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BEHAVIOR OF DIALKYLALLYL(4-HYDROXYBUT-2-YNYL)AMMONIUM BROMIDES TOWARD POWDERED SODIUM HYDROXIDE AND AQUEOUS ALKALI

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Under the influence of a twofold molar quantity of powdered sodium hydroxide in the presence of a few drops of methanol at room temperature dialkylallyl(4-hydroxybut-2-ynyl)ammonium bromides undergo a Stevens rearrangement with transfer of the reaction center, forming substituted amino alcohols with an allene group. Intramolecular cyclization of the products and concurrent hydration lead to the formation of a mixture of dialkyl(4-allyl-2,5-dihydrofuran-2-yl)amines and dialkylamino-3-allyl-4-hydroxybutanones with overall yields of 37-41%. During the aqueous-alkali cleavage of dialkylallyl(4-hydroxybut-2-ynyl)ammonium bromides the products from intramolecular cyclization were obtained with yields of 38-41%. Under the conditions both of Stevens rearrangement and of aqueous-alkali cleavage the secondary amines are also formed with yields of 15-17%. As nonamine products mixtures of compounds, which according to the IR spectra contain unconjugated and conjugated carbonyl groups, were obtained. The presence of an aldehyde group was established by a silver mirror reaction.

Keywords: dialkylallyl(4-hydroxybut-2-ynyl)ammonium bromides, sodium hydroxide, dialkyl(4-allyl-2,5-dihydrofuran-2-yl)amines, intramolecular cyclization, water-alkali cleavage, Stevens rearrangement.

Earlier we showed that enyne ammonium salts in the molecules of which there is an allyl substituent at position 1 of the diene fragment mostly undergo intramolecular cyclization [1]. It was also found that 1-substituted prop-2-ynyl and 4-hydroxybut-2-ynyl groups can be involved in intramolecular cyclization as π^2-fragment [2-4].

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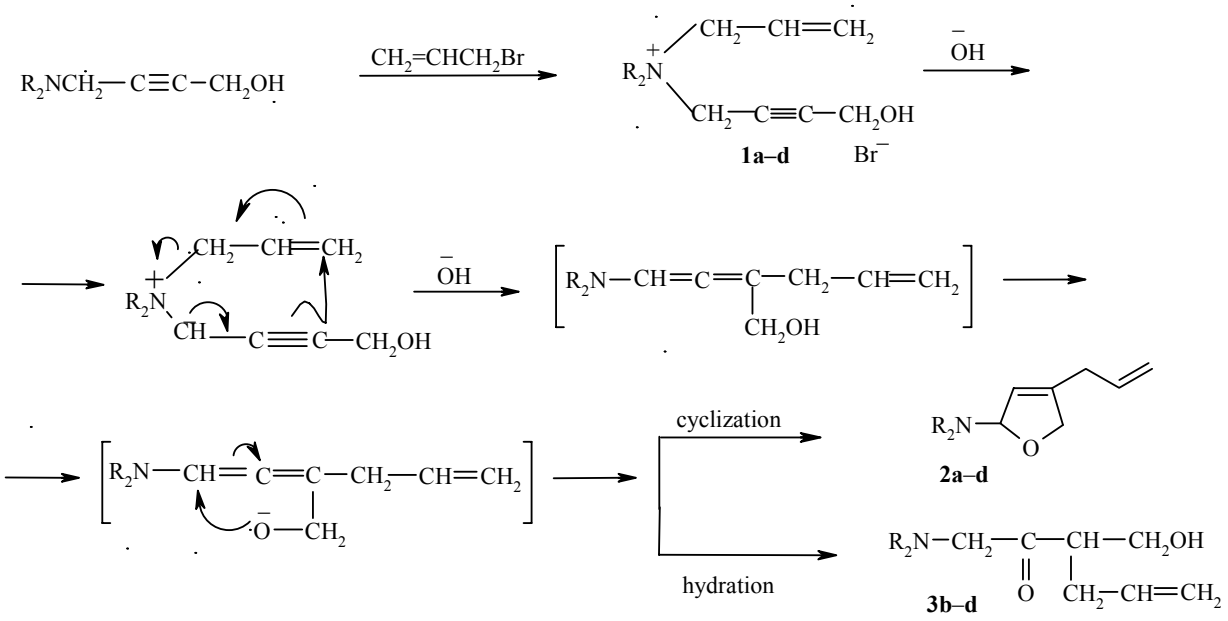
In a continuation of investigations into the base-catalyzed intramolecular cyclization of unsaturated ammonium salts we felt that it was interesting to study the ability of the 1-allyl-4-hydroxybut-2-ynyl group to enter into cyclization as a π^2-fragment.

We attempted to obtain the initial dialkyl(1-allyl-4-hydroxybut-2-ynyl)amines by the Stevens rearrangement of diethyl- (**1a**), dipropyl- (**1b**), and dibutylallyl(4-hydroxybut-2-ynyl)ammonium (**1c**), and allyl(4-hydroxybut-2-ynyl)morpholinium (**1d**) bromides.

Scheme 1



1a, **2a** R = Et; **1–3 b** R = Pr, **c** R = Bu, **d** R_2 = $(-CH_2)_2O(CH_2-)_2$

The investigations showed that during the action of twice the molar amount of powdered sodium hydroxide in the presence of a few drops of methanol at room temperature the salts **1b-d** undergo a Stevens rearrangement with transfer of the reaction center, forming substituted amino alcohols with an allene group. Intramolecular cyclization of the latter leads to (4-allyl-2,5-dihydrofuran-2-yl)dipropylamine (**2b**), (4-allyl-2,5-dihydrofuran-2-yl)dibutylamine (**2c**), and (4-allyl-2,5-dihydrofuran-2-yl)morpholine (**2d**). The reaction is accompanied by concurrent hydration of the Stevens rearrangement product with the formation of 3-allyl-dipropyl- (**3b**), 3-allyldibutylamino-4-hydroxy-2-butanones (**3c**), and 3-allyl-4-hydroxy-1-morpholyl-2-butanone (**3d**) with overall yields of 37-40%. In the IR spectra of the mixture of amines **2b-d** and **3b-d** absorption bands were found for $-C=CH_2$ in the regions of 910-990, 1630, and 3080-3100 characteristic of the amines **2b-d** and **3b-d**, for O–H in the region of 3200-3500 characteristic of the amines **3b-d**, and for >C=C< in the region of 1670 for the amines **2b-d**. There was also absorption in the region of 1000-1100 cm^{-1} characteristic both of the O–H groups and of the C–O–C groups. All attempts to obtain the above-mentioned amines in the individual form were unsuccessful. According to data from the IR spectrum, the 4-hydroxybutanones **3b-d** predominate in the mixture.

The proposed scheme for the cyclization of amino alcohols with an allene group corresponds to published data, according to which the cyclization of many acetylene compounds to heterocycles takes place through intermediate allene compounds [5] and the allene amines and alcohols undergo intramolecular cyclization in the presence of silver ions, forming 3-pyrrolines, substituted 2,5-dihydrofurans, and pyrans [6-16].

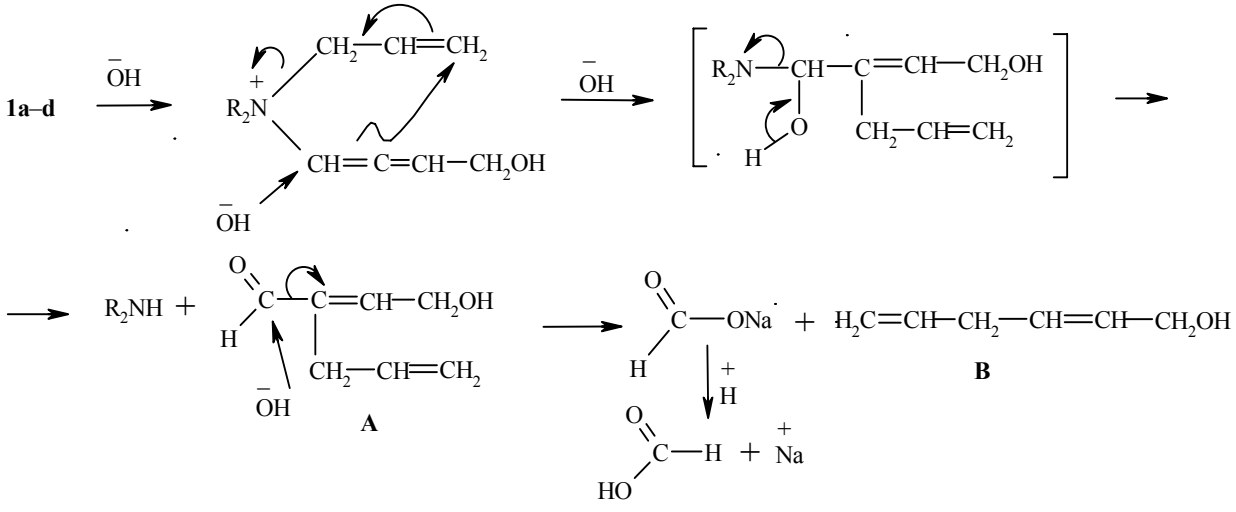
It should be noted that dialkyl(4-allyl-2,5-dihydrofuran-2-yl)amines **2a-d** are produced in the pure form with yields of 39-42% during aqueous alkaline cleavage of the salts **1a-d**.

The dihydrofuran structure of **2a-d** was proposed on the basis of the ^{1}H and ^{13}C NMR spectra. A characteristic feature of this structure is the presence of an asymmetric carbon atom at position 2 of the dihydrofuran ring, which is the reason for the non-equivalence of the geminal protons of the methylene groups both at position 5 in the ring and outside the ring. As a result of this the ^{1}H NMR spectra contain complex multiplet structure for the methylene groups of the allyl and amine fragments. In addition, long-range spin-spin coupling, leading either to broadening or to additional splitting of the signals, appears in the spectra. Thus, for example, the protons of the CH_2 group of the allyl fragment appear as two separate signals of the doublet of doublet type with $^{2}J \approx 16.5$ and $^{3}J = 6.9$ Hz. Moreover, as shown by double resonance experiments, these signals are further split on account of spin-spin couplings with the terminal protons of the vinyl group and the protons of the ring at positions 3 and 5. The presence of such couplings also leads to complications in the H-2 and H-3 signals. In the NOESY spectrum of compound **2d** coupling is observed between the H-2 and H-5 protons and also between the H-3 and H-5 protons, which also indicates a cyclic structure. The presence of a signal in the region of 100 ppm in the ^{13}C NMR spectra of compounds **2c** and **2d**, assigned on the basis of the {^{1}H, ^{13}C} HMQC 2D correlation spectrum to the carbon atom at position 2 of the dihydrofuran ring, is also typical.

It was established that compounds **1a-d** form dialkylamines with yields of 15-17%, identified in the form of picrates, both during the action of powdered NaOH, i.e., under the conditions of the Stevens rearrangement [17], and during aqueous alkaline cleavage.

The IR spectra of the mixture of non-amine products contained absorption bands for the $–CH=CH_2$ group at 930, 940, 970, 1640, and 3100 cm^{-1}, for the O–H group in the region of 1020, 1030, 1070, and 3300-3470 cm^{-1}, for the conjugated and unconjugated carbonyl groups at 1690 and 1710 cm^{-1} characteristic of compounds **A** and **B**, and also for the presence of the aldehyde hydrogen at 2730 cm^{-1}. The presence of compound **A**, formed according to Scheme 2, in the mixture of non-amine products was established by a silver mirror reaction. The non-amine products decomposed during vacuum distillation. The formation of formic acid according to scheme 2 was confirmed by a silver mirror reaction.

Scheme 2



It should be noted that in 1966 Babayan, Indzhikyan, and Gegelyan studied the aqueous alkaline cleavage of dimethylallyl(4-hydroxymethylbut-2-ynyl)ammonium bromide during the action of twice the molar amount of 25% KOH during heating with a descending condenser followed by distillation of the mixture [18].

Here dimethylamine (36%) and dimethylallylamine (42.5%) were obtained as amine products, and allylacetone (20%), acetone (3%), and formic acid (17%) as nonamine products. The authors did not obtain dimethyl(4-allyl-2,5-dihydrofuran-2-yl)amine since the formed dimethylamino-3-allyl-4-hydroxymethyl-1,2-propanediene evidently undergoes resinification under the conditions used in [18].

For the case of dibutylallyl(4-hydroxybut-2-ynyl)ammonium bromide it was shown that dialkyl(4-allyl-2,5-dihydrofuran-2-yl)amines can also be obtained with sodium carbonate as base, but in this case longer heating is required (3-4 h).

According to the data from preliminary pharmacological investigations the hydrochlorides of the two amines with a hydrogenated furan ring have pronounced hypotensive activity.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer in tablets with KBr or in vaseline oil. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 spectrometer (300 and 75 MHz respectively) at 30°C (303 K) in DMSO-d_6–CCl_4, 1:3, with TMS as internal standard.

The initial dialkyl(4-hydroxybut-2-ynyl)amines were obtained by the method in [19]. The composition of the obtained compounds was established by elemental analysis, and the purity by TLC on Silufol UV-254 in 10:2:1:5 *n*-butanol–ethanol–water–acetic acid, development with iodine vapor.

Synthesis of Salts 1a-d (General Method). To a solution of diethyl-, dipropyl-, or dibutyl-(4-hydroxybut-2-ynyl)amine or (4-hydroxybut-2-ynyl)morpholine (20 mmol) in absolute ether (20 ml) and acetonitrile (7 ml) we added twice the molar amount of allyl bromide. The reaction mixture was heated at 70-75°C for 5-6 h. The salts **1a-d** were then isolated by filtration and washed with absolute ether (2×25 ml).

Diethylallyl(4-hydroxybut-2-ynyl)ammonium Bromide (1a). Yield 4.98 g (95%); mp 123-124°C. IR spectrum, ν, cm^{-1}: 930, 970, 1630, 3100 (–CH=CH_2), 2230 (–C≡C–), 1020, 1080, 1100, 1150, 3200–3250 (O–H). Found, %: Br 30.18; N 5.57. $C_{11}H_{20}BrNO$. Calculated, %: Br 30.53; N 5.34.

Dipropylallyl(4-hydroxybut-2-ynyl)ammonium Bromide (1b). Yield 5.22 g (90%); mp 132-133°C. IR spectrum, ν, cm^{-1}: 920, 940, 950, 970, 1630, 3100 (–CH=CH_2), 2230 (–C≡C–), 1010, 1020, 1130, 1150, 3300–3500 (O–H). Found, %: Br 27.23; N 4.59. $C_{13}H_{24}BrNO$. Calculated, %: Br 27.59; N 4.83.

Dibutylallyl(4-hydroxybut-2-ynyl)ammonium Bromide (1c). Yield 5.5 g (87%); mp 77-78°C. IR spectrum, ν, cm^{-1}: 930, 950, 970, 1630, 3080 (–CH=CH_2), 2240 (–C≡C–), 1030, 1050, 1100, 3300-3480 (O–H). Found, %: Br 25.51; N 4.21. $C_{15}H_{28}BrNO$. Calculated, %: Br 25.16; N 4.40.

Allyl(4-hydroxybut-2-ynyl)morpholinium Bromide (1d). Yield 5.1 g (92%); mp 111-112°C. IR spectrum, ν, cm^{-1}: 940, 950, 990, 1640, 3080 (CH=CH_2), 2220 (–C≡C–), 1030, 1080, 3200-3300 (O–H). Found, %: Br 28.58; N 5.35. $C_{11}H_{18}BrNO_2$. Calculated, %: Br 28.99; N 5.07.

Aqueous Alkaline Cleavage of the Salts 1a-d (General Method). Twice the molar quantity of 25% NaOH solution was gradually added to a solution of the salts **1a-d** (10 mmol) in water (3 ml) The reaction mixture was heated at 90-92°C for 2 h. It was then cooled and extracted with ether (3×40 ml). The ether extract was titrated with a 0.1 N solution of sulfuric acid in an aqueous medium with shaking. The presence of 6.5-7 mmol (65-70%) of the amine product was established. The ether extract was treated with shaking with a 15% solution of HCl to an acidic reaction. The hydrochloric acid layer was separated from the ether layer, made alkaline, and extracted with ether, and the extract was dried with magnesium sulfate. The amines **2a-d** were obtained after removal of the ether.

The presence of secondary amines (15-17%) in the ether extract and in the water distilled from the mixture after alkaline treatment of the amine hydrochlorides was established by titration. They were identified in the form of the picrates. The picrates of the diethylamine (155°C), dipropylamine (75°C), dibutylamine (98-99°C), and morpholine (154-155°C) did not give a melting point depression with authentic samples. The ether

layer, containing the non-amine products, was dried with $CaCl_2$. After distillation of the ether from initial salt (10 mmol) we obtained ≈0.4 g of a mixture of nonamine products. Their IR spectra contained characteristic absorption bands for –CH=CH_2 at 930, 940, 970, 1640, and 3100, for O–H in the region of 1020-1030, 1070, and 3300-3470, for the conjugated and unconjugated carbonyl groups at 1690 and 1710, and for the aldehyde hydrogen at 2730 cm^{-1}. The presence of compound **A** in the mixture was established by a silver mirror reaction.

The reaction mixture after extraction with ether was acidified with hydrochloric acid, and the solvent was partly distilled off. The presence of formic acid in the distillate was established by a silver mirror reaction.

(4-Allyl-2,5-dihydrofuran-2-yl)diethylamine (2a). Yeld 0.75 g (36%); bp 65°C (1-2 mm Hg), n_D^{20} = 1.4645, mp of picrate 128-129°C(ethanol). IR spectrum, ν, cm^{-1}: 930, 950, 1630, 3100 (–CH=CH_2); 1670 (>C=C<); 1000, 1040 (C–O–C in ring). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.83 (1H, ddt, J_1 = 17.0, J_2 = 10.0, J_3 = 6.9, C<u>H</u>=CH_2); 5.67 (1H, q, *J* = 1.6, H-3); 5.38 (1H, m, H-2); 5.06 (1H, dq, J_1 = 17.0, J_2 ~ 1.5, =CH_2); 5.02 (1H, dq, J_1 = 10.0, J_2 ~ 1.5, =CH_2); 4.32–4.46 (2H, m, 5-CH_2); 2.77 (1H, dd, J_1 = 16.6, J_2 = 6.9, C<u>H</u>$_2$CH=CH_2); 2.67 (1H, dd, J_1 = 16.6, J_2 = 6.9, C<u>H</u>$_2$CH=CH_2); 2.60 (4H, m, NCH_2); 1.02 (6H, t, *J* = 7.2, CH_3). Found, %: C 72.55; H 10.81; N 7.44. $C_{11}H_{19}NO$. Calculated, %: C 72.93; H 10.50; N 7.73.

(4-Allyl-2,5-dihydrofuran-2-yl)dipropylamine (2b). Yield 0.79 g (38%), bp 91°C (1-2 mm Hg), n_D^{20} = 1.4648, mp of picrate 86-87°C (ethanol). IR spectrum, ν, cm^{-1}: 910, 950, 990, 1630, 3090 (–CH=CH_2); 1670 (>C=C<); 1040, 1070 (C–O–C in ring). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.82 (1H, ddt, J_1 = 17.0, J_2 = 10.0, J_3 = 6.9, C<u>H</u>=CH_2); 5.68 (1H, q, *J* = 1.6, H-3); 5.36 (1H, m, H-2); 5.05 (1H, dq, J_1 = 17.0, J_2 ~ 1.5, =CH_2); 5.03 (1H, dq, J_1 = 10.0, J_2 ~ 1.5, =CH_2); 4.32-4.46 (2H, m, 5-CH_2); 2.79 (1H, dd, J_1 = 16.4, J_2 = 6.9, C<u>H</u>$_2$CH=CH_2); 2.66 (1H, dd, J_1 = 16.4, J_2 = 6.9, C<u>H</u>$_2$CH=CH_2); 2.45 (4H, m, NCH_2); 1.44 (4H, m, C<u>H</u>$_2$$CH_3$); 0.86 (6H, t, *J* = 7.4, CH_3). Found, %: C 74.27; H 11.35; N 6.31. $C_{13}H_{23}NO$. Calculated, %: C 74.64; H 11.00; N 6.70.

(4-Allyl-2,5-dihydrofuran-2-yl)dibutylamine (2c). Yield 0.9 g (38%); bp 102°C (1-2 mm Hg), n_D^{20} = 1.4640, does not form a picrate. IR spectrum, ν, cm^{-1}: 910, 990, 1630, 3100 (−CH=CH_2); 1670 (>C=C<); 1050, 1080 (C–O–C in ring). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.82 (1H, ddt, J_1 = 17.0, J_2 = 10.0, J_3 = 6.9, <u>C</u>H=CH_2); 5.68 (1H, q, *J* = 1.6, H-3); 5.36 (1H, m, H-2); 5.05 (1H, dq, J_1 = 17.0, J_2 ~ 1.5, =CH_2); 5.04 (1H, dq, J_1 = 10.0, J_2 ~ 1.5, =CH_2); 4.32-4.46 (2H, m, 5-CH_2); 2.78 (1H, dd, J_1 = 16.6, J_2 = 6.9, C<u>H</u>$_2$CH=CH_2); 2.66 (1H, dd, J_1 = 16.6, J_2 = 6.9, C<u>H</u>$_2$CH=CH_2); 2.50 (4H, t, *J* = 7.2, NCH_2); 1.17-1.49 (8H, m, C<u>H</u>$_2$C<u>H</u>$_2$$CH_3$); 0.91 (6H, t, *J* = 7.2, CH_3). ^{13}C NMR spectrum, δ, ppm: 138.2 (C-4); 134.4 (<u>C</u>H=CH_2); 123.0 (C-3); 115.7 (=CH_2); 100.0 (C-2); 72.3 (C-5); 47.6 (NCH_2); 31.1 (4-C<u>C</u>H_2); 30.1 (CH_2); 19.9 (CH_2); 13.6 (CH_3). Found, %: C 75.47; H 11.71; N 5.63. $C_{15}H_{27}NO$. Calculated, %: C 75.95; H 11.39; N 5.91.

(4-Allyl-2,5-dihydrofuran-2-yl)morpholine (2d). Yield 0.8 g (41%); bp 85-86°C (1-2 mm Hg), n_D^{20} = 1.4985, mp of picrate 83-84°C (ethanol). IR spectrum, ν, cm^{-1}: 920, 960, 990, 1620, 3080 (–CH=CH_2); 1670 (>C=C<); 1030, 1070 (C–O–C in ring). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.85 (1H, ddt, J_1 = 17.0, J_2 = 10.0, J_3 = 6.9, C<u>H</u>=CH_2); 5.75 (1H, q, *J* = 1.6, H-3); 5.17 (1H, m, H-2); 5.08 (1H, dq, J_1 = 17.0, J_2 ~ 1.5, =CH_2); 5.04 (1H, dq, J_1 = 10.0, J_2 ~ 1.5, =CH_2); 4.45 (2H, m, 5-CH_2); 3.56 (4H, t, *J* = 4.8, OCH_2); 2.74 (2H, m, C<u>H</u>$_2$CH=CH_2); 2.61 (2H, dt, J_1 = 11.6, J_2 = 4.8, NCH_2); 2.48 (2H, dt, J_1 = 11.6, J_2 = 4.8, NCH_2). ^{13}C NMR spectrum, δ, ppm: 136.4 (C-4); 134.2 (<u>C</u>H=CH_2); 124.0 (C-3); 115.9 (=CH_2); 101.3 (C-2); 73.4 (C-5); 62.2 (OCH_2); 46.7 (NCH_2); 30.9 (4-C<u>C</u>H_2). Found, %: C 67.35; H 8.41; N 7.47. $C_{11}H_{17}NO_2$. Calculated, %: C 67.69; H 8.72; N 7.18.

REFERENCES

1. E. O. Chukhadzhyan, El. O. Chukhadzhyan, K. G. Shakhatuni, L. A. Manasyan, and A. T. Babayan, *Khim. Geterotsikl. Soedin.*, 213 (1994). [*Chem. Heterocycl. Comp.*, **30**, 192 (1994)].
2. A. T. Babayan, E. O. Chukhadjyan, and L. A. Manasyan, *Zh. Org. Khim.*, **15**, 942 (1979).
3. E. O. Chukhadjyan, A. R. Gevorkyan, El. O. Chukhadjyan, K. G. Shakhatuni, F. Kinoyan, and H. A. Panosyan, *Khim. Geterotsikl. Soedin.*, 34 (2004). [*Chem. Heterocycl. Comp.*, **40**, 29 (2004)].

4. A. R. Gevorkyan, E. O. Chukhadzhyan, El. O. Chukhadzhyan, and G. A. Panosyan, *Khim. Geterotsikl. Soedin.*, 212 (2004). [*Chem. Heterocycl. Comp*., **40**, 177 (2004)].
5. R. Fuks and H. G. Viehe, in: H. G. Viehe (editor), *Chemistry of Acetylenes,* Marcel Dekker, New York (1969), p. 425.
6. A. Claesson, C. Sahlberg, and K. Luthman, *Acta Chem. Scand*., B, **33**, 309 (1979).
7. R. Mantione, Y. Leroux, and H. Normant, *C. R. Acad. Sci*., C, **270**, 1808 (1970).
8. F. Toda, T. Komoda, and K. Akagi, *Bull. Chem. Soc. Jpn*., **41**, 1493 (1968).
9. R. Gelin, S. Gelin, and M. Bertrand, *Bull. Soc. Chim. Fr*., 720 (1972).
10. S. Hoff and L. Brandsma, *Rec. Trav. Chim*., **88**, 845 (1969).
11. G. Leandri, H. Monti, and M. Bertrand, *Tetrahedron*, **30**, 289 (1974).
12. R. Gelin, M. Albrand, and S. Gelin, *C. R. Acad. Sci*., C, **269**, 241 (1969).
13. R. Gelin, S. Gelin, and M. Albarand, *Bull. Soc. Chim. Fr*., 1946 (1972).
14. S. Hoff, L. Brandsma, and J. F. Arens, *Rec. Trav. Chim*., **88**, 609 (1969).
15. G. Bandz, *Ark. Kemi*, **14**, 475 (1959).
16. F. Bohlmann, P. Herbst, and H. Gleinig, *Chem. Ber*., **94**, 948 (1961).
17. E. O. Chukhadjian, M. K. Nalbandyan, and G. A. Panosyan, *Khim. Geterotsikl. Soedin.*, 528 (2007). [*Chem. Heterocycl. Comp*., **43**, 430 (2007)].
18. A. T. Babayan, Zh. G. Gegelyan, and M. G. Indzhikyan, *Zh. Org. Khim.*, **2**, 2117 (1966).
19. E. O. Chukhadjian, A. R. Gevorkyan, El. O. Chukhadjyan, and K. G. Shakhatuni, *Zh. Org. Khim.*, **36**, 1304 (2000).