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A NEW REARRANGEMENT OF CHLOROETHYNYLPYRAZOLES

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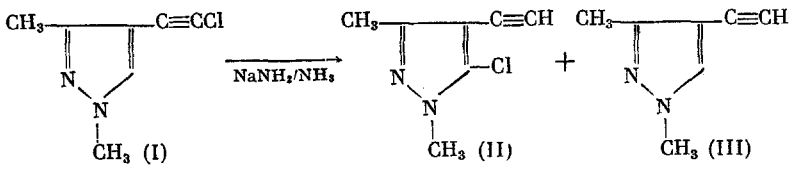
UDC 542.952.1:547.771

4-(Chloroethynyl)-N-methylpyrazoles containing a CH_3 group in position 5 react with $NaNH_2$ in liquid NH_3 to form the [5-(aminomethyl)pyrazolyl]acetylenes [1, 2]. Chloroethynylpyrazoles lacking the 5-methyl substituent, such as 4-(chloroethynyl)-1,3-dimethylpyrazole (I), under these conditions might be assumed mainly susceptible to halogen–metal exchange, like phenylchloroacetylene [2]. On the contrary we have found that chloroacetylene (I) in the presence of $NaNH_2$ isomerizes to 4-ethynyl-5-chloro-1,3-dimethylpyrazole (II) in 80% yield.* The reaction is accompanied by dehalogenation of 10% of chloride (I) to 4-ethynyl-1,3-dimethylpyrazole (III).



*Preliminary communication [3].

Institute of Chemical Kinetics and Combustion, Siberian Branch of the Academy of Sciences of the USSR, Novosibirsk. Translated from Izvestiya Akademiya Nauk SSSR, Seriya Khimicheskaya, No. 10, pp. 2306-2310, October, 1977. Original article submitted July 13, 1976.

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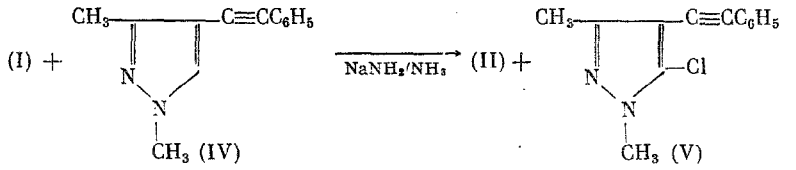
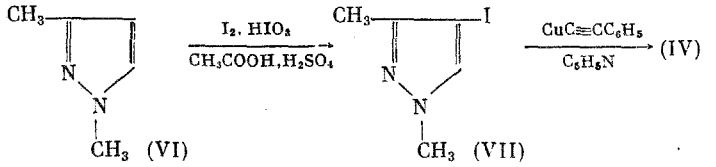
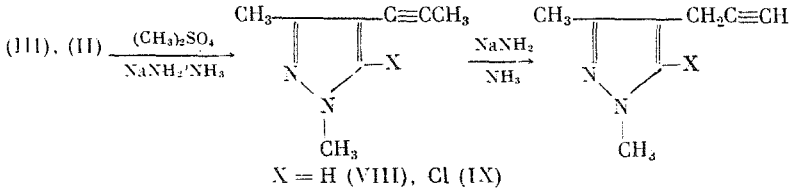
To ascertain whether chlorine migration is intramolecular or intermolecular, we examined the rearrangement of (I) in the presence of 4-(phenylethynyl)-1,3-dimethylpyrazole (IV) (molar ratio of (I):(IV) ≈ 2). Here ~40% of the chlorine contained in (I) migrates to position 5 of the heterocycle of the acceptor molecule (IV)



Thus rearrangement (I) is intermolecular. We synthesized pyrazole (IV) by iodination of 1,3-dimethylpyrazole (VI) with a mixture of I_2 and HIO_3 to 4-iodo-1,3-dimethylpyrazole (VII)* followed by condensation of (VII) with copper phenylacetylide (overall yield 74.5%)

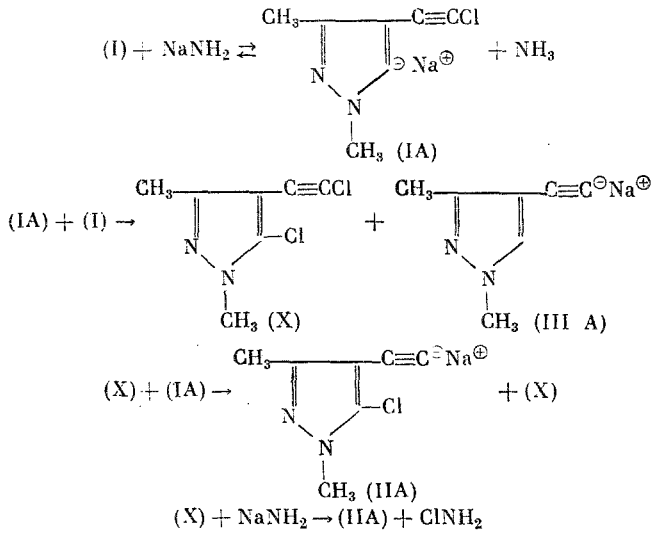


Unfortunately, the simplest structural analog of (I), 4-(1-propynyl)-1,3-dimethylpyrazole (VIII), proved unsuitable as chlorine acceptor and cross-reaction acceptor; its use would have greatly simplified the quantitative determination of the expected chlorinated product (IX) (direct analysis by PMR). Under the rearrangement conditions, $NaNH_2$ in NH_3 easily induces isomerization of (VIII) and (IX), causing triple-bond migration to the terminal position in conformity with the general rule [5] (but compare [6])



Furthermore, we were unable to detect halogen exchange in the rearrangement between (I) and 1,3-dimethylpyrazole (VI). The reactivity of (I) and (IV) as chlorine acceptors is probably much greater than that of (VI) because of the effect of the acetylenic groups in position 4.

This isomerization is undoubtedly related to the base-induced halogen migration in aromatic rings known in the halobenzenes as the halogen dance [7]. We can represent the isomerization mechanism as

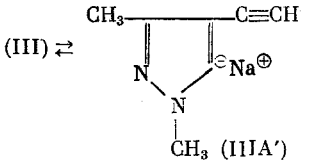


*Compound (VII) was erroneously assigned the structure of 4-iodo-1,5-dimethylpyrazole in [4]. We prepared the latter in 93% yield in the same way as (VII), by oxidative iodination of 1,5-dimethylpyrazole.

The key intermediate in this scheme is 4-(chloroethynyl)-5-chloro-1,3-dimethylpyrazole (X), which is generated by nucleophilic attack by pyrazolyl anion (IA) on the positive halogen atom of the original chloroacetylene (I). Compound (X), by reacting with anion (IA), exchanges halogen from the side chain for metal to form the final reaction product as acetylide (IIA). Since halogenation of (IA) simultaneously regenerates (X), the rearrangement is a chain reaction in which the reaction of (X) with (IA) represents chain propagation. Chain termination occurs in the reaction of (X) with $NaNH_2$.

Several considerations support this mechanism. When the reaction is carried out in the presence of (X) (8 mole %) containing a ^{36}Cl radiolabel in the acetylenic group, the major fraction of the ^{36}Cl (84%) is incorporated in the final ethynylchloropyrazole (II). Since a small fraction of the ^{36}Cl is inevitably lost in the dechlorination of (X) by $NaNH_2$, especially when it is added in its entirety in the initial period of the reaction, this result indubitably confirms the intermediacy of (X) in the rearrangement.

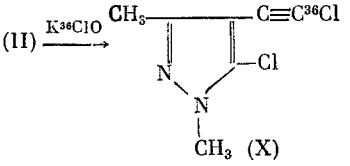
Another pathway is theoretically possible for the conversion of intermediate (X) to ethynylchloropyrazole (II), apart from that shown in the scheme, namely the intermolecular migration of chlorine from (X) to (IIIA). This must obviously consist of several elementary steps, such as the isomerization of acetylide anion (IIIA) to pyrazolyl anion (IIIA') and the nucleophilic substitution of one acetylenic moiety in (X) by the chlorine of another molecule (or moiety)



$$(X) + (IIIA') + NaNH_2 \rightarrow 2\,(IIA) + NH_3$$

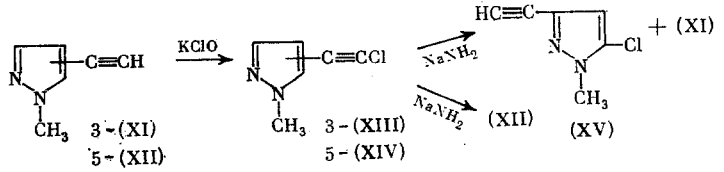
We cannot a priori exclude this version of the mechanism, the more so as the equivalent reactions involving formation and subsequent halogenation of dehalogenated products are actually significant in halogen migration in heterocycles [8]. However, a direct experiment revealed that there is almost no exchange of chlorine between (X) and pyrazolylacetylide (IIIA) in the presence of $NaNH_2$ in NH_3. The resulting (II) incorporates only 1.2% of the ^{36}Cl contained in (X) and consequently almost exclusive dechlorination of (X) by $NaNH_2$ prevails. Thus, halogenation of (IIIA) is of no importance in the isomerization of (I), which involves the chain mechanism.

We synthesized the labeled compound (X) by chlorination of 4-ethynyl-5-chloro-1,3-dimethylpyrazole (II) with $K^{36}ClO$ in aqueous KOH



Compound (X) can also be prepared by reaction of acetylide (IIA) with p-toluenesulfonyl chloride in ether.

To examine the reaction of $NaNH_2$ with pyrazolylchloroacetylenes containing the chloroethynylgroup in other positions in the ring, we synthesized compounds (XIII) and (XIV) by chlorination of 3-ethynyl-1-methylpyrazole (XI) and 5-ethynyl-1-methylpyrazole (XII) with KClO in ~100% yield. Rearrangement of (3-pyrazolyl)chloroacetylene (XIII) gives 3-ethynyl-5-chloro-1-methylpyrazole (XV) in ~70% yield; (XI) is simultaneously formed in 25% yield. When the chloroethynyl group is in position 5 of the starting pyrazole, halogen migration is completely suppressed by halogen-metal exchange. The concentrations of 3-pyrazolyl and 4-pyrazolyl anions are probably small, and they cannot compete with NH_2 anions for chlorine bonded to the acetylenic carbon.



EXPERIMENTAL

3-(Chloroethynyl)-1-methylpyrazole (XIII). Compound (XI) [9] (2 g) in 0.64 N KClO solution (145 ml) in 12.5% KOH was stirred at 20°C for 5 h. The product was extracted with ether and dried over K_2CO_3. Removal of the solvent gave (XIII) (2.6 g, 98%), n_D^{20} 1.5457. Found: C 51.28; H 3.64; Cl 25.18%. $C_6H_5ClN_2$. Calculated: C 51.25; H 3.59; Cl 25.22%. PMR spectrum (CCl_4, δ, ppm): 3.76 (NCH_3); 6.19 d (4-H); 7.16 d (5-H). IR spectrum (CCl_4, ν, cm^{-1}): 2230, 2240 (C≡C).

Similarly (XII) [9] gave 5-(chloroethynyl)-1-methylpyrazole (XIV), yield 94.8%, n_D^{20} 1.5510. Found: C 51.12; H 3.77; Cl 25.13%. $C_6H_5ClN_2$. Calculated: C 51.25; H 3.59; Cl 25.22%. PMR spectrum (CCl_4, δ, ppm): 3.87 (NCH_3); 6.35 d (4-H); 7.30 d (3-H). IR spectrum (CCl_4, ν, cm^{-1}): 2230 (C≡C).

Rearrangement of 4-(Chloroethynyl)-1,3-dimethylpyrazole (I). To $NaNH_2$ (from 4.8 g Na) in NH_3 (250 ml) was rapidly added an ethereal solution of (I) [10] (4.6 g); the reaction mixture was stirred for 0.5 h and then diluted with ether. After evaporation of NH_3, excess $NaNH_2$ was destroyed with water. The ethereal solution was dried over K_2CO_3 and the solvent was evaporated. The residue was sublimed at 50°C (1 mm) and chromatographed on Al_2O_3 (activity V) with ether–petroleum ether (2:1). We obtained (III) (0.3 g, 8.4%), mp 34.5-35.5°C (from petroleum ether) [10] and 4-ethynyl-5-chloro-1,3-dimethylpyrazole (II) (3.7 g, 80.5%), mp 51.5-52°C (from petroleum ether). Found: C 54.27; H 4.45; Cl 22.65%. $C_7H_7ClN_2$. Calculated: C 54.38; H 4.56; Cl 22.93%. PMR spectrum (CCl_4, δ, ppm): 3.16 (HC≡C); 3.73 (NCH_3); 2.22 ($3-CH_3$). IR spectrum (CCl_4, ν, cm^{-1}): 3328 (CH≡C), 2128 (C≡C).

Similarly (XIII) gave (XI) (26.5%) and 3-ethynyl-5-chloro-1-methylpyrazole (XV) (67.8%), mp 71-72°C. Found: C 51.25; H 3.56; Cl 25.29%. $C_6H_5ClN_2$. Calculated: C 51.25; H 3.59; Cl 25.22%. PMR spectrum (CCl_4, δ, ppm): 2.86 (HC≡C); 3.74 (NCH_3); 6.18 (4-H). IR spectrum (CCl_4, ν, cm^{-1}): 3323 (HC≡C), 2135 (C≡C). Under the same conditions (XIV) formed only 5-ethynyl-1-methylpyrazole (XII) in 76% yield.

Methylation of Ethynylpyrazoles (III) and (II). To $NaNH_2$ (from 0.6 g Na) in NH_3 (150 ml) was added (III) (2.5 g) in absolute ether (12 ml); the mixture was stirred for 0.5 h, whereupon $(CH_3)_2SO_4$ (3.8 g) in ether (10 ml) was slowly added and stirring was continued for a further 3 h. The reaction mixture was diluted with ether (200 ml) containing water (~10 ml) and NH_3 was evaporated. After removal of solvent from the ethereal solution containing the product, the residue was taken up in alcohol (5 ml) and treated with Ag_2O in aqueous ammonia. The resulting acetylide was separated and washed with water and ether; the filtrate was extracted with ether. The combined extract was dried over K_2CO_3. The yield of 4-(1-propynyl)-1,3-dimethylpyrazole (VIII) was 2.0 g (71.5%), mp 26-27°C (from petroleum ether). Found: N 20.84%. $C_8H_{10}N_2$. Calculated: N 21.03%. IR spectrum (CCl_4, ν, cm^{-1}): 2253 (C≡C).

4-(1-Propynyl)-5-chloro-1,3-dimethylpyrazole (IX) was prepared similarly from (II). The contaminating terminal acetylene was precipitated as the copper acetylide; the yield of (IX) was 75.8%, mp 57-57.5°C (from petroleum ether). Found: Cl 20.98%. $C_8H_9ClN_2$. Calculated: Cl 21.03%. IR spectrum (CCl_4, ν, cm^{-1}): 2252 (C≡C).

Compound (VIII) when stirred in NH_3 with a sevenfold excess of $NaNH_2$ was almost completely isomerized after 20-30 min to 4-(2-propynyl)-1,3-dimethylpyrazole (as shown by chromatography and IR spectra). PMR spectrum (CCl_4, δ, ppm): 1.97 t (HC≡C); 3.24 d (CH_2); 3.70 (NCH_3); 2.12 ($3-CH_3$); 7.12 (5-H).

4-Iodo-1,3-dimethylpyrazole (VII). Compound (VI) [11] (9.6 g), I_2 (10.2 g), and HIO_3 (3.5 g) in a mixture of AcOH (60 ml), water (15 ml), concentrated H_2SO_4 (3 ml), and CCl_4 (3 ml) was heated at 75-80°C for 30 min. After addition of $CHCl_3$ the reaction mixture was cooled while it was neutralized with aqueous NaOH. The chloroform extract was dried over K_2CO_3 and distilled. The yield of (VII) was 21.4 g (96.2%), bp 107-108°C (12 mm), n_D^{20} 1.5670 [4].

Similarly 1,5-dimethylpyrazole [11] gave 4-iodo-1,5-dimethylpyrazole, yield 93.3%, mp 113-113.5°C (from CCl_4) [4].

4-(Phenylethynyl)-1,3-dimethylpyrazole (IV). Compound (VII) (10.6 g) and copper phenylacetylide (8.6 g) in absolute pyridine (120 ml) were heated in an atmosphere of N_2 for 18 h. After dilution with ether (500 ml) the precipitated CuI was separated and ether and pyridine were removed. The residue in ether was filtered through a layer of anhydrous Al_2O_3. The product was taken up in a small quantity of ether and deposited on Al_2O_3 and chromatographed;

the impurity was eluted with petroleum ether and (IV) with ether. The yield of (IV) was 7.3 g (78%), mp 57-57.5°C (from petroleum ether). Found: N 14.11%. $C_{13}H_{12}N_2$ Calculated: N 14.28%. PMR spectrum (CCl_4, δ, ppm): 3.60 (NCH_3); 2.22 (3-CH_3); 7.19 (5-H); 7.0-7.4 m (C_6H_5). IR spectrum (CCl_4, ν, cm^{-1}): 2227 (C≡C).

Interaction of Pyrazoles (I) and (IV) in the Presence of $NaNH_2$. The reaction of (I) (2.1 g) with $NaNH_2$ (from 2.2 g Na) in NH_3 (200 ml) was carried out in the presence of (IV) (1.4 g) over 15 min and the reaction mixture was treated in the usual way. The residue after removal of ether was dissolved in alcohol (5 ml) and Ag_2O in aqueous ammonia (from 2.7 g $AgNO_3$) was added. The precipitated acetylide was filtered off and the filtrate was extracted with ether. The products contained in the extract were separated by preparative TLC on Al_2O_3 (activity V) with ether–petroleum ether (1:1). We obtained (IV) (0.2 g, 14.3%) and 4-(phenylethynyl)-5-chloro-1,3-dimethylpyrazole (V) [1.2 g, 72.7% based on (IV)], bp 135-136°C (1 mm), n_D^{20} 1.6160. Found: C 67.80; H 4.87; Cl 15.42%. $C_{13}H_{11}ClN_2$. Calculated: C 67.68; H 4.81; Cl 15.37%. PMR spectrum (CCl_4, δ, ppm): 3.65 (NCH_3); 2.22 (3-CH_3); 7.1-7.5 m (C_6H_5). IR spectrum (CCl_4, ν, cm^{-1}): 2230 (C≡C). The precipitated acetylides were dissolved in saturated $Na_2S_2O_3$ solution and extracted with ether. We obtained a mixture (1.7 g) of 4-ethynyl-5-chloro-1,3-dimethylpyrazole (II) (~1 g, 47.7%) and 4-ethynyl-1,3-dimethylpyrazole (III) (~0.7 g, 42.9%).

Rearrangement of (I) (1 g) in the presence of (IV) (1.2 g) and $NaNH_2$ (from 1.1 g Na) gave (II) (0.7 g, 70%). We did not detect any chlorinated dimethylpyrazole in the reaction products.

4-(Chloroethynyl)-5-chloro-1,3-dimethylpyrazole (X). a) To a suspension of the Na salt prepared from (II) (3.4 g) and $NaNH_2$ (from 1 g Na) in ether (40 ml) was added over 1 h an ethereal solution (50 ml) of p-toluenesulfonyl chloride (8.4 g). The reaction mixture was refluxed for 3.5 h, whereupon the precipitate was filtered off and the solvent was removed. Chromatography of the residue (5.1 g) on Al_2O_3 with petroleum ether–ether (1.2:1) gave (X) (2.3 g, 55.3%), mp 56.5-57°C. Found: C 44.26; H 3.32; Cl 37.49%. $C_7H_6Cl_2N_2$. Calculated: C 44.47; H 3.20; Cl 37.51%. PMR spectrum (CCl_4, δ, ppm): 3.63 (NCH_3); 2.17 (3-CH_3). IR spectrum (CCl_4, ν, cm^{-1}): 2237 (C≡C).

b) Compound (II) (0.60 g) and 0.64 N KClO (30 ml) in 12.5% KOH at 20°C after 30 h in the same way as (XIII) gave (X) (0.64 g, 87.2%).

Transformation of Dichloride (X) under the Conditions of Rearrangement of (I). a) Compound (I) (1 g) was subjected to rearrangement as described above, but in the presence of 4-(β-chloroethynyl)-5-chloro-1,3-dimethylpyrazole-4β-^{36}Cl (X) (0.10 g) with total activity 4283 counts/sec. Preparative TLC gave 4-ethynyl-5-chloro-1,3-dimethylpyrazole-^{36}Cl (II) (0.81 g, 75%) with activity 3614 counts/sec.

b) To $NaNH_2$ (from 0.43 g Na) in NH_3 (120 ml) was rapidly added an ethereal solution of labeled (X) (0.40 g) (17133 counts/sec) and (III) (0.32 g); after 15 min stirring, NH_4Cl (2 g) was added and NH_3 was removed. Preparative TLC on silica gel with ether–$CHCl_3$ (2:1) gave (II) (0.32 g) with activity 199 counts/sec and (III) (0.32 g).

We thank V. V. Moralev for assistance with this work.

CONCLUSIONS

1. Isomerization of 4- and 3-(chloroethynyl)-N-alkylpyrazoles to [5-chloro-N-alkylpyrazolyl]acetylenes is induced by $NaNH_2$ in NH_3.

2. In 5-(chloroethynyl)-N-methylpyrazole under these conditions halogen is exchanged for metal (sodium).

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REACTION OF NITRO COMPOUNDS WITH IMINIUM SALTS.

1. NITROVINYLATION OF INDOLES

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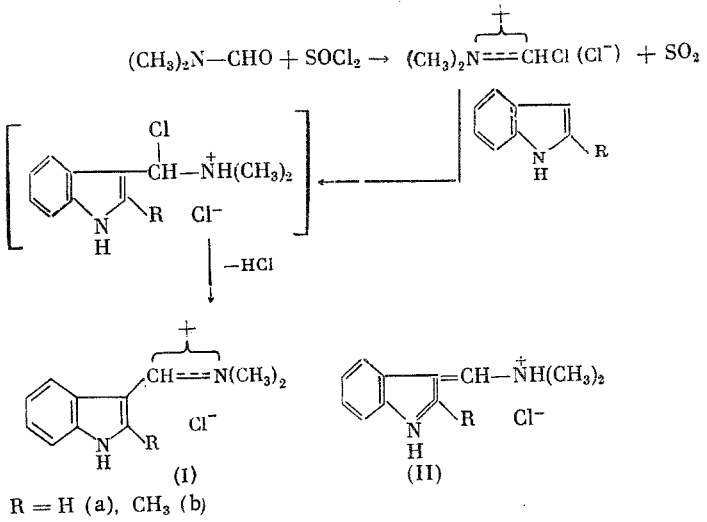
The formation of iminium salts in the protonation of enamines makes possible nucleophilic addition to the α-carbon atom of these compounds, which is widely used for the reduction of enamines with complex metal hydrides and for reactions with Grignard reagents, alcohols, amines, and cyanide and thiophenoxide ions [1]; the protonation of enamines is also closely related to their hydrolysis [2].

Here we report a study of the reaction of iminium salts with aliphatic nitro compounds (nitroalkanes, methyl nitroacetate) as a possible method for the synthesis of conjugated α,β-unsaturated nitro compounds in the indole series. Our chosen model compound was the stable iminium salt — (3-indolyl)methylenedimethyliminium chloride (I), prepared by the Vilsmeier—Haack reaction from indole, $SOCl_2$, and DMF



Contrary to Smith's results [3] this reaction takes place at ~20°C with ~100% yield of (I). The spectral parameters indicate the iminium structure of the synthetic compound.

The inequivalence of the CH_3 groups, shown by the presence of two signals of the $(CH_3)_2N$ protons in the PMR spectrum, which persists even at 150°C, and the intense UV absorption in the 340 nm region [4] are fully consistent with the thermodynamically favored [2] iminium rather than the enammonium (II) structure for salt (I). The compounds derived from 2-methyl- and 2,5-dimethylindole also have such structures.

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