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Organosilicon Synthesis of Isocyanates: IV.[1] Synthesis of Isocyanates from Aliphatic and Alkylaromatic Amino Acid Esters

A. V. Lebedev, A. B. Lebedeva, V. D. Sheludyakov, V. V. Shatunov, and S. N. Ovcharuk

State Research Institute of Chemistry and Technology of Organoelement Compounds, shosse Entuziastov 38, Moscow, 111123 Russia

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Abstract — Treatment of an alcoholic suspension of amino acids with trimethylchlorosilane yielded phenylglycine, valine, β-phenylalanine, and homovaline ester hydrochlorides. Their saccharin-catalyzed silylation with hexamethyldisilazane proceeds quantitatively and involves only one proton of the amino group. The best conversion of the amino acid esters to the corresponding isocyanates was achieved by phosgene treatment of their monosilyl urethanes, rather than of the silylated amino esters. Monosilyl urethanes are formed quantitatively by treatment of the amino acid ester hydrochlorides with the hexamethyldisilazane–CO_2 system. The ^{1}H NMR spectra show that monosilyl urethanes derived from α- and β-amino acid esters are characterized by intramolecular interaction of the silicon atom and the oxygen atom of the carboxy group.
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We have reported previously [1] on the organosilicon synthesis of isocyanates from amino acid esters. Proceeding with these studies, we examined some specific features of the synthetic route to isocyanates derived from aliphatic and alkylaromatic α- and β-amino acid esters. Phenylglycine **Ia**, valine **Ib**, homovaline **Va**, and β-phenylalanine **Vb** were chosen as the starting substances.

The amino acids were esterified by treating their alcoholic solutions with a twofold molar amount of trimethylchlorosilane in the temperature range 5–7°C. The yields of the amino ester hydrochlorides **IIIa**–**IIIc**, **VIa**, and **VIb** exceeded 98%.

$$\underset{\text{NH}_2}{\overset{|}{\text{RCHCOOH}}} + 2\text{Me}_3\text{SiCl} + \text{R}^1\text{OH}$$

Ia, Ib **IIa, IIb**

$$\longrightarrow \underset{\text{NH}_2\cdot\text{HCl}}{\overset{|}{\text{RCHCOOR}^1}} + \text{HCl} + (\text{Me}_3\text{Si})_2\text{O},$$

IIIa–IIIc **IV**

I, R = Ph (**a**), *i*-Pr (**b**); **II**, R = Me (**a**), Et (**b**); **III**, R = Ph, R^1 = Me (**a**); R = *i*-Pr, R^1 = Me (**b**), Et (**c**).

$$\underset{\text{NH}_2}{\overset{|}{\text{RCHCH}_2\text{COOH}}} + 2\text{Me}_3\text{SiCl} + \text{EtOH}$$

Va, Vb

$$\longrightarrow \underset{\text{NH}_2\cdot\text{HCl}}{\overset{|}{\text{RCHCH}_2\text{COOEt}}} + \text{HCl} + \textbf{IV},$$

VIa, VIb

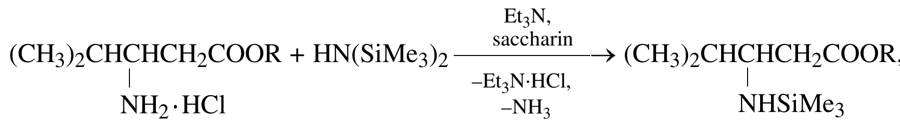
V, VI, R = *i*-Pr (**a**), Ph (**b**).

This esterification procedure is no less efficient than the previously reported [1] treatment of an alcoholic amino acid solution with thionyl chloride.

Silylation of the resulting amino ester hydrochlorides with trimethylchlorosilane or hexamethyldisilazane in the presence of triethylamine proceeds in no more than 15–20% yield. It is known [2] that *N,O*-silylation of the amino acids, e.g., glycine, with hexamethyldisilazane is catalyzed by saccharin. Using this catalyst for the silylation of hydrochlorides of homovaline **VIc** and its ethyl ester **VIa**, we prepared *N*-monosilyl derivatives **VIIa** and **VIIb** in quantitative yield. No *N,N*-bis-silyl derivatives were detected.

Phosgene treatment of the silyl derivatives **VIIa** and **VIIb** was carried out in 25% toluene solution of phosgene (10% excess) at 0–5°C with the subsequent

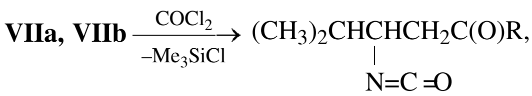
[1] For communication III, see [1].



VIa, VIc **VIIIa, VIIb**

VI, R = Et (**a**), H (**c**); **VII**, R = Et (**a**), $SiMe_3$ (**b**).

distillation of trimethylchlorosilane and toluene. The corresponding isocyanates **VIIIa** and **VIIIb** were obtained in 58 and 41% yields, respectively.



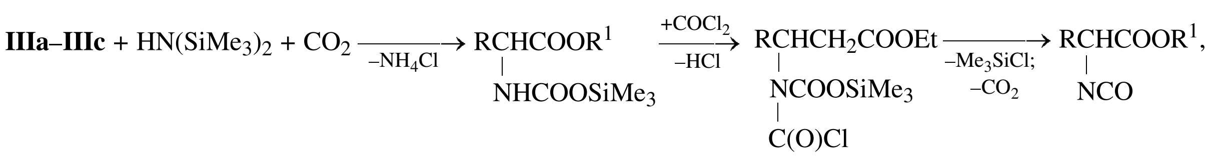
VIIIa, VIIIb

VIII, R = OEt (**a**), Cl (**b**).

Isocyanate **VIIIb** easily transforms into compound **VIIIa** under the action of an equimolar mixture of ethanol and triethylamine at the decreased temperature.

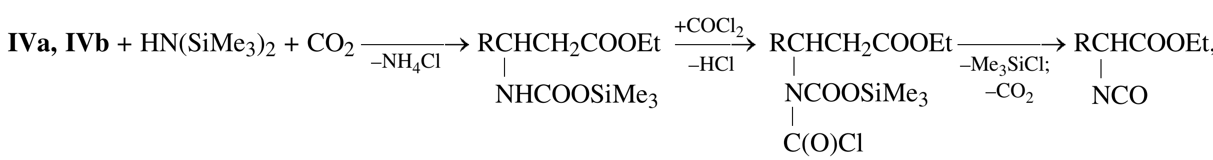
$$\textbf{VIIIb} + EtOH + Et_3N \xrightarrow{<5°C} \textbf{VIIIa}.$$

The yield of isocyanates **VIIIa** and **VIIIb** obtained by phosgene treatment of *N*-silyl derivatives **VIIa** and **VIIb** does not excees 60%, probably because of the side formation of insoluble amino ester hydrochlorides under the action of hydrogen chloride released in the course of the reaction [3]. Therefore, the isocyanates derived from phenylglycine, valine, homovaline, and β-phenylalanine esters were prepared by the scheme involving the intermediate formation of urethanes **IXa**–**IXc**, **XIIa**, and **XIIb**, followed by treatment with a 25% phosgene solution in toluene taken in a 10% excess. The desired isocyanates **VIIIa**, **VIIIc**, and **XIa**–**XIc** were synthesized in 80–85% yield.



IXa–IXc **Xa–Xc** **XIa–XIc**

IX, X, XI, R^1 = Me, R = Ph (**a**), *i*-Pr (**b**); R^1 = Et, R = *i*-Pr (**c**).

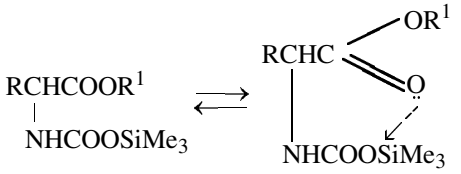


XIIa, XIIb **XIIIa, XIIIb** **VIIIa, VIIIc**

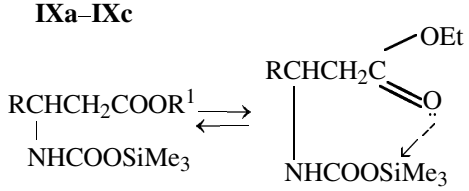
VIII, R = *i*-Pr (**a**), Ph (**c**); **XII, XIII**, R = *i*-Pr (**a**), Ph (**b**).

Urethanes **IX** and **XII** are formed quantitatively as colorless liquids. They can be readily isolated by simple filtration and vacuum treatment of the reaction mixture. Contrary to the lower aliphatic amine hydrochlorides [4, 5] reacting with the hexamethyldisilazane–CO_2 system with the heat evolution and formation of a mixture of mono- and bis-silylurethanes, urethanes **IX** and **XII** are obtained only under continuous heating of the reaction mixture at 90–95°C. Monosilylated urethanes are formed exclusively, which is evidently caused by steric hindrance to introduction of the second trimethylsilyl group. The ^{1}H NMR spectra show that urethanes **IX** and **XII** are characterized by braked rotation about the C–C bond involving the carbon atom adjacent to the amino group. This is proved by the presence of additional signals of the NH, chiral CH, CH_2, and OCH_3 groups, and also of the trimethylsilyl substituent. The rotation hindrance is caused probably by the weak transannular interaction of the silicon atom and the oxygen atom

of the ester group. Such donor–acceptor interactions are characteristic of organosilicon urethanes [6–8].



IXa–IXc



XIIa, XIIb

Formation of isocyanates **VIIIa**, **VIIIc**, and **XIa–XIc** in the course of phosgene treatment of urethanes proceeds evidently through the intermediate generation of carbamoyl chlorides **Xa–Xc**, **XIIIa**, and **XIIIb**, which decompose under mild conditions to the corresponding isocyanates with the liberation of trimethylchlorosilane and CO_2 without side formation of isocyanatocarboxylic acid chlorides, characteristic of glycine and β-alanine [1], which increases the isocyanate yield to 85%.

EXPERIMENTAL

The ^{1}H NMR spectra were taken on a Bruker AM-360 spectrometer (360.14 MHz) in $CDCl_3$ or DMSO-d_6, with the residual proton signals of the solvents used as references.

The mass spectra were recorded on an MAT-311A spectrometer at the ionizing electron energy of 70 eV, with direct sample inlet.

Synthesis of the amino acid alkyl ester hydrochlorides. To a suspension of 1 mol of amino acid **Ia**, **Ib**, **Va**, or **Vb** in 1 l of appropriate absolute alcohol (methanol or ethanol), 2 mol of trimethylchlorosilane was added dropwise with stirring at 5–6°C. After the addition was complete, the reaction mixture was slowly heated to room temperature and then refluxed for 2–3 h until the solution became almost clear. The resulting mixture was filtered, and the volatiles were distilled off at atmospheric pressure. After that, 500 ml of anhydrous toluene was added, and the solvent was distilled off at atmospheric pressure and then in a vacuum (3 mm) to give the corresponding amino ester hydrochlorides **IIIa–IIIc**, **VIa**, and **VIb** in almost quantitative yield.

Phenylglycine methyl ester hydrochloride IIIa. Yield 98.2%. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.71 s (3H, OCH_3), 5.21 s (1H, CH), 7.44 m ($3H_{arom}$), 7.52 t ($2H_{arom}$), 8.19 s (3H, NH_3^+).

Valine methyl ester hydrochloride IIIb. Yield 98.4%. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.97 q (6H, $2CH_3$), 2.28 m (1H, CH), 3.72 s (3H, OCH_3), 3.75 d (1H, CH), 8.70 s (3H, NH_3^+).

Valine ethyl ester hydrochloride IIIc. Yield 99.1%. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.97 q (6H, $2CH_3$), 1.23 t (3H, CH_3), 2.28 m (1H, CH), 3.75 d (2H, CH), 4.20 q (2H, OCH_2), 8.69 s (3H, NH_3^+).

Homovaline ethyl ester hydrochloride VIa. Yield 99%. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.91 d (6H, $2CH_3$), 1.20 t (3H, CH_3), 1.96 m (1H, CH), 2.60 q (1H, CH_2), 2.65 q (1H, CH_2), 3.27 m (1H, CH), 4.10 q (2H, OCH_2), 8.22 s (3H, NH_3^+).

β-Phenylalanine ethyl ester hydrochloride (VIb). Yield 98.7%. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.1 t (3H, CH_3), 3.0 q (1H, CH_2), 3.20 q (1H, CH_2), 3.98 m (2H, OCH_2), 4.56 q (1H, CHN), 7.4 m ($3H_{arom}$), 7.56 d ($2H_{arom}$), 8.75 s (3H, NH_3^+).

Silylation of homovaline. To a suspension of 1 mol of homovaline hydrochloride **VIc** or its ethyl ester hydrochloride **VIa** in 1 l of anhydrous toluene, 0.005 mol of saccharin was added. The reaction mixture was heated to 100°C, and a mixture of 1 mol of triethylamine and 1.1 mol of hexamethyldisilazane in the case of acid **VIc** or 0.55 mol of hexamethyldisilazane in the case of ester **VIa** was added dropwise with stirring. The reaction mixture was refluxed for 2–3 h until the sublimation of triethylamine hydrochloride into the reflux condenser ceased. After removing the solvent and excess hexamethyldisilazane, the residue was distilled in a vacuum to give compounds **VIIb** and **VIIa**, respectively, in 100% yield.

***N*-Trimethylsilylhomovaline ethyl ester VIIa:** bp 60–62°C (2 mm Hg). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.07 s (9H, $NSiMe_3$), 0.92 q (6H, $2CH_3$), 1.26 t (3H, CH_3), 1.62 m (1H, CH), 2.20 q (1H, CH_2), 2.40 q (1H, CH_2), 3.02 m (1H, CH), 4.15 q (2H, OCH_2). Mass spectrum (*m/z*): 231 ($[M]^{+\cdot}$). $C_{11}H_{25}NO_2Si$. Calculated: molecular mass 231.40.

***N*-Trimethylsilylhomovaline trimethylsilyl ester VIIb:** bp 61–62°C (2 mm Hg). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.04 s (9H, $OSiMe_3$), 0.28 s (9H, $OSiMe_3$), 0.84 q (6H, $2CH_3$), 1.58 m (1H, CH), 2.25 q (1H, CH_2), 2.45 q (1H, CH_2), 3.05 m (1H, CH). Mass spectrum (*m/z*): 275 ($[M]^{+\cdot}$). $C_{12}H_{29}NO_2Si_2$. Calculated: molecular mass 275.53.

Phosgene treatment of amino ester *N*-trimethylsilyl derivatives. To a solution of 0.22 mol of phos-

gene in 80 ml of toluene, a solution of 0.2 mol of silylamine **VIIa** or **VIIb** in 40 ml of toluene was added dropwise with stirring at 0°C. After the addition was complete, the trimethylchlorosilane and toluene were distilled off until the vapor temperature reached 105°C. The residue was distilled in a vacuum to obtain the target products **VIIIa** and **VIIIb**.

Ethyl 3-isocyanato-4-methylpentanoate VIIIa. Yield 58%, bp 76°C (1.5 mm Hg), n_D^{20} 1.4339. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.97 q (6H, $2CH_3$), 1.27 t (3H, CH_3), 1.77 m (1H, CH), 2.48 d (2H, CH_2), 3.83 q (1H, CH), 4.17 q (2H, OCH_2). Mass spectrum (*m/z*): 185 ($[M]^{+\cdot}$). $C_9H_{15}NO_3$. Calculated: molecular mass 185.22.

3-Isocyanato-4-methylpentanoyl chloride VIIIb. Yield 41%, bp 74°C (1.5 mm Hg), n_D^{20} 1.4510. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.01 q (6H, $2CH_3$), 1.83 m (1H, CH), 3.07 d (2H, CH_2), 3.93 q (1H, CH). Mass spectrum (*m/z*): 175 ($[M]^{+\cdot}$). $C_7H_{10}ClNO_2$. Calculated: molecular mass 175.61.

Esterification of the acid chloride. To a solution of 17.5 g of acid chloride **VIIIb** in 20 ml of dry toluene, 10.1 g of triethylamine was added at 0–2°C. After that, 4.6 g of absolute ethanol was added dropwise. The reaction mixture was left until its temperature reached 20°C. After that, the precipitate of triethylamine hydrochloride was filtered off, and the filtrate was distilled in a vacuum to obtain 17 g of isocyanate **VIIIa**. Yield 92%.

***N*-Siloxycarbonylation of the amino ester hydrochlorides.** A mixture of 1 mol of compound **IIIa**–**IIIc**, **VIa**, or **VIb**, 0.62 mol of hexamethyldisilazane, and 300 ml of toluene was heated with stirring in a CO_2 flow for 5 h at 90–95°C. After completion of the gas bubbling, the reaction mixture was cooled, and the precipitate was filtered off. After the distillation of excess hexamethyldisilazane and the solvent, urethanes **IXa**–**IXc**, **XIIa**, and **XIIb** were obtained in 99–100% yield based on the starting amino ester hydrochloride.

Methyl 2-phenyl-2-(trimethylsiloxycarbonylamino)ethanoate. ^{1}H NMR spectrum, δ, ppm: 0.26 s, 0.28 s (83 : 17, 9H, $SiMe_3$); 3.70 s, 3.72 s (16 : 84, 3H, OCH_3); 5.17 d, 5.32 d (17 : 83, 1H, CH); 5.55 d, 5.70 d (17 : 83, 1H, NH); 7.35 m ($5H_{arom}$). Mass spectrum (*m/z*): 281 ($[M]^{+\cdot}$). $C_{13}H_{19}NO_4Si$. Calculated: molecular mass 281.38.

Methyl 2-(trimethylsiloxycarbonylamino)-3-methylbutanoate IXb. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.27 s, 0.29 s (88 : 12, 9H, $SiMe_3$); 0.88 d, 0.95 d, 0.90 d, 0.97 d (88 : 12, 6H, $2CH_3$); 2.04 m, 2.14 m (12 : 88, 1H, CH); 3.71 s, 3.73 s (12 : 88, 3H, OCH_3); 4.08 q, 4.23 q (12 : 88, 1H, CH); 4.92 d, 5.17 d (13 : 87, 1H, NH). Mass spectrum (*m/z*): 247 ($[M]^{+\cdot}$). $C_{10}H_{21}NO_4Si$. Calculated, %: molecular mass 247.36.

Ethyl 2-(trimethylsiloxycarbonylamino)-3-methylbutanoate IXc. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.27 s, 0.29 s (88 : 12, 9H, $SiMe_3$); 0.88 d, 0.95 d, 0.90 d, 0.97 d (88 : 12, 6H, $2CH_3$); 1.27 t (3H, CH_3); 2.04 m, 2.14 m (12 : 88, 1H, CH); 4.08 m, 4.22 m (12 : 88, 3H, CH + OCH_2); 4.94 d, 5.18 d (13 : 87, 1H, NH). Mass spectrum (*m/z*): 261 ($[M]^{+\cdot}$). $C_{11}H_{25}NO_4Si$. Calculated, %: molecular mass 261.39.

Ethyl 3-(trimethylsiloxycarbonylamino)-4-methylpentanoate XIIa. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.25 s, 0.27 s (85 : 15, 9H, $SiMe_3$); 0.91 s (6H, $2CH_3$); 1.25 t (3H, CH_3); 1.73–1.86 m (1H, CH); 2.39–2.55 m (2H, CH_2); 3.74 m (1H, CH); 4.12 q (2H, OCH_2); 4.66 d, 5.05 d (15 : 85, 1H, NH). Mass spectrum (*m/z*): 275 ($[M]^{+\cdot}$). $C_{12}H_{25}NO_4Si$. Calculated: molecular mass 275.41.

Ethyl 3-phenyl-3-(trimethylsiloxycarbonylamino)propanoate XIIb. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.25 s, 0.27 s (86 : 14, 9H, $SiMe_3$); 1.17 t (3H, CH_3); 2.70–2.90 m (2H, CH_2); 4.07 q (2H, OCH_2); 4.98 q, 5.10 q (14 : 86, 1H, CH); 5.37 d, 5.67 d (14 : 86, 1H, NH); 7.20–7.32 m ($5H_{arom}$). Mass spectrum (*m/z*): 309 ($[M]^{+\cdot}$). $C_{15}H_{23}NO_4Si$. Calculated: molecular mass 309.43.

Phosgene treatment of silylurethanes derived from amino esters. To a solution of 0.22 mol of phosgene in 80 ml of toluene, a solution of 0.2 mol of urethane **IXa**–**IXc**, **XIIa**, or **XIIb** in 50 ml of toluene was added dropwise with stirring at 0°C. After the addition was complete, the reaction mixture was slowly heated to 50°C and kept at this temperature until the CO_2 liberation ceased. After that, the trimethylchlorosilane and toluene were distilled off at 50 mm Hg. Vacuum distillation of the residue (2–3 mm Hg) gave the target products **XIa**–**XIc**, **VIIIa**, and **VIIIc** in yields of 84, 81, 80, 85, and 82%, respectively.

Methyl 2-phenyl-2-isocyanatoethanoate XIa: bp 90–93°C (1.5 mm Hg). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.76 s (3H, OCH_3), 5.07 s (1H, CH), 7.39 m ($5H_{arom}$). Mass spectrum (*m/z*): 191 ($[M]^{+\cdot}$). $C_{10}H_9NO_3$. Calculated: molecular mass 191.18.

Methyl 2-isocyanato-3-methylbutanoate XIb: bp 61–62°C (2 mm Hg). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.86 d (3H, CH_3), 0.99 d (3H, CH_3), 1.27 t (3H, CH_3), 2.20 m (1H, CH), 3.87 d (1H, CH), 4.23 m (2H, OCH_2). Mass spectrum (*m/z*): 171 ($[M]^{+\cdot}$). $C_8H_{13}NO_3$. Calculated: molecular mass 171.19.

Ethyl 3-phenyl-3-isocyanatopropanoate VIIIc: bp 113–115°C (3 mm Hg). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.27 t (3H, CH_3), 2.73 q (1H, CH_2), 2.83 q (1H, CH_2), 4.19 q (2H, OCH_2), 5.13 q (1H, CH), 7.35 m ($5H_{arom}$). Mass spectrum (*m/z*): 205 ($[M]^{+\cdot}$). $C_{11}H_{11}NO_3$. Calculated: molecular mass 205.21.

REFERENCES

1. Lebedev, A.V., Lebedeva, A.B., Sheludyakov, V.D., Ovcharuk, S.N., Kovaleva, E.A., and Ustinova, O.L., *Zh. Obshch. Khim.,* 2006, vol. 76, no. 7, p. 1118.
2. Bruynes, S.A. and Jurriens, T.K., *J. Org. Chem.,* 1982, vol. 47, no. 20, p. 3966.
3. Davidovich, Yu.A., Butaeva, V.I., Galkin, O.M., Sentsova, T.N., and Rogozhin, S.V., *Izv. Akad. Nauk SSSR, Ser. Khim.,* 1977, no. 7, p. 1682.
4. Mironov, V.F. and Kozyukov, V.P., *Zh. Obshch. Khim.,* 1984, vol. 54, no. 6, p. 1217.
5. Lebedev, A.V., Lebedeva, A.B., Sheludyakov, V.D., Ovcharuk, S.N., Kovaleva, E.A., and Ustinova, O.L., *Zh. Obshch. Khim.,* 2006, vol. 76, no. 3, p. 493.
6. Sheludyakov, V.D., Gusev, A.I., Dmitrieva, A.B., Los', M.G., and Kirilin, A.D., *Zh. Obshch. Khim.,* 1983, vol. 53, no. 10, p. 2276.
7. Sheludyakov, V.D., Dmitrieva, A.B., Gusev, A.I., Apal'kova, G.M., and Kirilin, A.D., *Zh. Obshch. Khim.,* 1984, vol. 54, no. 10, p. 2298.
8. Sheludyakov, V.D., Lebedeva, A.B., Kisin, A.V., Nikishina, I.S., Lebedev, A.V., and Kirilin, A.D., *Zh. Obshch. Khim.,* 1988, vol. 58, no. 2, p. 393.