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Synthesis of 2-Propargylaminoethanols from α,β-Acetylenic Aldimines

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Abstract — A method of synthesis of 2-propargylaminoethanols, perspective synthons for a one-pot synthetic technology excluding isolation of unstable prop-2-ynylideneaminoethanols is developed. A number of 2-propargylaminoethanol hydrochloride derivatives are synthesized, and their ^{1}H and ^{13}C NMR spectra were discussed.

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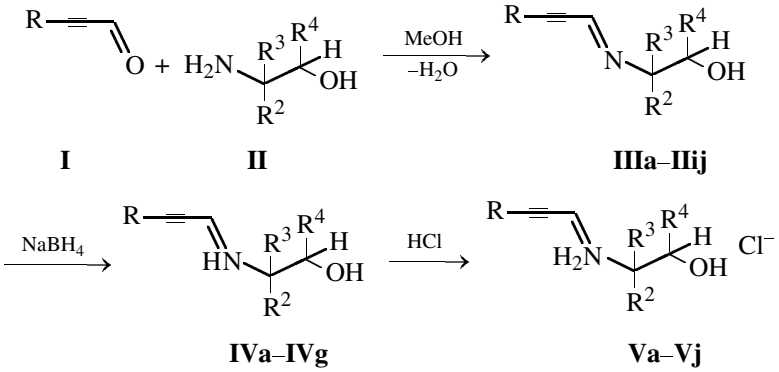
Some 2-propargylaminoethanols are known to be interesting because of their biological activity [1–3] or due to the possibility of their application as intermediate compounds in fine organic synthesis [4–11]. In the present communication we report on the results of developing new routes to 2-propargylmonoaminoethanols by hydrogenation of α,β-acetylenic aldimines prepared from accessible 2-aminoethanols and acetylenic aldehydes (Scheme 1).

Earlier [12] azomethines were prepared by mixing equimolar amounts of prop-2-ynal and primary aliphatic amines in low-polarity aprotic solvents (ether or methylene chloride) at room temperature. The reaction mixture was additionally dried with anhydrous magnesium sulfate, and the solvent was then distilled off at reduced pressure. Thus isolated 1-aza-1-en-3-ynes, as a rule, were used without additional purification.

Our attempts to prepare azomethines **III** by this procedure were unsuccessful. After removal of the solvent removal, the reaction mixtures, as follows from its ^{1}H NMR spectra, contained a polymeric substance only. However, the ^{1}H NMR spectra of freshly prepared reaction mixtures contained characteristic singlets in the region of δ_H 7.3–7.8 ppm, which, according to published data, could be assigned to the methine protons of the *E* and *Z* isomers of expected azomethines **IIIa**–**IIIj**. We presumed that such readily

Scheme 1.



I **II** **IIIa–IIij**

IVa–IVg **Va–Vj**

Va (R^1 = Ph, R^2 = R^3 = R^4 = H); **Vb** (R^1 = Ph, R^2 = R^3 = H, R^4 = Me); **Vc** (R^1 = Ph, R^2 = R^3 = Me, R^4 = H); **Vd** (R^1 = Ph, R^2 = Et, R^3 = R^4 = H); **Ve** (R^1 = Ph, R^2 = R^3 = H, R^4 = Ph); **Vf** (R^1 = Ph, R^2 = H, R^3 = Me, R^4 = Ph); **Vg** (R^1 = *t*-Bu, R^2 = R^3 = Me, R^4 = H); **Vh** (R^1 = *t*-Bu, R^2 = R^3 = H, R^4 = Ph); **Vi** (R^1 = *t*-Bu, R^2 = H, R^3 = Me, R^4 = Ph); **Vj** (R^1 = H, R^2 = H, R^3 = Me, R^4 = Ph).

Table 1. Yields, melting points, and elemental analyses of compounds **IVc** and **Va**–**Vj**

Comp. no.	Yield, %	mp, °C	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
Va	40	106	62.11 62.23	6.74 6.81	6.41 6.51	$C_{11}H_{14}ClNO$	62.41	6.67	6.62
Vb	40	105	63.48 63.58	6.98 7.07	6.09 6.11	$C_{12}H_{16}ClNO$	63.85	7.14	6.21
IVc	55	71	76.94 77.01	8.53 8.49	6.77 6.69	$C_{13}H_{17}NO$	76.81	8.43	6.89
Vc	55	178–180	64.87 65.02	7.41 7.39	5.67 5.74	$C_{13}H_{18}ClNO$	65.13	7.57	5.84
Vd	45	116–117	64.97 65.15	7.68 7.77	5.98 5.95	$C_{13}H_{18}ClNO$	65.13	7.57	5.84
Ve	65	178–179	70.71 70.82	6.09 6.30	5.01 4.97	$C_{17}H_{18}ClNO$	70.95	6.30	4.87
Vf	80	185	71.69 71.68	6.59 6.78	4.76 4.77	$C_{18}H_{20}ClNO$	71.63	6.68	4.64
Vg	65	178–180	60.37 60.28	10.23 10.01	6.22 6.27	$C_{11}H_{22}ClNO$	60.12	10.09	6.37
Vh	65	178–179	66.98 67.11	8.11 8.09	5.37 5.29	$C_{15}H_{22}ClNO$	67.28	8.28	5.23
Vi	80	185–190	68.22 68.17	8.37 8.44	5.05 5.07	$C_{16}H_{24}ClNO$	68.19	8.58	4.97
Vj	25	175	62.27 62.37	6.53 6.49	6.37 6.49	$C_{11}H_{14}ClNO$	62.41	6.67	6.62

polymerizable compounds could be introduced to the reaction without isolation. On this basis we succeeded in synthesizing target 2-propargylaminoethanols **Va**–**Vj** by a one-pot procedure: Immediately after short-term refluxing of equimolar amounts of the corresponding propynal and monoethanolamine in methanol, sodium boron hydride (20% molar excess) was added.

After dilution of the reaction mixture with water followed by extraction and solvent removal, the resulting 2-propargylaminoethanols (bases) were converted into hydrochlorides (Table 3). The last stage was necessary because the free bases were mostly viscous hardly purifiable liquids. In the studied series, 2-methyl-2-(3-phenylprop-2-ynylamino)propan-1-ol (**IVc**) was the only compound crystalline both as hydrochloride and as a free base, and it was isolated individual in the latter form.

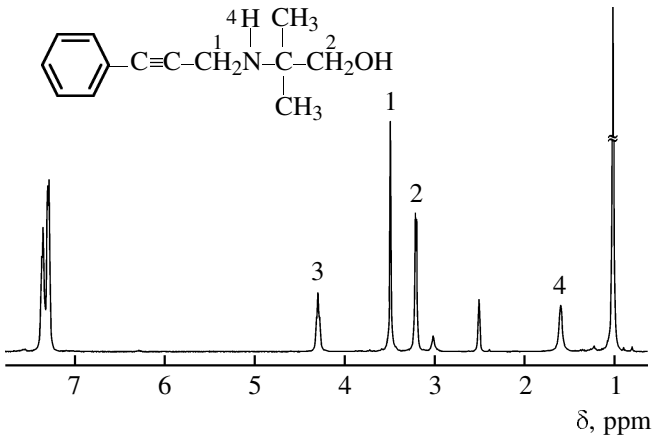


Fig. 1. ^{1}H NMR spectrum of compound **IVc**.

In accordance with the proposed structure, the ^{1}H NMR spectrum of acetylenic aminoalcohol **IVc** (Fig. 1, Table 1) showed a signal at δ_H 1.02 ppm (6H), corresponding to methyl protons, and a slightly broadened signal at δ_H 1.60 ppm. corresponding to the proton at the nitrogen atom. The doublet at δ_H 3.20 ppm (2H, $^3J_{HH}$ 5.09 Hz) and the singlet at δ_H 3.49 ppm (2H) are assignable to protons of the methylene groups at the oxygen and nitrogen atoms, respectively. The hydroxyl proton appears as a triplet at δ_H 4.29 ppm (1H, $^3J_{HH}$ 5.09 Hz), and the phenyl protons, as two ill-resolved multiplets at δ_H 7.28–7.30 (3H) and 7.33–7.38 ppm (2H).

The ^{13}C NMR spectrum of compound **IVc** is shown in Fig 2. The quartet at δ_C 24.37 ppm ($^1J_{CH}$

Table 2. ^{1}H NMR spectra of acetylenic aminoalcohol hydrochlorides **Va**–**Vj** [R^1–C≡C–CH_2–NH_2^+–CR^2R^3–CH^cR^4OH] Cl^-, δ_H, ppm

Comp. no.	C≡C–CH_2	NH_2^+	–OH	R^1	R^i
Va	4.08 s	9.88 [a]	5.21 [a]	Ph 7.33–7.38 m (3H) 7.46–7.52 m (2H)	(R^2 = R^3 = H) 3.79 m, R^4 = H) 3.13–3.17 m
Vb	4.06 s	9.83 [a]	5.35 [a]	Ph 7.33–7.38 m (3H) 7.46–7.52 m (2H)	(R^2 = R^3 = H) 2.87–3.08 m, R^4 = Me) 1.20 d, $^3J_{HH}$ 6.54 Hz, 4.13 m (H^c)
IVc [b]	3.49 s	–	4.30 t $^3J_{HH}$ 5.10 Hz	Ph 7.28–7.30 m (3H) 7.33–7.38 m (2H)	(R^2 = R^3 = Me) 1.1 s, (R^4 = H) 3.20 d, $^3J_{HH}$ 5.10 Hz
Vc	4.06 s	9.64 [a]	5.51 [a]	Ph 7.35–7.39 m (3H) 7.46–7.50 m (2H)	(R^2 = R^3 = Me) 1.35 s, R^4 = H) 3.54 s
Vd	4.06–4.18 m	9.73 [a]	5.26 [a]	Ph 7.35–7.39 m (3H) 7.46–7.51 m (2H)	(R^2 = H), (R^3 = Et) 3.14–3.26 m (1H), 1.66–1.91 m (CH_2), 1.03 t (Me), $^3J_{HH}$ 15.2 Hz, R^4 = H) 3.63–3.86 m
Ve	4.07–4.19 m	10.10 [a]	6.15 [a]	Ph 7.20–7.53 m (5H)	(R^2 = R^3 = H) 3.07–3.25 m, 5.17 d, $^3J_{HH}$ 10.2 Hz (H^c), (R^4 = Ph) 7.20–7.53 m
Vf	*AB* 4.30, 4.16 $^2J_{HH}$ 16.72 Hz	9.92 [a]	6.03 [a]	Ph 7.23–7.49 m (5H)	(R^2 = H) 3.53–3.60 m, (R^3 = Me) 1.09 d, $^3J_{HH}$ 6.54 Hz, 5.36 s (H^c), (R^4 = Ph) 7.23–7.49 m
Vg	3.74 s	9.69 [a]	5.51 [a]	*t*-Bu 1.23 s	(R^2 = R^3 = Me), 1.3 s, 3.48 s (R^4 = H)
Vh	2.94–3.18 m	9.60 [a]	6.14 [a]	*t*-Bu 1.25 s	(R^2 = R^3 = H), 3.75–3.86 m, 5.10 d, $^3J_{HH}$ 9.0 Hz (H^c), (R^4 = Ph) 7.23–7.42 m
Vi	*AB* 3.79, 3.98 $^2J_{HH}$ 16.71 Hz	9.67 [a]	6.03 [a]	*t*-Bu 1.28 s	(R^2 = H) 5.27 s, (R^3 = Me) 1.03 d, $^3J_{HH}$ 6.0 Hz (3H),3.40–3.52 m (H^c), R^4 = Ph) 7.20–1.39 m
Vj	*AB* 3.91,4.07 $^2J_{HH}$ 16.71 Hz	9.82 [a]	6.00 [a]	H 3.33 s	(R^2 = H) 5.30 s, (R^3 = Me) 1.02 d, $^3J_{HH}$ 6.54 Hz, 3.40–3.52 m (H^c), (R^4 = Ph) 7.23–7.42 m

[a] Broad signal. [b] Compound **IVc** does not correspond to the general formula and is a free base (see text). [c] Single proton signal.

128.61 Hz) corresponds to the carbon atoms of two chemically equivalent methyl groups. The C^γ carbon atom of the CH_2N methylene group appears as a triplet at δ_C 32.73 ppm ($^1J_{CH}$ 137.33 Hz) and the CH_2OH carbon atoms, as a triplet at δ_C 68.92 ppm ($^1J_{CH}$ 139.51 Hz). The C^α and C^β atoms of the triple bond resonate in their characteristic fields at δ_C 82.54 and 91.31 ppm, respectively.

Table 3. ^{13}C NMR spectra of acetylenic aminoalcohol hydrochlorides **Va**–**Vj** [R^1–C^α≡C^β–$C^\gamma H_2$–NH_2^+–$C^\delta R^2R^3$–$C^\varepsilon HR^4OH$] Cl^-, δ_C, ppm

Comp. no.	C^α	C^β	C^γ	C^δ	C^ε	R^1	R^2	R^3	R^4
Va	87.83	81.77	37.16	49.00	57.19	Ph [c]	H	H	H
Vb	87.83	81.75	37.42	53.44	63.06	Ph [c]	H	H	Me, 22.01
IVc [a, b]	82.54	91.31	32.77	54.58	68.92	Ph [c]	Me, 24.37	Me, 24.37	H
Vc [b]	87.18	82.89	32.23	60.84	65.84	Ph [c]	Me, 21.38	Me, 21.38	H
Vd	87.69	81.93	35.26	58.65	60.15	Ph [c]	H	H	CH_2Me, CH_2 21.06, Me 10.73

Table 3. (Contd.)

Comp. no.	C^{α}	C^{β}	C^{γ}	C^{δ}	C^{ε}	R^1	R^2	R^3	R^4
Ve	87.93	81.72	37.48	53.65	69.01	Ph[c]	H	H	Ph[c]
Vf	87.80	81.96	35.26	58.75	69.93	Ph[c]	Me, 10.17	H	Ph[c]
Vg	96.15	71.76	31.74	60.63	65.49	Me_3C, C 27.93, Me 31.21	Me, 21.41	Me, 21.41	H
Vh	97.39	70.67	36.89	53.20	68.80	Me_3C, C 27.99, Me 31.24	H	H	Ph[c]
Vi	97.26	70.78	34.75	58.14	69.80	Me_3C, C 28.04, Me 31.24	Me,10.12	H	Ph[c]
Vj [b]	80.29	75.96	34.44	58.44	69.85	H	Me, 9.96	H	Ph[c]

[a] Compound **IVc** does not correspond to the general formula and is a free base (see text). [b] Proton-coupled ^{13}C NMR spectra. [c] The chemical shifts of phenyl carbon signals fit tabulated values (δ_C 122–142 ppm).

As expected, the ^1H NMR spectral patters of acetylenic aminoalcohol **IVc** and its hydrochloride **Vc** (Figs. 1 and 3, respectively) are essentially identical. However, protonation causes downfield shifts of almost all nonequivalent proton signals (Table 2).

As to the ^{13}C NMR spectra, the protonation of the nitrogen atom causes expected downfield shifts of the C^{α} and C^{δ} signals (~5 ppm). At the same time, the chemical shifts of methyl carbons and C^{γ} and C^{ε} are scarcely affected, while the C^{β} signal is even shifted upfield by about 8.5 ppm (Fig. 4).

If the phenyl group at the triple bond (compounds **Va**–**Vf**, R^1 = Ph) is replaced by *tert*-butyl (compounds **Vg**–**Vi**, R^1 = t-Bu), the C^{α} signal is shifted downfield by 10 ppm (96–97 ppm), and the C^{β} signal upfield by 10 ppm as well (70–71 ppm).

The assignment of the chemical shifts of C^{α} and C^{β}, presented in Table 3, was made in view of the fact that the C^{β} signal in the all the studied cases is a triplet with the $^2J_{CH}$ constant of 9 Hz, due to coupling with two protons at C^{γ}.

The resulting data show that neither the structure of the starting 2-aminoethanol nor the nature of the R^1 radical at the triple bond (*t*-Bu, Ph) affect the

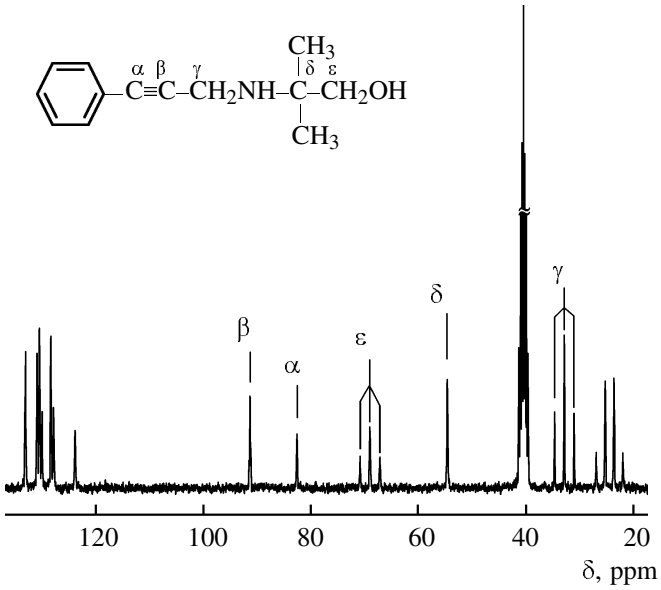


Fig. 2. ^{13}C NMR spectrum of compound **IVc**.

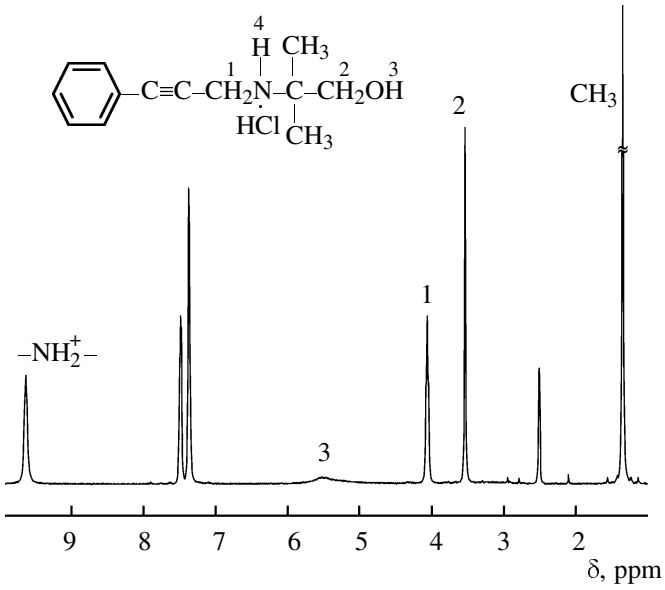


Fig. 3. ^1H NMR spectrum of compound **Vc**.

chemo- and regioselectivity of the hydrogenation reaction, and the triple bond always remains intact. The only compound that behaves unusually is azomethine **IVj** which, due to the hydrolytic instability of the Si–C_{sp} bond forms 2-propargylaminoethanol hydrochloride with a terminal acetylenic fragment (compounds **Vj**).

The data in Table 3 show that the yields of the aminoalcohols within the series in question are independent on the nature of the amino group (which can be primary, secondary, or tertiary), structure and nature of radicals R^2, R^3, and R^4 (methyl, ethyl, phenyl), as well as radical R^1 at the triple bond, varying from 45 to 80%. The low yields of hydrochlorides **Va**, **Vb**, and **Vj** are probably due to their better solubility in acetone.

The sample of aminoalcohol hydrochloride **Vc** prepared either by the reaction of amine **IVc** with HCl in acetone or by the procedure excluding the amine isolation step showed the same melting points and ^{1}H NMR spectra.

Hydrochlorides **Va**–**Vj** are colorless crystals stable in air and readily soluble in ethanol and water. The yields, melting points, and elemental analyses of the prepared compounds are listed in Table 3, and the ^{13}C NMR spectral parameters, in Table 2.

EXPERIMENTAL

The solvents and reagents were of analytical grade. The ^{1}H and ^{13}C NMR spectra were registered on a Varian XL-300 spectrometer at 300.013 and 75.45 MHz, respectively, in DMSO-d_6 solutions. 2-Aminoethanol, 2-aminopropanol, 2-aminobutanol, and 2-methyl-2-aminopropanol were purchased from Acros and (±)-2-methyl-2-amino-1-phenylethanol, from Fluka. The main substance content in all the reagents was 98 mol % or higher. The starting aldehydes were synthesized by known procedures: 4,4-dimethylpent-2-ynal [13], 3-methylsilylprop-2-ynal [14], and 3-phenylprop-2-ynal [15].

2-Methyl-2-(3-phenylprop-2-ynylamino)propan-1-ol (IVc). To a solution of 0.01 mol of freshly distilled 3-phenylprop-2-ynal in 50 ml of methanol, a solution of 0.01 mol of 2-methyl-2-aminopropanol in 10 ml of methanol was added dropwise at room temperature with stirring. The mixture was stirred for a few minutes and then quickly heated to boil and cooled to room temperature. A 1.2-fold molar excess of $NaBH_4$ was then added to the solution in small portions. The reaction mixture got warm and foamed up. The mixture was cooled to room temperature and diluted with a 10-fold excess of water, and the

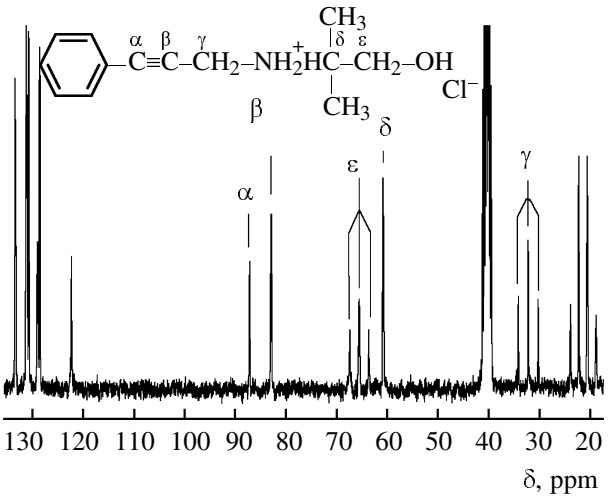


Fig. 4. ^{13}C NMR spectrum of compound **Vc**.

emulsion that formed was left overnight. Crystals formed and were filtered off and washed with water, and the filtrate was extracted with two portions of methylene chloride. The extract was evaporated, and the residue was dissolved in 50 ml of ethanol and combined with the crystals obtained before. The resulting material was diluted with a little water and cooled in a freezer. The crystalline residue was then filtered off and dried in air to obtain 1.12 g (55%) of aminoalcohol **IVc**, mp 71°C, ^{1}H NMR spectrum, δ_H (ppm): 1.02 s (6H), 1.60 s (1H), 3.20 d, $^3J_{HH}$ 5.09 Hz, (2H), 3.49 s (2H), 5.53 t, 5.09 Hz, (1H), 7.28–7.36 m (5H). ^{13}C NMR spectrum, δ_C (ppm): 24.37 q $^1J_{CH}$ 128.61 Hz, 32.73 t, $^1J_{CH}$ 137.33 Hz; 68.92t, $^1J_{CH}$ 139.51 Hz; 82.54 s; 91.31 t, $^3J_{CH}$ 8.72 Hz.

Aminoalcohols IVa, IVb, and IVd–IVj *(general procedure)*. A solution of 2-aminoalcohol in 10 ml of methanol was added dropwise at room temperature to a stirred solution of 0.01 mol of freshly distilled prop-3-ynal in 50 ml of methanol. The mixture was stirred for 1–2 min and quickly heated to boil and cooled to room temperature, after which a 1.2-fold molar excess of $NaBH_4$ was immediately added in small portions. Therewith, the reaction mixture got warm and foamed up. It was cooled and diluted with a 10-fold excess of water. The resulting was extracted with methylene chloride (3 × 50 ml). The extract was dried with calcined magnesium sulfate and then evaporated at reduced pressure. The prepared aminoalcohols were oily light yellow liquids.

Aminoalcohol hydrochlorides Va–Vj *(general procedure)*. To a solution of crude aminoalcohol in 50 ml of acetone, concentrated hydrochloric acid was added dropwise with stirring to a weakly acidic reac-

tion of the medium (pH 5.5). The mixture was kept in a freezer for 1 day. Crystals precipitated and were filtered off and dried in air. The compounds obtained are colorless crystals stable in air, readily soluble in ethanol and water, and poorly soluble in benzene and toluene. The yields, melting points, and elemental analyses of the prepared compounds are listed in Table 3.

REFERENCES

1. Stanek, J., Frei, J., Mett, H., Schneider, P., and Regenass, U., *J. Med. Chem.,* 1992, vol. 35, no. 8, p. 1339.
2. Kaneko, T., Wong, H., Howell, H.G., Rose, W.C., Bradner, W.T., Doyle, T.W., *J. Med. Chem.,* 1985, vol. 28, no. 7, p. 9589.
3. Ogura, H., Kobayashi, H., Nagai, K, Nishida, T., Naito, T, Tatsumi, Y., Yokoo, M. and Arika, T., *Chem. Pharm. Bull.,* 1999, vol. 47, no. 10, p. 417.
4. Tsujihara, K., Ozeki, M., Morikawa, T., Taga, N., Miyazaki, M., Kawamori, M., and Arai, Y., *Chem. Pharm. Bull.,* 1981, vol. 29, no. 11, p. 3262.
5. Tsuzuki, K., Sunazuka, T., Marui, S., Toyoda, H., Omura, S., Inatomi, N. and Iton, Z., *Chem. Pharm. Bull.,* 1989, vol. 37, no. 10, p. 2687.
6. Bottini, A.T. and Vasu, D., *J. Org. Chem.,* 1962, vol. 27, no. 8, p. 968.
7. Ince, J., Ross, T.M., and Shipmann, M., *Tetrahedron: Assymetry,* 1996, vol. 7, no. 12, p. 3397.
8. Courtois, G., and Miginiac, L., *J. Organomet. Chem.,* 1988, vol. 340, p. 127.
9. Blanchet, J., Bonin, M., Chiaroni, A., Micouin, L., Riche, C., and Husson, H.-P., *Tetrahedron Lett.,* 1999, vol. 40., no. 15, p. 2935.
10. Blanchet, J., Bonin, M., Micouin, L., and Husson, H.-P., *J. Org. Chem.,* 2000, vol. 65, no. 20, p. 6423.
11. Atavin, A.S., Dmitrieva, Z.T., Trofimov, B.A., and Kron, A.A., USSR Inventor's Certificate no. 225 873, *Byull. Izobret.,* 1968, no. 28.
12. Stadnichuk, M.D., Khramchikhin, A. V., Piterskaya, Yu.L., and Suvorova, I.V., *Zh. Obshch. Khim.,* 1999, vol. 69, no. 4, p. 616.
13. Bohlman, F., *Chem. Ber.,* 1953, vol. 86, no. 1, p. 63.
14. Komarov, N.V., Yarosh, O.G., and Astaf'eva, A.N., *Zh. Obshch. Khim.,* 1966, vol. 36, no. 5, p. 907.
15. *Organic Syntheses,* 1948, coll. vol. 3. Translated under the title *Sintezy organicheskikh preparatov,* Moscow: Inostrannaya literatura, 1952. vol. 4, p. 445.