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STUDIES ON THE CHEMISTRY OF HETEROCYCLICS. XXIV.[1] PREPARATION OF THIENYLACETYLENES

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Previous attempts to synthesize thienylacetylenes by standard procedures have resulted in anomalous reactions (1, 2) or in extremely low yields (3). The present study discloses a new method involving dehydrohalogenation of 2-(1,1-dichloroethyl)thiophene or 2-(1-chlorovinyl)thiophene with sodium amide in liquid ammonia. Yields as high as 65% have been obtained when aniline is employed in catalytic quantities. As starting material for this preparation the readily available 2- and 3-acetothienones were chosen, which were prepared as heretofore.

It seems that to obtain better yields of the acetylenic compounds in the heterocyclic as well as in the aromatic series we will have to take advantage of the high reactivity of alkali metal amides in inert solvents or eventually in liquid ammonia as dehydrohalogenation agents. The sodamide method of dehydrohalogenation has been modified by Bodroux (6), who found that the presence of small amounts of aniline resulting in the formation of NHPhNa with sodamide facilitated the conversion:

$$RCH{=}CHBr + NHPhNa \rightarrow RC{\equiv}CH + NH_2Ph + NaBr$$

Accordingly, these reactions could be carried out in ether at an ordinary temperature. The use of sodamide or potassium hydroxide in inert solvents at high temperatures for the same purpose suffers from the disadvantage that acetylenes frequently rearrange under these conditions and are more readily polymerized and decomposed. This is especially the case with thiophene derivatives, which are less stable and decompose more readily.

We have found that by using sodium amide in liquid ammonia in the presence of small amounts of aniline, the dehydrohalogenation proceeds readily at the boiling point of liquid ammonia and decomposition and polymerization at this temperature are appreciably diminished. Consequently, the yields could be increased up to 65%. The aniline used could be easily separated as its hydrochloride.

The chlorination of the acetothienones with phosphorus pentachloride furnished the corresponding chlorinated thiophene derivatives. The yields of the chlorinated products amounted to 40–60%. The mixtures of the above chlorinated products gave the same 2-thienyl- or substituted 2-thienyl- or 3-thienylacetylenes respectively. The amount of sodium amide used was from 3 to 4 moles to 1 mole of the corresponding chlorinated thiophene derivative.

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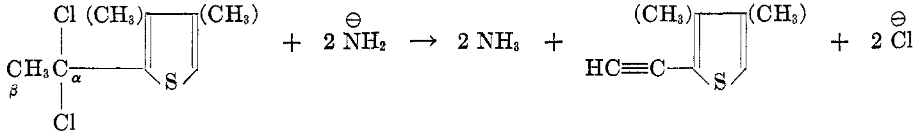
[2] Condensed from a portion of the dissertation of A. V. submitted to the Graduate School of Fordham University in partial fulfillment of the requirements of the Ph.D. degree.

The yields of the thienylacetylenes obtained depend on the substituents of the thiophene ring. We have found that the presence of methyl groups on the thiophene nucleus increased slightly the yields, while the presence of halogens had an opposite effect. Yields as high as 65% could be obtained when 3-methyl- or 4-methyl-2-acetothienones were used as starting materials.

Considering that the elimination reaction proceeds by the E-2 mechanism, where the α-carbon bears the two or one halogens respectively on the thiophene nucleus, and that the heterocyclic ring will behave in an analogous manner as an aromatic substituent with its inductive electron attraction:

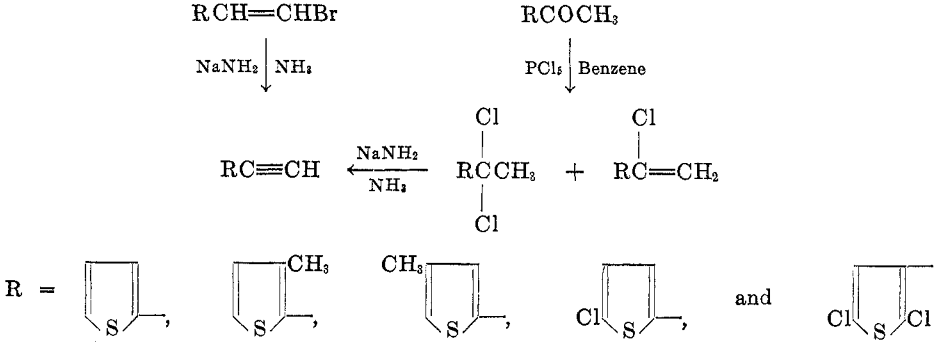


(−I effect, arising from the $\overset{\delta_+}{\text{—C}}\text{—}\overset{\delta_-}{\text{Th}}$ dipole). This would assist the electromeric effect in the β-position, while a small or second order inductive effect will be relayed, when it is in the α-position (7). Consequently, we could expect that the electron-releasing substituents on the heterocyclic ring would rather slightly retard the elimination reaction. The observed higher yields with the methyl derivatives are probably due not to the facility of the elimination reaction but to the increased yields of the chlorinated products with phosphorus pentachloride. These would proceed with higher yields, when the thiophene nucleus is bearing electron-releasing groups.

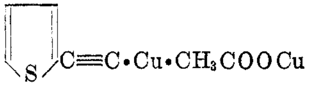
It is known that compounds of the type RCH=CHBr yield acetylenic hydrocarbons when further unsaturation is created. The corresponding 2-(2-bromovinyl)thiophene was prepared as reported earlier (3). The dehydrohalogenation of the latter with sodium amide in liquid ammonia readily gave the 2-thienylacetylene in yields of 65%. This is in agreement with the E-2 mechanism, whereby the H^+ elimination from the β-carbon would be facilitated by the presence of the thiophene nucleus attached to it.

All the above reactions carried out are summarized in Chart I.

CHART I



The thienylacetylenes obtained were identified by elemental analysis and by their metallic derivatives. These acetylenes possess a hydrogen atom attached to an acetylenic carbon, which is relatively mobile, susceptible to being replaced by metals and halogens and which lends itself to many more complex reactions. Such acetylenes readily gave the yellow cuprous derivatives with the Ilosvay reagent (8). To obtain the precipitates more quantitatively the solutions were slightly buffered with ammonium carbonate (9). Ammoniacal silver nitrate gave the white precipitates of the corresponding silver derivatives of the thienylacetylenes. Furthermore, the cuprous derivatives were readily oxidized to the corresponding diacetylenic compounds, and the sodium salts were converted to acetylenic acids and their esters respectively (10). Strong mineral acids, *e.g.* hydrochloric acid, immediately decomposed the cuprous derivatives with liberation of the true acetylenic compounds. The cuprous derivative of 2-thienylacetylene dissolved in boiling acetic acid to give an orange-yellow solution containing all the copper in the form of an oxidizable complex, which could be isolated in an amorphous form by precipitation in ice-water. From analogy (9) the composition of that compound would probably be as follows:



EXPERIMENTAL[3]

Materials. 2-Acetothienone and substituted 2- and 3-acetothienones were prepared as usual (5). 2-Chlorothiophene and 2,5-dichlorothiophene were furnished through the courtesy of the Jefferson Chemical Co., Inc., New York 22, N.Y. The thiophene used in this work was obtained through the courtesy of Drs. C. A. Hochwalt and O. J. Weinkauff of the Monsanto Chemical Co., Inc., St. Louis, Mo.

General procedure for the preparation of 2- and 3-(1,1-dichloroethyl)thiophene and substituted thiophene derivatives. The procedure is essentially analogous to that described earlier (3), except that the temperature in the case when substituted 2- and 3-acethienones were used as starting materials did not rise so suddenly, and the reaction had to be initiated while heating the reaction mixture up to 40–45°. The chlorination of the substituted acetothienones was performed while heating the reaction mixture up to 85–90°. Usually at the end of two hours all the phosphorus-pentachloride had reacted. The dark brown solution was cooled and poured carefully with stirring into a mixture of 850 g. of ice and 350 ml. of ether, when 1 mole of the substituted acetothienone was used. The ether layer was separated and treated with ice-cold water (3). Usually the products were not isolated by rectification but were directly used for the dehydrohalogenation reaction with sodium amide in liquid ammonia. However, when isolated, they furnished two fractions of the corresponding chlorinated products. The 5-chloro-2-(1,1-dichloroethyl)thiophene and 2,5-dichloro-3-(1,1-dichloroethyl)thiophene were more stable and did not darken so readily on distillation under diminished pressure as the corresponding 3-methyl- and 4-methylthiophene derivatives. The products were most probably mixtures of mono- and di-chlorinated products, because the elemental analysis were unsatisfactory despite careful redistillation under diminished pressure. However, the crude mixtures furnished the corresponding thienylacetylenes in good yields.

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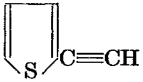
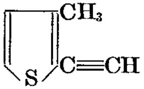
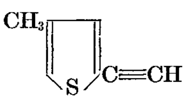
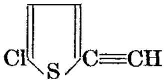
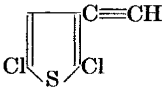
[3] The analyses were carried out by Drs. G. Weiler and F. B. Strauss, Microanalytical Lboratory, Oxford, England.

TABLE I

PHYSICAL PROPERTIES AND ELEMENTAL ANALYSIS OF THIENYLACETYLENES AND SUBSTITUTED THIENYLACETYLENES

COMPOUND	STRUCTURAL FORMULA	B.P.,[b] °C.	MM.	YIELD, %	n_D^{20}	ELEMENTAL ANALYSIS					
						Cal'd			Found		
						C	H	Cl	C	H	Cl
2-Thienylacetylene[a]		31–33	3	60	1.5886	66.66	3.7		66.37	3.75	
3-Methyl-2-thienylacetylene		53	7	65	1.5725	68.9	4.9		68.75	4.75	
4-Methyl-2-thienylacetylene		62	7	63	1.5770	68.9	4.9		68.6	4.9	
5-Chloro-2-thienylacetylene		82	5	24	1.5876	50.55	2.12	24.2	50.25	2.2	24.4
2,5-Dichloro-3-thienylacetylene		95	10	45	1.5898	40.8	1.13	40.2	41.0	1.4	40.4

[a] Reported by Keskin, Miller, and Nord, *J. Org. Chem.*, **16**, 199 (1951).
[b] The boiling points are not corrected.

General procedure for the preparation of 2-thienylacetylene and substituted 2- and 3-thienylacetylenes. One gram-atom of metallic sodium was converted to sodium amide by using hydrated iron nitrate as catalyst in 1.5 l. of liquid ammonia (4) while using a 4-liter Pyrex glass beaker without any insulation or a deep temperature bath. Then 0.3–0.4 mole of the chlorinated thiophene derivative dissolved in 3 volumes of absolute ether was added in the course of 15–30 minutes. A small quantity (0.5–3 g.; 0.006–0.032 mole) of aniline facilitated the dehydrohalogenation. Usually the beaker was covered by a thick layer of ice, which satisfactorily slowed down the evaporation of the liquid ammonia. The stirring was continued for an additional one-half hour, and then the mixture was hydrolyzed carefully by adding 400 ml. of water. The dark brown solution was extracted twice with ether and the combined extracts were washed twice with ice-cold water, then with dilute (1 *N*) hydrochloric acid, and finally were dried over a Drierite or potassium hydroxide and calcium chloride mixture. After removing the solvent the corresponding 2- and 3-thienylacetylenes were rectified *in vacuo*. The yields could be improved when low bath temperatures and nitrogen atmosphere were maintained during the distillation. Yields varied from 24–65%. Some resinous material, which remained in the distilling flask was easily soluble in acetone and gave films on drying, which were resistant to concentrated acids and alkalies. Some (usually not over 10%) of the starting material was recovered, which could be used again in the dehydrogenation reaction. The physical properties as well as elemental analyses and the yields obtained are recorded in Table I.

Preparation of 2-thienylacetylene from 2-(2-bromovinyl)thiophene. The starting materials were prepared according to earlier descriptions (3), and the dehydrohalogenation of the 2-(2-bromovinyl)thiophene was carried out in a similar way as described above. From 2.5 g. (0.0137 mole) of 2-(2-bromovinyl)thiophene there was obtained 0.9 g. of 2-thienylacetylene, b.p. 33°/3 mm., yield 65%.

SUMMARY

Sodium amide in liquid ammonia was successfully applied in the thiophene series for the formation of the triple bond from 2-(1,1-dichloroethyl)thiophene, 2-(1-chlorovinyl)thiophene, and corresponding substituted derivatives as well as from 2-(2-bromovinyl)thiophene. The yields were as high as 60–80%. Four new thienylacetylenes were synthesized.

New York 58, N. Y.

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(10) Vaitiekunas and Nord, *J. Am. Chem. Soc.* **76**, 2733 (1954).