SYNTHESIS OF 1-(ARYLETHYNYL)AZIRIDINES

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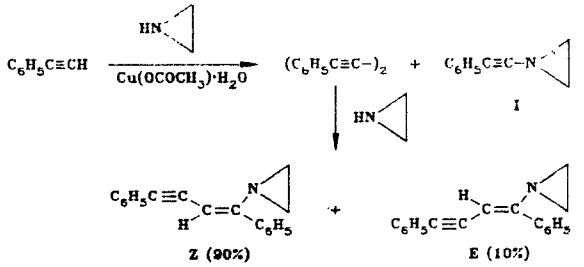
Studies have been made on the possible synthesis of 1-(arylethynyl)aziridines by oxidative condensation of phenylacetylene with aziridine and by alkylation of aziridine with 1-halo-2-arylacetylenes.

Ynaziridinoesters, which were obtained by us for the first time [1], have proved to be very reactive compounds with chemical properties distinct from those of ynamines [2]. The high reactivity of ynaziridinoesters is shown, in particular, in their low thermodynamic stability, as a result of which it is possible to keep them and work successfully with them only in aprotic solvents. The low stability of ynaziridinoesters is evidently due to the presence of a strong acceptor (methoxycarbonylethynyl substituent) on the nitrogen atom of the aziridine ring. The marked electron-withdrawing nature of the methoxycarbonylethynyl substituent is born out, for example, by the lower field resonance absorption from the protons from the aziridine ring in the PMR spectrum of methyl 3-aziridinopropynoate in comparison with methyl trans-3-aziridinoacrylate as a standard (δ 2.29 and 1.96 ppm, respectively). The simultaneous action of a —C effect and a strong —I effect (due to the increased electronegativity of the sp-hybridized carbon atom) from the methoxycarbonylethynyl substituent causes a destabilization of the strained aziridine ring.

The low stability of ynaziridinoesters causes complications when working with them. We therefore carried out an investigation into ways of synthesizing 1-(arylethynyl)aziridines not containing strong electron-withdrawing substituents.

One of the interesting methods for synthesizing such types of ynamines consists of the reaction of phenylacetylene with secondary amines in the presence of oxygen and copper acetate as for the oxidative dimerization of acetylenes [3]. We have studied this reaction using aziridine as the secondary amine. It has been established that the nature of the solvent has little effect on the ratio of reaction products (Table 1). The most favorable result [20% 1-(phenylethynyl)aziridine in a mixture with diphenyldiacetylene] was achieved when the reaction was carried out in THF in the presence of 20% copper acetate. Pure 1-(phenylethynyl)aziridine was isolated from the reaction mixture by means of high-performance liquid chromatography (HPLC). In contrast to ynamines, which very readily pick up water to form phenylacetamides, ynaziridine I obtained proved to be a stable compound which was not susceptible to hydration.

For a longer reaction time (48 h) without solvent in excess aziridine, isomeric products of the addition of aziridine to diphenyldiacetylene are formed together with the ynaziridine:



The predominance of the Z-isomer in the mixture is an indication of the stereoselective trans-addition of aziridine to the triple bond of diphenyldiacetylene [4].

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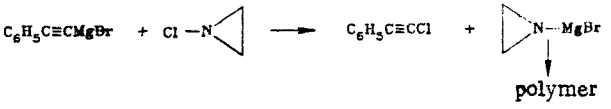
TABLE 1. Ratio of Reaction Products in Different Solvents

Solvent	Content, %*		Solvent	Content, %*	
	I	1,4-Diphenyl-butadiyne		I	1,4-Diphenyl-butadiyne
Ethanol	2	98	THF	20	80
Acetonitrile	5	95	Benzene	16	84
Pyridine	3	97	Hexane	4	96

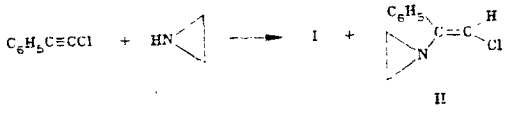
*Content of products in reaction mixture was determined by GLC.

According to the information in [5] the formation of ynamines is possible as a result of the exchange interaction of Iotsich complexes with halogens. Using phenylethynylmagnesium bromide and 1-chloroaziridine as an example, we established that the reaction proceeds with the formation of 1-chloro-2-phenylacetylene and cannot be used in the synthesis of ynaziridines:



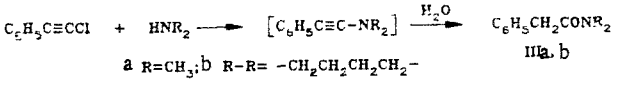
Another possible approach to the synthesis of 1-(phenylethynyl)aziridine is alkylation of aziridine with 1-chloro or 1-bromo-2-phenylacetylene. In recent years, definite progress has been achieved in nucleophilic substitution reactions at an sp-hybridized carbon atom [6]. However, it should be noted that reactions with anion-type nucleophiles, tertiary amines, and phosphines are achieved the most successfully. Information about the interaction of secondary amines with haloacetylenes is contradictory and sparse [7, 8]. Allowing for the relatively low nucleophilicity of aziridine, the alkylation reactions were carried out by us under conditions of interphase catalysis. However, even in this case conversion of aziridine is low. Thus on boiling 1-chloro-2-phenylacetylene with a fivefold excess of aziridine for 20 h over solid sodium hydroxide in benzene in the presence of an interphase catalyst, the degree of conversion of 1-chloro-2-phenylacetylene to 1-(phenylethynyl)aziridine does not exceed 10% according to the GLC data. The use of other solvents when alkylation is carried out under conditions of interphase catalysis does not have any significant effect on the yield of the required product. The reaction of 1-bromo-2-phenylacetylene with aziridine under conditions of interphase catalysis also proceeds slowly, with the formation of phenylacetylene as main product resulting from nucleophilic attack on the more "positive" halogen — bromine [9].

It is known [10] that 4-dimethylaminopyridine is an effective catalyst in alkylation reactions. We attempted to alkylate aziridine with 1-chloro-2-phenylacetylene in the presence of this compound. It transpired that even in this case the yield of 1-(phenylethynyl)-aziridine (I) did not exceed 5%. Moreover, as a result of nucleophilic addition of aziridine to the triple bond, 1-(1-phenyl-2-chlorovinyl)aziridine (II) is also formed in small quantities (3%); the structure of this product is confirmed by the agreement of the experimental chemical shift of the olefinic proton with that calculated empirically.



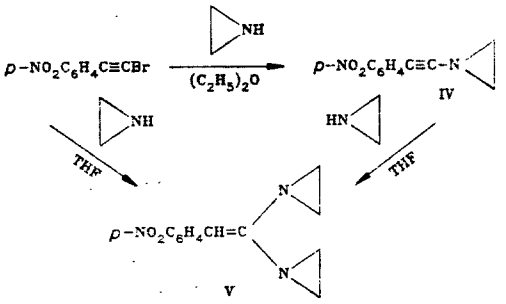
II

On the other hand, with secondary amines, pyrrolidine, and dimethylamine in the presence of dimethylaminopyridine the reaction goes virtually to completion, giving products derived from hydration of ynamines — phenylacetamides IIIa,b:

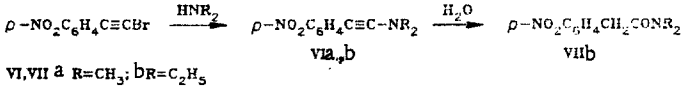


The experimental data obtained indicate that 1-chloro- and 1-bromo-2-phenylacetylene are insufficiently active substrates in nucleophilic substitution reactions. Increasing the

electrophilicity of the haloacetylene may be achieved by introduction of an electron-withdrawing group into the aromatic ring. We have shown that 1-bromo-2-p-nitrophenylacetylene, synthesized according to the method in [11], reacts under mild conditions with aziridine to form the stable crystalline ynaziridine IV. The nature of the solvent has a substantial influence on the course of the reaction. Thus, when the reaction is carried out under the same conditions in a more polar solvent (THF), a consecutive addition of the nucleophile to the triple bond of the ynaziridine occurs with the formation of a by-product — enaziridine V.



1-Bromo-2-p-nitrophenylacetylene readily reacts also with secondary amines to form the previously unknown ynamines VIa,b, which are characterized by their facile hydration to amides:



EXPERIMENTAL

PMR spectra were recorded on a Bruker WH-90 (90 MHz) spectrometer in $CDCl_3$ with TMS as internal standard. IR spectra were recorded on a Perkin-Elmer 580-B instrument in nujol or as a liquid film. The course of the reactions was monitored by means of GLC [Biokhrom-1 instrument, flame ionization detector, glass column 2.5 m × 3 mm, 10% ES-30 on Chromosorb-750, 30-60 mesh, helium carrier gas (25 ml/min)] and TLC (Silufol UV-254). Preparative HPLC was carried out on a DuPont 830 Prep LC chromatograph with UV-Spectrophotometer detector and Zorbax SIL column 22.7 × 250 mm.

1-(Phenylethynyl)aziridine (I). To a solution of 3.5 g (80 mmole) of aziridine in 20 ml of THF was added 0.4 g (1 mmole) of copper acetate hydrate. A solution of 1 g (10 mmole) of phenylacetylene in 20 ml of THF was then added dropwise with agitation and cooling to 5°C over a period of 30 min in a current of oxygen. The temperature was raised to 20°C and maintained thus for 2 h. The reaction mixture was diluted with 40 ml of ether, washed with a saturated solution of potassium carbonate, and dried with anhydrous potash. The solvent was evaporated and the residue comprised a mixture of 20% 1-(phenylethynyl)aziridine and 80% diphenyldiacetylene, according to the data of GLC. Ynaziridine I was isolated by means of HPLC (hexane–2-propanol, 20:1). 0.12 g (15%) of compound I was obtained, bp 34-36°C (0.01 mm). IR spectrum: 2230 cm^{-1} (C≡C). PMR spectrum: 7.24 (5H, m, C_6H_5), 2.24 ppm (4H, s, CH_{ring}). Found, %: C 83.5, H 6.2, N 10.1. $C_{10}H_9N$. Calculated, %: C 83.9, H 6.3, N 9.8.

Oxidative Condensation of Phenylacetylene in Excess Aziridine. To a mixture of 3.5 g (80 mmole) of aziridine and 0.2 g (0.5 mmole) of copper acetate hydrate at 0°C was added dropwise 1 g (10 mmole) of phenylacetylene; oxygen was bubbled through the reaction mixture for a period of 30 min and it was then left at 20°C for 48 h. A 60-ml portion of ether was added, and the solution was washed with water and dried with anhydrous magnesium sulfate. The solvent was evaporated and the residue was chromatographed by means of HPLC (hexane–2-propanol, 20:1). 0.1 g (12%) of 1-(phenylethynyl)aziridine was obtained, as well as 0.65 g (58%) of 1-(1-phenyl-2-phenylethynylvinyl)aziridine, mp 127-129°C. IR spectrum: 2185 cm^{-1} (C≡C). PMR spectrum: 7.0-7.6 (10H, m, C_6H_5), 5.51 (1H, s, Z-CH═), 5.11 (1 H, s, E-CH═), 2.28 ppm (4H, s, CH_{ring}). Found, %: C 88.0, H 6.3, N 5.5. $C_{18}H_{15}N$. Calculated, %: C 88.2, H 6.1, N 5.7.

Reaction of Phenylethynylmagnesium Bromide with 1-Chloroaziridine. To a solution of 100 mmole of ethylmagnesium bromide in 40 ml of absolute ether was added a solution of 10.2 g

(100 mmole) of phenylacetylene in 30 ml of absolute ether with agitation and at 20°C, and the mixture was boiled for 2 h 30 min. The reaction mixture was cooled to 5°C and a solution of 7.7 g (100 mmole) of 1-chloroaziridine in 20 ml of absolute ether was added dropwise. The temperature was raised to 20°C and the mixture was agitated for 3 h. The ethereal solution was washed three times with 20 ml of water and dried with anhydrous magnesium sulfate. The solvent was removed and the residue was distilled under vacuum. 12.1 g (89%) of 1-chloro-2-phenylacetylene was obtained, bp 65-66°C (10 mm), n_D^{20} 1.5780. According to the data of [12]: bp 65°C (10 mm), n_D^{20} 1.5783.

Alkylation of Aziridine with 1-Chloro-2-phenylacetylene. A. To a suspension of 0.58 g (15 mmole) of sodium hydroxide in 20 ml of benzene were added 0.5 g (15 mmole) of aziridine, 1 g (7 mmole) of 1-chloro-2-phenylacetylene, and 0.1 g (0.3 mmole) of tributylbenzylammonium chloride. The reaction mixture was boiled with agitation for 20 h. According to the data of GLC, it contained 90% 1-chloro-2-phenylacetylene and 10% 1-(phenylethynyl)aziridine. Compound I was isolated by means of HPLC (hexane–2-propanol, 20:1). Yield 0.1 g (9.6%).

B. A mixture of 1.1 g (8 mmole) of chlorophenylacetylene, 0.7 g (16 mmole) of aziridine, and 0.1 g (0.8 mmole) of 4-dimethylaminopyridine in 15 ml of absolute THF was boiled for 20 h. The precipitate formed was filtered off and washed with ether. The filtrate was evaporated and the residue was chromatographed by means of HPLC (hexane–2-propanol, 20:1). 0.9 g (85%) of initial 1-chloro-2-phenylacetylene, 0.06 g (5%) of 1-(phenylethynyl)aziridine, and also 0.04 g (3%) of 1-(1-phenyl-2-chlorovinyl)aziridine (II) were obtained. PMR spectrum: 7.89 (2H, m, H_{ortho}), 7.35 (3H, m, H_{meta} and H_{para}), 5.78 (1H, s, =CH-), 2.11 ppm (4H, s, CH_{ring}). Found, %: C 66.7, H 5.5, N 7.9. $C_{10}H_{10}ClN$. Calculated, %: C 67.0, H 5.6, N 7.8.

Reaction of 1-Bromo-2-phenylacetylene with Aziridine. To a suspension of 0.48 g (12 mmole) of sodium hydroxide in 20 ml of benzene were added 0.86 g (20 mmole) of aziridine, 1.8 g (10 mmole) of bromophenylacetylene, and 0.3 g (1 mmole) of tributylbenzylammonium chloride. The reaction mixture was agitated for 20 h at 70°C. GLC analysis of the reaction mixture indicated the presence of phenylacetylene (55%), 1-bromo-2-phenylacetylene (40%), and 1-(phenylethynyl)aziridine (5%).

Reaction of 1-Chloro-2-phenylacetylene with Secondary Amines. A mixture of 0.68 g (5 mmole) of chlorophenylacetylene, 10 mmole of dimethylamine or pyrrolidine, and 0.06 g (0.5 mmole) of 4-dimethylaminopyridine in 20 ml of dry THF was agitated for 8 h at 60°C. The precipitated salt was filtered off; the filtrate was evaporated, the residue was dissolved in 40 ml of ether, and the solution was filtered through a thin layer of alumina. The solvent was evaporated and the residue distilled under vacuum. Compound IIIa. bp 125°C (5 mm), mp 41-43°C. According to the data of [13]: mp 43.5°C. IR spectrum: 1660 cm^{-1} (C=O). PMR spectrum: 7.47 (5H, m, C_6H_5), 3.72 (2H, s, CH_2), 2.98 ppm (6H, d, NCH_3). Yield 0.61 g (74%). Compound IIIb. bp 126-128°C (0.01 mm). IR spectrum: 1660 cm^{-1} (C=O). PMR spectrum: 7.23 (5H, m, C_6H_5), 3.62 (2H, s, CH_2), 3.42 (4H, m, NCH_2), 1.84 ppm (6H, m, CH_3). Found, %: C 76.0, H 8.1, N 7.5. $C_{12}H_{15}NO$. Calculated, %: C 76.2, H 7.9, N 7.4. Yield 0.65 g (69%).

1-(p-Nitrophenylethynyl)aziridine (IV). To a solution of 0.3 g (1.3 mmole) of 1-bromo-2-p-nitrophenylacetylene in 10 ml of absolute ether was added 0.22 g (5.2 mmole) of aziridine, and the reaction mixture was kept for 48 h. The precipitated salt was filtered off, the filtrate was evaporated, and the residue recrystallized from hexane. 0.15 g (62%) of aziridine IV was obtained, mp 107-109°C. IR spectrum: 2210 cm^{-1} (C≡C). PMR spectrum: 8.04 (2H, d, H_{arom}), 7.36 (2H, d, H_{arom}), 2.35 ppm (4H, s, CH_{ring}). Found, %: C 63.5, H 4.3, N 15.1. $C_{10}H_8N_2O_2$. Calculated, %: C 63.8, H 4.2, N 14.9.

Reaction of Aziridine with 1-Bromo-2-p-nitrophenylacetylene in THF. To a solution of 0.3 g (1.3 mmole) of 1-bromo-2-p-nitrophenylacetylene in 10 ml of dry THF was added 0.22 g (5 mmole) of aziridine, and the mixture was agitated for 24 h. The precipitated salt was filtered off and the filtrate was evaporated. The residue was chromatographed by means of HPLC (hexane–2-propanol, 2.3:1). 0.1 g (42%) of compound IV and 0.11 g (37%) of the oily enaziridine V were obtained. PMR spectrum: 8.11 (2H, d, H_{arom}), 7.38 (2H, d, H_{arom}), 5.36 (1H, s, -CH=), 2.24 (4H, s, CH_{ring}, 2.13 ppm (4H, s, CH_{ring}). Found, %: C 62.0, H 5.4, N 18.5. $C_{12}H_{13}N_3O_2$. Calculated, %: C 62.3, H 5.6, N 18.2.

N-(p-Nitrophenylethynyl)dialkylamines (VIa,b). To a solution of 3.6 mmole of dimethyl- or diethylamine in 10 ml of absolute ether was added 0.2 g (0.9 mmole) of 1-bromo-2-p-nitro-

phenylacetylene, and the mixture was agitated for 3 h. The precipitated salt was filtered off and the filtrate was evaporated. Compound VIa. Dark yellow crystals, mp 100-102°C (from petroleum ether). IR spectrum: 2195 cm^{-1} (C=C). PMR spectrum: 8.0 (2H, d, H_{arom}), 7.18 (2H, d, H_{arom}), 2.91 ppm (6H, s, NCH_3). Found, %: C 63.1, H 5.2, N 14.9. $C_{10}H_{10}N_2O$. Calculated, %: C 63.2, H 5.3, N 14.7. Compound VIb. Dark red oil. IR spectrum: 2190 cm^{-1} (C≡C). PMR spectrum: 8.0 (2H, d, H_{arom}), 7.18 (2H, d, H_{arom}), 3.09 (4H, q, CH_2), 1.27 ppm (6H, t, CH_3). Found, %: C 66.0, H 6.2, N 13.0. $C_{12}H_{14}N_2O_2$. Calculated, %: C 66.1, H 6.4, N 12.8. Yield 0.16 g (80%).

Diethylamide of p-Nitrophenylacetic Acid (VIIb). A 0.26-g (1.2 mmole) portion of ynamine VIb was dissolved in 10 ml of moist ether. After 30 min the ethereal solution was dried with anhydrous magnesium sulfate and evaporated. 0.25 g (92%) of compound VIIb was obtained, mp 28-29°C. IR spectrum: 1680 cm^{-1} (C=O). PMR spectrum: 8.11 (2H, d, H_{arom}), 7.38 (2H, d, H_{arom}), 3.76 (2H, s, CH_2), 3.37 (4H, q, CH_2), 1.16 ppm (6H, t, CH_3). Found, %: C 61.1, H 6.5, N 12.1. $C_{12}H_{16}N_2O_3$. Calculated, %: C 61.0, H 6.8, N 11.9.

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