SYNTHESIS OF SUBSTITUTED CHLOROACETYLENES FROM METHYL KETONES

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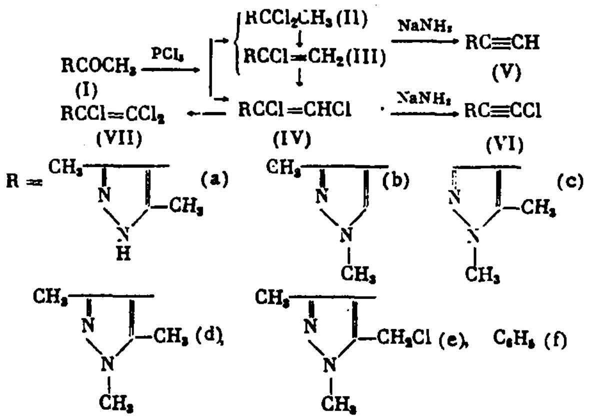
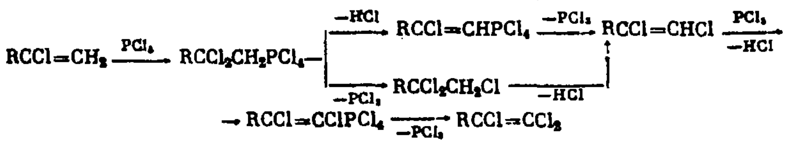
Earlier it was shown that the reaction of 4-acetyl-3,5-dimethylpyrazole (Ia) with phosphorus pentachloride leads to the formation of the vicinal dichloride 4-α,β-dichlorovinyl-3,5-dimethylpyrazole (IVa) in addition to 4-α-chlorovinyl- and 4-α,α-dichloroethyl-3,5-dimethylpyrazole (IIIa) and (IIa) [1]. In reaction with sodium amide in liquid ammonia compound (IVa) eliminates a molecule of hydrogen chloride and is converted into 4-β-chloroethynyl-3,5-dimethylpyrazole (VIa). By varying the conditions it is possible to carry out the reaction of the ketone (Ia) with phosphorus pentachloride selectively in any of the above-mentioned directions.

During investigation of the effect of the specific characteristics of the structure of compound (Ia) on its behavior in this reaction we found that N-methylated pyrazolyl ketones (Ib-d) can also be converted with yields of 50-90% either into the "normal" products from substitution of the carbonyl oxygen by chlorine (IIb-d) and (IIIb-d) or to the corresponding α,β-dichloroethylenes (IVb-d):



The formation of the dichlorides (IV) is aided by increased temperature (60-80°C) and by an excess of phosphorus pentachloride [2.2-2.3 moles/mole (I)]. With a larger excess of phosphorus pentachloride further chlorination of the compounds occurs. With 3 moles of phosphorus pentachloride at 80°C in benzene the ketones (Ib, c) give pyrazolyltrichloroethylenes (VIIb, c) with yields of 75%. The reaction takes place in stages, and the dichlorides (IVb-c) are converted quantitatively into compounds (VIIb, c) after 1 h under these conditions. Chlorination at the β position of the side chain is probably the result from phosphorylation of the intermediate vinyl chlorides followed by degradation of the phosphorus-containing products [2]:



From comparison of the data in [2-4] it evidently follows that the vinyl compounds are phosphorylated more readily in benzene than in $POCl_3$. In accordance with this only the chlorides (IIb) and (IIIb) are formed from 4-acetyl-1,3-dimethylpyrazole (Ib) in $POCl_3$, in spite of the 35% excess of PCl_5, whereas it is not possible to avoid the formation of the vicinal dichloride (IVb) completely in benzene even with an equimolar amount of PCl_5.

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In addition, it is clear that the presented scheme does not exhaust all the possible paths of "anomalous" chlorination in the ketone — PCl_5 system [5]. In contrast to the pyrazolyl ketones (Ib, c), 4-acetyl-1,3,5-trimethylpyrazole (Id) with 4-5 moles of phosphorus pentachloride gives mainly 4-α,β-dichlorovinyl-5-chloromethyl-1,3-dimethyl-1,3-dimethylpyrazole (IVe), and its precursor (according to GLC data) is the dichloride (IVd).

It is not impossible that in the 4-chlorovinyl derivatives of pyrazole chlorination at the β position is facilitated on account of the electron-donating characteristics of the 4-pyrazolyl radical [6]. However, this reaction is due not only to the structure of the ketone but is even due rather to the conditions of its realization and has general significance. Thus, with a 30% excess of phosphorus pentachloride in benzene at 60°C acetophenone is converted into a mixture of (IIf) and (IIIf), containing as little as ~3% of the α,β-dichloride (IVf). With a larger amount of phosphorus pentachloride at 60-80°C compound (IVf) and α,α,β-trichloroethylbenzene become the main reaction products. The production of 3-(α,β-dichlorovinyl)-4,5,5-trimethyl-Δ^3-butenolide from the corresponding ketone or α-substituted vinyl chloride has also been described [4]. All this clearly gives reason to state that α-chlorovinyl or α,β-dichlorovinyl aromatic derivatives can in general be synthesized selectively from methyl aryl ketones with phosphorus pentachloride by controlling the reaction conditions. It should be noted that the vicinal dichlorides can, in addition, be obtained from α-chloromethyl ketones.

As known, the action of bases on α-arylvinyl chlorides leads to monosubstituted acetylenes. By using sodium amide in ammonia as base, we synthesized compounds (Vb-d) with yields of 40-85%, calculated on compound (I). The elimination of hydrogen halides from dichloroethylenes as a method for the synthesis of halogenoacetylenes has not been sufficiently developed on account of secondary reactions between the halogenoacetylene and bases. The exception is sodium (or lithium) chloroacetylide, which is formed almost quantitatively in the reaction of 1,2- or 1,1-dichloroethylene with sodium amide (or lithium amide) in ammonia and phenyllithium (or methyllithium) in ether [7, 8]. The absence of side reactions of exchange of the halogen in the case of 4-β-chloroethynyl-3,5-dimethylpyrazole (VIa) is probably explained by the fact that the sodium salt, in the form of which it is obtained, is insufficiently soluble with ammonia and is similar in this respect to the chloroacetylide.

It can be supposed that the rates of dehydrochlorination of other vicinal dichlorides (IV) by sodium amide are also higher than the rates of the succeeding processes. In fact, by using the stoichiometric amount of the base, we obtained the chloroacetylenes (VIc, d, f) from these compounds with yields of 80-90%. With an excess of sodium amide compounds (VI) underwent further transformations and could not be isolated. Compounds (IVb, d, f) were successfully dehydrochlorinated to (VIb, d, f) with a 25% alcohol solution of potassium hydroxide.

The structures and individualities of the synthesized compounds were proved by elemental analysis, PMR and IR spectra, GLC, and TLC. In the PMR spectra of the vicinal dichlorides (IV) and the acetylenes (V) there are signals for the vinyl (6.08-6.33 ppm) and ethynyl (2.99-3.10 ppm) protons, respectively. The presence of a monosubstituted acetylene group in (V) and a disubstituted acetylene in (VI) is confirmed by absorption at 2112-2125 and 3315-3325 cm^{-1} and at 2217-2230 cm^{-1} in the IR spectra of these compounds. In the PMR spectrum of the trichloride (IVe), in addition to signals for the ethylene protons (6.33 ppm), the CH_3 groups at the nitrogen (3.77 ppm), and the ring carbon (2.17 ppm), there is a signal for the CH_2 group (4.49 ppm) formed as a result of substitution of the H atom in one of the C-methyls by chlorine. Elimination of HCl by the action of the stoichiometric amount of sodium amide on (IVe) leads to the chloroacetylene (VIe). The upfield shift of the signal for the chloromethyl group with slight change in the position of the signal for the C-methyl group in its PMR spectrum on replacement of the nonpolar solvent by an aromatic solvent makes it possible reliably to establish [9] that the second of them is at the 3 position of the hetero ring. Consequently, the trichloride (IVe) is 4-α,β-dichlorovinyl-5-chloromethyl-1,3-dimethylpyrazole. The configuration and isomeric purity of compound (IV) was not determined.

EXPERIMENTAL

4-Ethynyl-1,3-dimethylpyrazole (Vb). A mixture of 9 g of compound (Ib) [10] and 18.5 g of phosphorus pentachloride in 30 ml of phosphorus oxychloride was heated at 90-100°C until compound (Ib) had disappeared from the reaction mixture (GLC control). On cooling, the mixture was diluted with 300 ml of ether and neutralized with a 20% aqueous solution of sodium hydroxide. The obtained ether solution of compounds (IIb) and (IIIb) was dried with potassium carbonate, added to sodium amide (from 3 g of sodium) in 200 ml of ammonia, and stirred for 1 h. The ammonia was removed by the addition of moist ether. After chromatography on

TABLE 1. Di- and Trichlorovinyl Derivatives of Pyrazole

Compound	Yield, %	bp, °C (p, mm Hg)	mp, °C (from petroleum ether) or n_D^{20}	Empirical formula	Cl found/calculated, %	PMR spectrum (CCl_4, δ, ppm)
(IVb)	51,8	108—110 (3)	31,5—32,5	$C_7H_8Cl_2N_2$	37,08/37,12	6,31 $\left(CHCl{=}C\langle\right)$; 3,74 ($NCH_3$); 2,25 (3-$CH_3$); 7,34 (5-H)
(IVc)	51,6	94—97 (1)	28—29	$C_7H_8Cl_2N_2$	37,08/37,12	6,26 $\left(CHCl{=}C\langle\right)$; 3,71 ($NCH_3$); 2,32 (5-$CH_3$); 7,31 (3-H)
(IVd)	52,7	94—96 (1)	1,5400	$C_8H_{10}Cl_2N_2$	34,33/34,57	6,08 $\left(CHCl{=}C\langle\right)$; 3,62 ($NCH_3$); 2,12 and 2,21 (3- and 5-CH_3)
(IVe)	60*	118—120 (1)	1,5640*	$C_8H_9Cl_3N_2$	—	6,33 $\left(CHCl{=}C\langle\right)$; 3,77 ($NCH_3$); 4,49 ($CH_2Cl$); 2,17 (3-$CH_3$)
(VIIb)	74,3	125—126 (5)	1,5576	$C_7H_7Cl_3N_2$	47,13/47,17	3,71 (NCH_3); 2,17 (3-CH_3); 7,31 (5-H)
(VIIc)	77,7	126—128 (4)	47—48	$C_7H_7Cl_3N_2$	47,26/47,17	3,71 (NCH_3); 2,24 (5-CH_3); 7,30 (3-H)

*The crude product.

aluminum oxide (of V activity) in a 1 :1 mixture of ether and petroleum ether we obtained 6.8 g (87%) of compound (Vb); mp 34.5-35.5°C (from petroleum ether). Found %: N 23.27. $C_7H_8N_2$. Calculated %: N 23.31. PMR spectrum (carbon tetrachloride, δ, ppm): 2.99 ($HC{\equiv}C$); 3.76 (NCH_3); 2.24 (3-CH_3); 7.12 (5-H). IR spectrum (carbon tetrachloride, ν, cm^{-1}): 2125, ($C{\equiv}C$), 3325 ($HC{\equiv}C$).

4-Ethynyl-1,5-dimethylpyrazole (Vc). The reaction of 10 g of (Ic) [10] with 18.2 g of phosphorus pentachloride in 80 ml of benzene was realized at 40-60°C for 5 h. The reaction mass was treated as described above. A 9.2-g yield of the mixture of chlorides was isolated by distillation; bp 110-130°C (6 mm Hg). According to PMR and GLC data, it contained 6.6 g (58.2%) of (IIc) [PMR spectrum, δ, ppm: 5.23 and 5.27 ($CH_2{=}CCl$); 3.68 (NCH_3); 2.27 (5-CH_3); 7.44 (3-H)] and 2.6 g (18.7%) of (Ivc). The obtained mixture of compounds (IIc) and (IVc) was dehydrochlorinated with sodium amide (from 10 g of sodium) in 1 liter of ammonia. Compound (Vc) was separated from the accompanying compounds by chromatography on aluminum oxide (V activity) in a 2 :1 mixture of ether and petroleum ether. The yield was 3.5 g [69% on (IIc)]; mp 63-63.5°C (from petroleum ether). Found %: N 23.21. $C_7H_8N_2$. Calculated %: N 23.31. PMR spectrum (chloroform, δ, ppm): 3.10 ($HC{\equiv}C$); 3.74 (NCH_3); 2.32 (5-CH_3); 7.48 (3-H). IR spectrum (carbon tetrachloride, ν, cm^{-1}): 2123 ($C{\equiv}C$); 3323 ($HC{\equiv}C$).

4-Ethynyl-1,3,5-trimethylpyrazole (Vd) was obtained similarly [11].

4-α,β-Dichlorovinyl-1,3-dimethylpyrazole (IVb). A mixture of 30 g of compound (Ib) and 95.5 g of phosphorus pentachloride in 240 ml of benzene was stirred at 40°C until the vigorous reaction had ceased and then at 60°C for 6.5 h. After the usual treatment 21.5 g (51.8%) of compound (IVb) was isolated by distillation (Table 1).

The dichlorides (IVc,d) and trichlorides (IVe) and (VIIb,c) were prepared by a similar method (Table 1). In the preparation of compounds (VIIb,c) and (IVe) 3.2 and 4.6 moles, respectively, of phosphorus pentachloride were used for 1 mole of compound (I). The reaction was carried out at 80°C.

α,β-Dichlorovinylbenzene (IVf). a. To a stirred solution of 100 g of ω-chloroacetophenone in 500 ml of benzene at 20°C we added 162 g of phosphorus pentachloride in two portions. The temperature was gradually raised to 60°C, and the reaction mass was kept at this temperature for 4 h. On cooling, it was poured into a mixture of chloroform, saturated sodium bicarbonate solution, and ice. The organic layer was dried with potassium carbonate and submitted to fractional distillation. The fractions (43.5 g) boiling at 85-88°C (1 mm Hg), n_D^{20} 1.5855, consisted of the practically pure compound (IVf). PMR spectrum (δ, ppm): 6.26 ($CHCl{=}C\langle$), 6.9-7.3 m (C_6H_5). The predistillate (7.8 g, bp 80-85°C/1 mm Hg, n_D^{20} 1.5730) contained in addition to (IVf) compounds (IIf) and (IIIf), which were identified by GLC by comparison with the mixture of chlorides obtained by the action of phosphorus pentachloride on the acetophenone (If) (1.3 mole/mole) at 60°C. The fractions (38.5 g) boiling at 88-95°C (1 mm Hg) (n_D^{20} 1.5660-1.5760) represented a mixture of mainly three compounds, i.e., (VIf), α,α,β-trichloroethylbenzene, and possibly α,α,β-trichlorovinylbenzene.

TABLE 2. Substituted Chloroacetylenes (VI)

Compound	Yield, %[*]	mp, °C (from petroleum ether)	Empirical formula	Cl found/calculated, %	PMR spectrum (CCl_4, δ, ppm)	$\nu_{C\equiv C}$, cm^{-1}
(VIb)	85,8 (b)	32—33	$C_7H_7ClN_2$	$\frac{23,07}{22,94}$	3,70 (NCH_3); 2,20 (3-CH_3); 7,28 (5-H)	2230
(VIc)	89,4 (a)	n_D^{20} 1,5513[†]	$C_7H_7ClN_2$	$\frac{22,91}{22,94}$	3,59 (NCH_3); 2,17 (5-CH_3); 7,25 (3-H)	2217
(VId)	89,7 (a) 88,2 (b)	83—84	$C_8H_9ClN_2$	$\frac{21,02}{21,03}$	3,54 (NCH_3); 2,10 and 2,17 (3- and 5-CH_3)	2230
(VIf)	79,0 (a) 58,5 (b)	bp 68—70° (12 mm) n_D^{20} 1,5775 [12]	C_8H_5Cl	—	6,8–7,3 м (C_6H_5)	2230

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[*] The method of preparation is given in parentheses.

[†] Purified by chromatography on aluminum oxide (V activity) in a 2 :1 mixture of ether and petroleum ether.

b. From 7.2 g of (If) and 30.2 g of phosphorus pentachloride in 200 ml of benzene at 80°C (10 h) we obtained 8.3 g of a product consisting predominantly of (IVf) and α,α,β-trichloroethylbenzene.

4-β-Chloroethynyl-1,3,5-trimethylpyrazole (VId). a. A 6.1-g sample of compound (IVd) in 150 ml of ether was added to sodium amide (from 1 g of sodium) in 300 ml of ammonia and stirred for 0.5 h. The compound (VId), isolated in the usual way, was sublimed at 70–80°C (1 mm Hg). The yield was 4.5 g (89.7%). Its constants are given in Table 2.

b. An 8.4-g sample of compound (IVd) in 10 ml of benzene was gradually added to a solution of 3.6 g of potassium hydroxide in 12 ml of ethanol, stirred at 80°C for 4 h, and poured into a mixture of ether and ice. The organic layer was removed, the aqueous layer was extracted with chloroform, and the combined solution of the product was dried with potassium carbonate. After sublimation 6.1 g (88.2%) of compound (VId) was obtained. The chloroacetylenes (VIb, c, f) were synthesized the same way (Table 2).

4-β-Chloroethynyl-5-chloromethyl-1,3-dimethylpyrazole (VIe). Compound (VIe) was obtained from 9.5 g of the unpurified compound (IVe) and sodium amide (from 1.1 g of sodium) as described for (VId). Yield was 2.5 g (37.3%); mp 81-82°C (from petroleum ether). Found %: C 47.12; H 3.84; Cl 34.79. $C_8H_8Cl_2N_2$. Calculated %: C 47.31; H 3.97; Cl 34.92. PMR spectrum (carbon tetrachloride, δ, ppm): 3.88 (NCH_3); 4.63 (CH_2Cl; in chloroform 4.63, benzene 4.00); 2.21 (3-CH_3; in chloroform 2.30, benzene 2.18). IR spectrum (carbon tetrachloride, ν, cm^{-1}): 2230 ($C\equiv C$).

CONCLUSIONS

1. Depending on the conditions, the reaction of methyl aryl ketones with phosphorus pentachloride leads to products from substitution of the carbonyl oxygen by chlorine, α,β-dichlorovinylarenes, or compounds with higher degrees of chlorination.

2. By eliminating a molecule of hydrogen chloride under the influence of an equimolar amount of sodium amide in ammonia, substituted α,β-dichloroethylenes give high yields of the respective 1-chloroacetylenes.

3. The synthesis of a series of ethynyl- and β-chloroethynylpyrazoles from methylpyrazolyl ketones was realized.

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REACTIONS OF SOME HALOACETYLENES WITH SODIUM AMIDE

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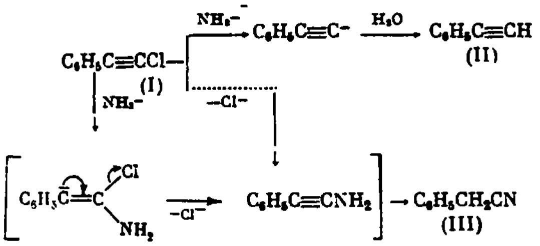
Substituted chloroacetylenes are formed with high yields in the reaction of 1-aryl(heteroaryl)-1,2-dichloroethylenes with an equimolar amount of $NaNH_2$ in ammonia [1]. With an excess of the base the chloroacetylenes as a rule undergo further transformations. In this connection we investigated the reaction of $NaNH_2$ with certain chloroacetylenes, which were obtained earlier from vicinal dichloroethylenes.

In reaction with sodium amide in ammonia phenylchloroacetylene (I) exchanges the halogen atom by the metal to the extent of ≥60%, and this can be interpreted as nucleophilic substitution of the phenylacetylene residue at the "positivized" halogen by an amino group [2]. At the same time, phenylacetonitrile (III) is formed with a yield of 16% as a result of the competing nucleophilic substitution of the chlorine at the sp-carbon atom:



In 4-chloroethynyl-1,3,5-trimethylpyrazole (IVa), in contrast to (I), the halogen is substituted almost exclusively by an amino group, and exchange of chlorine for sodium only takes place to a small degree. The reaction product, obtained with a yield of 80%, is an isomer of the expected pyrazolylacetonitrile and has the composition $C_8H_{11}N_3$. In its PMR spectrum (Fig. 1), together with the signals for the CH_3 group at the nitrogen (3.79 ppm) and one CH_3 group at the ring carbon (2.26 ppm), there are signals at 3.22, 3.90, and 1.45 ppm, corresponding to one, two, and two protons in intensity. They must clearly be assigned to the acetylene proton, the CH_2 group formed during substitution of a hydrogen atom in one of the C-methyls of the initial compound (IVa), and the amino group which has substituted this hydrogen. The presence of the amino group and the ethynyl group in the obtained compound is also confirmed by the IR spectrum. The chemical shift of the protons of the C-methyl group changes much less than the shift of the protons of the methylene group in the transition from a nonpolar to an aromatic solvent (Fig. 1). Since the shift induced by benzene on account of the solvent ($\delta_{CDCl_3} - \delta_{C_6H_6}$) is a quantity in the order of 0.5 ppm for $5\text{-}CH_3$ in substituted pyrazoles and 0.1 ppm for $3\text{-}CH_3$ [3, 5], the aminomethyl group in the obtained compound is at position 5 of the hetero ring, and

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