NUCLEOPHILIC REPLACEMENT OF BROMINE IN 1-BROMO-1-ALKOXYMETHYLALLENE COMPOUNDS BY AMINES

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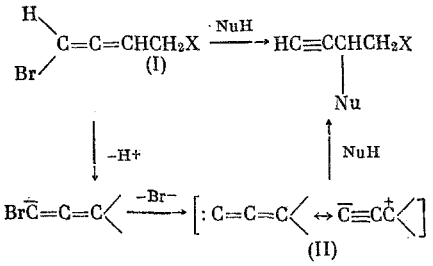
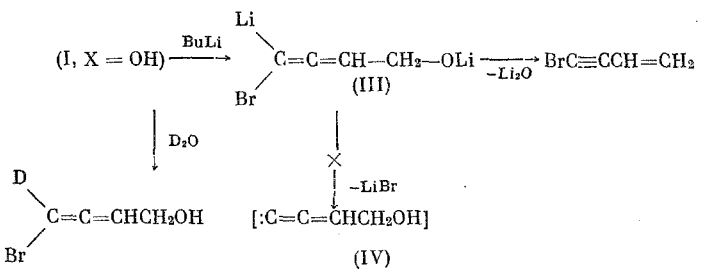
Previously it was found [1, 2] that bromoallenes of the (I) type react with various neutral and ionic nucleophilic reagents to give difunctional derivatives of the acetylene series.

In principle, substitution at the vinyl center can proceed by several mechanisms [3, 4]. In our case the scheme given in [4] seemed to be most probable, which includes the formation of the bipolar carbene intermediate (II)



X=OH, NRR¹, SAc; Nu = NHR, NRR¹, SAc

Previously it was shown [5] that substituted bromoallenes (I) actually undergo direct isotope exchange at the bromoallenyl grouping. However, when the generation of the carbene was attempted under the conditions of its probable formation, i.e., via the H-metalation of 1-bromo-1,2-butadien-4-ol (I, X = OH) by treatment with BuLi, we were unable to record the formation of hydroxymethylvinylidenecarbene (IV); the reaction unexpectedly led to the stabilization of the postulated lithium organobromo derivative (III) to the neutral bromovinylacetylene [6], evidently via the cleavage of Li_2O. If BuLi fails to cause the α,α-cleavage of HHal, then it is even less probable that it can occur by treatment with weaker bases like amines, which even at high temperature are incapable of cleaving HHal from nonactivated vinyl halides. Consequently, the formation of a type (II) "carbene" by treatment with amines cannot be assumed in order to explain the replacement of bromine in allenyl halides.



As a continuation of these studies, and in particular to ascertain the effect of a substituent attached to the haloallenyl grouping, we studied the replacement of bromine by amines in the series of aliphatic

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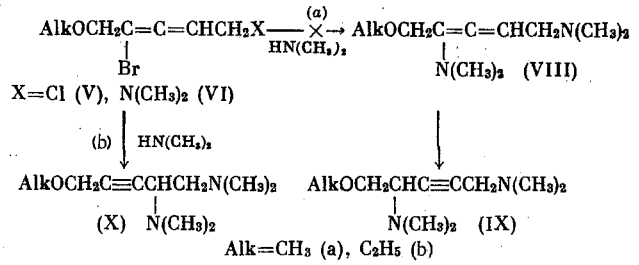
bromoallenes (V)-(VII), which lack an α-H atom. The alkoxy-substituted bromoallenes (V)-(VII) were obtained previously [7] from the condensation products of chloromethyl alkyl ethers with bromovinylacetylene.

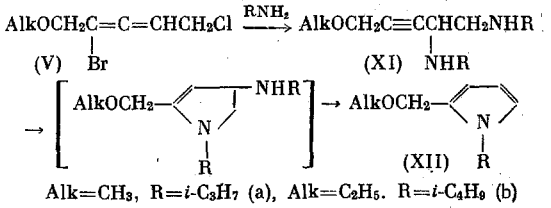
The same acetylenic diamines are formed in 33-50% yield when either (V) or (VI) is heated with excess Me_2NH in CH_3CN at 40°C for 10-15 h. This indicates that the reaction can proceed as replacement of the bromine, with simultaneous allene–acetylene rearrangement.

The process can be depicted as: a) attack by the nucleophilic reagent on the carbon bearing the bromine atom (C_1), which leads to allenyldiamine (VIII), which then undergoes prototropic rearrangement to the corresponding 1,4-diamine (IX), or b) S_N1 (or S_N2') attack on the C_3 carbon of the allene system, which immediately leads to the 1,2-diaminoacetylene (X)

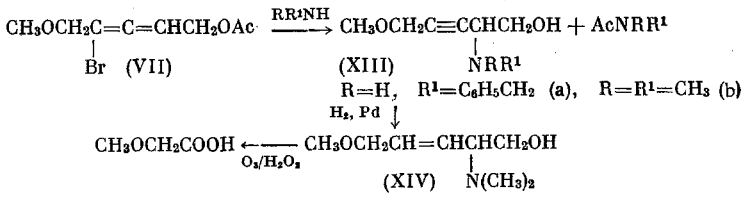


The structure of the obtained diamines as being compounds of the (X) type ensues from the following data. Their IR spectrum contains a weak band at 2210 cm^{-1}, which is characteristic for a disubstituted triple bond. The NMR spectrum of these compounds has signals at δ 2.37 (2H, d, J = 7 Hz, CH_2N), 3.36 (1H, m, ≡CCHN), and 4.0 ppm (2H, d, J = 2 Hz, ≡CCH_2O). The chemical shift and the character of the splitting indicate the presence of the $OCH_2C{\equiv}CCH(N)CH_2N$ grouping. All of this is in full agreement with the structure of 1,2-bis(dimethylamino)-5-alkoxy-3-pentyne (X) and excludes structure (IX).

Their conversion to pyrroles serves as convincing proof of the structure of the diamines and as additional confirmation of the fact that the reaction proceeds by path b). If a mixture of the allene halide (V) and a primary amine is heated in CH_3CN at 120° for 10-20 h then pyrroles of the (XII) type are formed, the structure of which unequivocally follows from their NMR spectra (group of signals in the 5.6-6.5 ppm region, which are characteristic for the protons of a pyrrole ring). The formation of pyrroles of such structure is possible only by the intramolecular cyclization of the intermediately formed acetylenic diamine (XI), which, in turn, can arise only as the result of initial progress of a reaction of the b) type. Similar intramolecular cyclizations of acetylenic diamines with a monosubstituted triple bond, as was shown previously [8], leads to alkylpyrroles



The bromoallenic acetate (VII), when reacted with Me_2NH or benzylamine, behaves in the same manner as (V) and (VI). The reaction is accompanied by saponification of the acetate group and leads to the corresponding acetylenic amino alcohols of the (XIII) type



Since the structure of the formed amino alcohol cannot be proved on the basis of the data of the NMR spectra (the signals of the protons of the $\equiv CCH(N)CH_2O$ grouping proved to be equivalent) the chemical route was used to confirm its structure. Amino alcohol (XIIIb) was selectively hydrogenated over Lindlar catalyst to the ethylene derivative (XIV), the cleavage of which with ozone in the presence of H_2O_2 gave the known methoxyacetic acid (60% yield). These results confirm the fact that the acetylenic amino alcohols, formed from (VII), actually have the structure of (XIII).

As a result, we were the first to obtain data on the ability of nonactivated bromoallene compounds to undergo nucleophilic substitution reactions.

EXPERIMENTAL METHOD

The GLC analyses were run on a "Khrom-31" instrument equipped with a glass column (2 m × 3 mm spiral); the stationary phase was 8% Silicone SE-30 + 2% PEGA deposited on silanized Chromosorb W. The NMR spectra were taken on Varian DA-60-IL and Perkin–Elmer R-12 instruments, using HMDS as the internal standard.

1,2-Bis(dimethylamino)-5-methoxy-3-pentyne (Xa). A mixture of 1.28 g of amine hydrochloride (VIa) and a 5- to 6-fold excess of Me_2NH in 25 ml of CH_3CN was heated in a sealed ampul at 40° for 12 h. The mixture was diluted with water, extracted with ether, and dried over BaO. Distillation gave 0.51 g (55%) of amine (Xa), bp 58-60° (0.4 mm); n_D^{22} 1.4603. NMR spectrum (CCl_4, δ, ppm): 2.12 (s, NMe_2), 2.19 (s, NMe_2), 2.37 (d, J = 7 Hz, CH_2N), 3.23 (s, CH_3O), 3.36 (m, ≡CCHN), 4.0 (d, J = 2 Hz, ≡CCH_2O). Found: C 65.28; H 10.90; N 15.40%. $C_{10}H_{20}ON_2$. Calculated: C 65.21; H 10.86; N 15.21%. Bishydrochloride of the base, mp 155-157° (from DMF). The IR spectrum contains the absorption band of the C≡C bond at 2220 cm^{-1}.

In a similar manner, the same diamine (Xa) was obtained in 32% yield from 2.3 of dihalide (Va) with excess Me_2NH in CH_3CN (40°, 14 h).

1,2-Bis(dimethylamino)-5-ethoxy-3-pentyne (Xb). A solution of 2.4 g of dihalide (Vb) was heated with excess Me_2NH under the same conditions as above for 15 h. Distillation gave 0.61 g (~30%) of diamine (Xb), bp 69-71° (0.4 mm); n_D^{22} 1.4640. Bishydrochloride of the base, mp 151-152° (from absolute alcohol–ether). Infrared spectrum: 2220 cm^{-1} (C≡C). NMR spectrum (CD_3OD, δ, ppm): 1.1 (t, J = 7 Hz, CH_3), 2.93 (s, NMe_2), 3.0 (s, NMe_2), 3.53 (qu, J = 7 Hz, OCH_2), 3.85 (d, J = 7 Hz, CH_2N), 4.27 (d, J = 2 Hz, ≡CCH_2O), 4.83 (2NH), 5.15 (m, ≡CCHN). Found: C 48.45; H 8.78; N 10.45; Cl 26.02%. $C_{11}H_{24}Cl_2N_2O$. Calculated: C 48.71; H 8.85; N 10.33; Cl 26.20%.

N-Isopropyl-2-methoxymethylpyrrole (XIIa). A solution of 2.3 g of dihalide (Va) and excess i-$PrNH_2$ in 20 ml of CH_3CN was heated in a glass ampul at 120° for 16 h. The solution was diluted with 2% HCl solution, and the neutral products were extracted and dried over K_2CO_3. Distillation gave 0.33 g (~22%) of pyrrole (XVIIa), bp 45-48° (1 mm), n_D^{18} 1.4802, which, based on the GLC data, contained 84% of the principal compound. NMR spectrum (CCl_4, δ, ppm): 1.1 (d, J = 7 Hz, 2·CH_3), 3.04 (s, CH_3O). 3.1-3.4 (unresolved m, CHN), 4.14 (s, CH_2O), 5.76 (2H of ring), 6.34 (1H of ring). The acid portion was saturated with K_2CO_3 and extracted with ether. Distillation at 0.06 mm (200°) gave 0.6 g of substance with n_D^{22} 1.4698, which is apparently the acetylenic diamine (XI, R = i-Pr).

N-Isobutyl-2-ethoxymethylpyrrole (XIIb). In a similar manner, a solution of 2.4 g of dihalide (Vb) and excess i-$BuNH_2$ in CH_3CN was kept at 80° for 12 h and then at 120° for 14 h. The mixture was separated into neutral and acid portions. Distillation gave 0.62 g (35%) of the pyrrole, bp 54-56° (1 mm); n_D^{18} 1.4716. Based on the GLC data, the amount of the principal product was 94-96%. NMR spectrum (CCl_4, δ, ppm): 0.82 (d, J = 7 Hz, $2CH_3$), 1.05 (t, J = 7 Hz, CH_3), 1.45 (m, 1H), 3.29 (qu, J = 7 Hz, OCH_2), 3.6 (d, J = 7.5 Hz, CH_2N), 4.26 (s, CH_2O), 5.85 (2H), 6.43 (1H). Found: N 7.42%. $C_{11}H_{19}NO$. Calculated: N 7.73%.

2-N-Benzylamino-5-methoxy-3-pentyn-1-ol (XIIIa). A mixture of 1.2 g of the bromoallenic acetate (VII) (86% pure) and 2.7 g of benzylamine in 20 ml of CH_2CN was kept at 40° for 15 h. The solvent was distilled off, and 110 ml of 2% HCl solution was added to the residue. The acid portion was saturated with K_2CO_3, extracted with ether, and purified by column chromatography on neutral Al_2O_3. We obtained 0.29 g (29%) of amino alcohol (XIIIa) as cottonlike needles with mp 730° (from ether–petroleum ether). NMR spectrum (CCl_4, δ, ppm): 3.25 (s, CH_3O), 2.9-4.1 (masked signals of $OCH_2C{\equiv}CCH(NHCH_2)CH_2OH$ grouping), 7.18 (broad s, C_6H_5). Found: N 6.02%. $C_{13}H_{17}O_2N$. Calculated: N 6.39%.

2-Dimethylamino-5-methoxy-3-pentyn-1-ol (XIIIb). A mixture of 2.1 g of acetate (VII) and excess Me_2NH was kept at 40° for 10 h and then at 70° for 15 h. The reaction products were separated into neutral and acid portions; after saturation with K_2CO_3, extraction and distillation (120°, 0.1 mm), from the acid portion we obtained 0.45 g of amino alcohol (XIIIb) as a mixture with its acetate, n_D^{22} 1.4608-1.4665 (based on the data of the IR and NMR spectra, the amount of the acetate was 38%). The saponification of this mixture with 2% KOH solution and subsequent chromatographing of the residue of Al_2O_3 gave 0.27 g of amino alcohol (XIIIb) as an oil, n_D^{20} 1.4698. NMR spectrum (JNM-4H-100 instrument, 100 MHz, CCl_4, δ,

ppm): 2.26 (NMe_2), 3.04 (OH), 3.28 (s, CH_3O), 3.46 (s, $\equiv CCH(N)CH_2O$, 4.10 (s, $\equiv CCH_2O$). The hydrochloride of the base was obtained as a noncrystallizing oil.

Hydrogenation of Amino Alcohol (XIIIb) and Ozonization of Obtained Product. A solution of 0.4 g of (XIIIb) in 20 ml of ethyl acetate was hydrogenated in the presence of 5% Lindlar Pd catalyst until 1 equiv of H_2 had been absorbed (14 h). From the residue, after removal of the catalyst and solvent, we isolated 0.32 of the vinyl amino alcohol (XIV) as an oil, n_D^{22} 1.4642. Infrared spectrum (ν, cm^{-1}): 1632 (CH=CH). With cooling in an ice–salt mixture, a stream of ozone was passed for 2.5 h (0.4 g of ozone/h) through a solution of 0.3 g of the obtained alcohol (XIV) in 20 ml of absolute $CHCl_3$. The ozonide was decomposed with 3% H_2O_2 solution. Neutral products were not detected when the ozonide was decomposed. Careful vacuum-distillation of the mixture of acids gave us 110 mg (60%) of the low-boiling methoxyacetic acid, which was characterized as the methyl ester (by treatment with CH_2N_2), the IR spectrum and GLC parameters of which proved to be identical with the parameters of the authentic specimen.

CONCLUSIONS

1-Alkoxymethyl-substituted 1-bromoallenes react with primary and secondary amines by the usual scheme of nucleophilic substitution and lead to the formation of polyfunctional acetylenic compounds, which excludes the carbene mechanism of similar reactions.

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