuch as the change from chlorine to bromine and from an epoxide in which one of the ring carbon atoms is primary to an epoxide in which both are secondary would definitely tend to favor an increase in attack at the halogen-bearing carbon.

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[1] H. P. Cady Fellow, 1950–1952.

[2] See, for example, W. Traube and E. Lehrman, *Ber.*, **34**, 1941 (1901).

[3] L. W. Trevoy and W. G. Brown, THIS JOURNAL, **71**, 1675 (1949).

[4] H. Gilman, C. S. Sherman, C. C. Price, R. C. Elderfield, J. T. Maynard, R. H. Reitsema, L. Tolman, S. P. Massie, Jr., F. J. Marshall and L. Goldman, *ibid.*, **68**, 1291 (1946).

[5] N. S. Droszdov and O. M. Cherntzov, *J. Gen. Chem.* (*U.S.S.R.*), **4**, 969 (1934); see also N. S. Droszdov and O. M. Cherntzov, *ibid.*, 1305 (1934).

[6] L. J. Haynes, I. Heilbron, E. R. H. Jones and P. Sondheimer, *J. Chem. Soc.*, 1583 (1947).