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SYNTHESIS OF N'-SUBSTITUTED AMIDINES THROUGH THE CLEAVAGE AN OXADIAZOLONE HETEROCYCLE BY WEAKLY BASIC NUCLEOPHILES. EFFECT OF THE NATURE OF THE NUCLEOPHILE AND OF THE NUCLEOPHILE/ SUBSTRATE MOLAR RATIO *

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The reaction of 1-ethoxycarbonylmethyl-5,5,7,7-tetramethyl-2-oxo-tetrahydroimidazo[1,5-b]oxadiazol-6-oxyl with the weakly basic nucleophiles NaN_3, NaCN, KF, KBr, KCl and $NaNO_2$ has been studied. It was shown for the first time that, as in the case of NaOH and MeONa, the reaction occurs with opening of the oxadiazolone ring to form exo-N-substituted amidines. It was shown that the weakly basic nucleophiles readily react with substrates which contain a substituent sensitive to attack by such nucleophiles as NaOH or MeONa. The effect of the nature of the nucleophiles on the reaction course for opening of the oxadiazolone ring was also studied. It was found that the reactivity of the nucleophiles in DMSO changes in the series $F^- > CN^- > N_3^- > NO_2^- > Cl^- > Br^-$ and qualitatively correlates with their basicities in this solvent. Examination of the effect of the ratio of the reagents on the degree of conversion of the starting oxadiazolone has shown that a quantity of nucleophiles less than one equivalent also allowed the cleavage reaction of the oxadiazolone heterocycle to go to completion through just increasing the reaction time. The experimental data obtained lends support to the proposed reaction scheme.

Keywords: amidine, nucleophile, nitroxyl radicals, tetrahydroimidazo[1,5-*b*][1,2,4]oxadiazol-2-one, 1,3-dipolar cycloaddition, EPR spectroscopy.

The 1,3-dipolar cycloaddition reaction of isocyanates to aldonitrones is one of the most efficient methods of synthesizing heterocyclic compounds. The cycloadducts formed (1,2,4-oxadiazol-5-one derivatives) are characterized by high stability and are used to capture unstable nitrones in order to identify them in an

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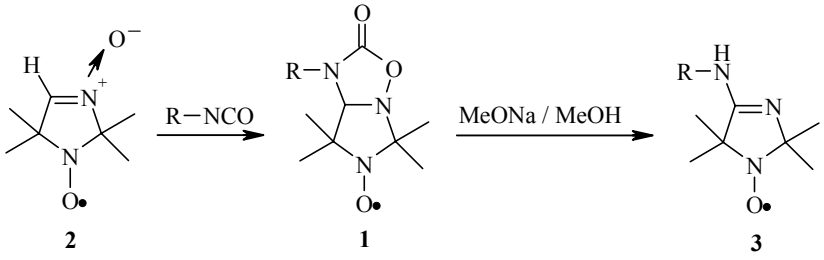
analytically pure state [1]. In addition, 1,2,4-oxadiazol-5-ones are of interest as biologically active compounds [2]. The thermolysis [3, 4] and basic hydrolysis [5, 6] of oxadiazolones can give N'-substituted amidines which, in turn, are used as starting materials in the synthesis of heterocycles [7, 8] and ligands [9, 10] as well as in medicine, e.g. as inhibitors of cytomegalovirus DNA polymerase [11]. Hydrolysis of the oxadiazolones **1**, prepared by cycloaddition of isocyanates to the nitroxyl radical 2,2,5,5-tetramethyl-1-oxyl-3-imidazoline 3-oxide **2**, leads to the preparation of the amidine radicals **3** (Scheme 1), the EPR spectroscopic magnetic parameters of which were sensitive to reversible protonation of the amidine group [12].

Scheme 1



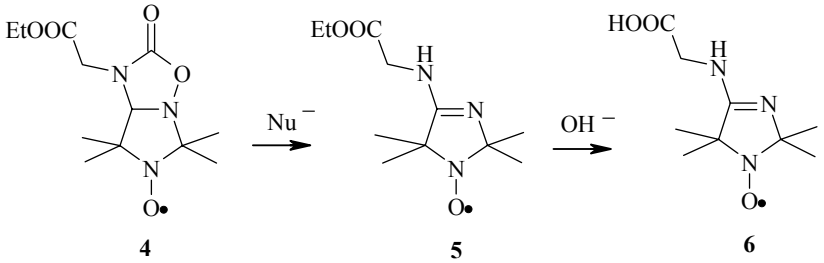
2 **1** **3**

Alkaline hydrolysis using NaOH or MeONa is the most general method for opening of an oxadiazolone ring but the presence in the substrate of a group sensitive to basic medium significantly limits its use [13].

We have recently found that the use of NaN_3 and KBr in DMSO or DMF leads to opening of an oxadiazolone ring in high yields under mild conditions (~ 55ºC) without affecting functional groups such as an ester which are sensitive to the action of the basic nucleophiles NaOH and MeONa [14]. We also found a marked difference in the reactivity of azide and bromide ions in the splitting reaction of the oxadiazolone ring. Bearing in mind that opening of an oxadiazolone heterocycle is one of the basic methods for preparing N'-substituted amidines and also with the aim of optimizing the conditions of the reaction and getting a deeper understanding of the its mechanism we have studied in more detail the qualitative effects of the nature of the nucleophiles, the solvents (aqueous, anhydrous conditions), and the ratio of nucleophiles to substrate on the product yield and the reaction time. It should be noted that a qualitative series of reactivities of certain nucleophiles reacting with cycloadducts **1** has been described [15]. However, unfortunately, the authors did not give the exact structure of the cycloadducts studied in the work or the conditions (temperature, reaction time) and product yields. In the absence of this data a logical use of the results of the work quoted presents difficulties in practise.

In our work we have used as substrate the cycloadduct **4**, the ester group of which (as previously shown) is stable to the conditions for ring splitting by such nucleophiles as NaN_3 or KBr [14]. The nucleophilic reagents used were NaN_3, NaCN, KF, KBr, KCl, and $NaNO_2$. Opening of the oxadiazolone was carried out at 55ºC for a solution of compound **4** in anhydrous DMSO with and without the addition of 5 vol. % of water. The reaction gave the ester derivative of the amidine **5** (Scheme 2).

Scheme 2



4 **5** **6**

TABLE 1. Cleavage of the Oxadiazolone Ring in the Cycloadduct **4** Using Nucleophilic Reagents

Nucleophile	F^-	CN^-	N_3^-	NO_2^-	Cl^-	Br^-
Reaction time, DMSO, h	4	12	14	21.5	310	362
Yield*, DMSO, %	74	82	74	62	59	52
Hardness (according to Pearson)	7.0	5.3	4.9	4.5	4.7	4.2
pK_a of the conjugate acid (in DMSO)	15	12.9	7.9	7.5	1.8	0.9
pK_a of the conjugate acid (in H_2O)	3.2	9.1	5	3.4	-7	-9
Yield*, DMSO+5 vol.% H_2O, %	12	10	10	10	12	14
Reaction time, DMSO+5 vol.% H_2O, h	369	171	753	800	486	383

* Preparative yield given.

The results of the opening of the oxadiazolone heterocycle in aqueous and anhydrous conditions using the reagents listed above is given in Table 1. The nucleophilic reagents are given in the order of increasing reaction time in anhydrous conditions (DMSO). The most active reagent in this series is the fluoride ion. The order of reactivity of the nucleophiles seen in DMSO ($F^- > CN^- > N_3^- > NO_2^- > Cl^- > Br^-$) correlates qualitatively with the order of their basicities in this solvent [16] (Table 1).

The order of nucleophile reactivities also closely follows the series of nucleophile hardness parameters due to Pearson [17, 18]. An exclusion is the nitrite ion. It is possible that the deviation of the nitrite ion from the overall series is due to its bidentate nature [19].

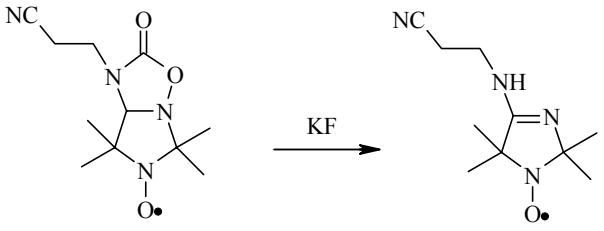
It is known that the addition of 5% water to a polar solvent inhibits the rate of nucleophilic substitution [20, 21] but the addition of 9% water to DMF [21] and of 30% to DMSO [22] restores the reaction order typical of protonic solvents. As evident from Table 1, the addition of 5% water to the reaction mixture leads to a marked increase in the reaction time and significant reduction in the preparative yield of the product of ring opening (**5**). In addition, the observed reaction times in the DMSO-H_2O mixture did not correlate with the series of nucleophile basicities in either water or in DMSO (Table 1).

Hence the most suitable preparative conditions for nucleophilic oxadiazolone ring opening (based on the reaction time and yield) uses anhydrous KF in dry DMSO. The efficiency and synthetic value of the method we have developed for oxadiazolone ring opening are illustrated by the examples given below.

An attempt to prepare the amidine acid **6** under traditional conditions of alkaline hydrolysis of cycloadduct **4** (MeONa/MeOH) gave a complex mixture of products, the amidine acid product **6** being obtained in only 6% yield. Opening of the oxadiazolone ring in compound **4** under mild nucleophilic conditions (KF/DMSO) and subsequent alkaline hydrolysis of the ester **5** gave the amidine acid **6** in good yield (45%) and this had a pH dependent EPR spectrum (Scheme 2). We propose that the reason for the low yield of compound **6** under alkali hydrolysis conditions is the high CH-acidity of the methylene hydrogen atoms in compound **4**. Efficient stabilization of the carbanion formed can be achieved through its enolization as well as the electron-acceptor effect of the ester and carbamate groups and also perhaps as an effect of chelation of the cation by the groups mentioned. Attack of the carbanion, formed under alkaline conditions, on the ester group or carbamate fragment of the oxadiazolone ring can lead to formation of side products. Evidently, in the case of the ester derivative of the amidine **5** the efficiency of stabilization of the transition state leading to the carbanion is not so high and this results in a lowered acidity of the methylene protons and the absence of the side reactions reported above.

Under analogous conditions (KF/DMSO) splitting of the oxadiazolone ring in the cycloadduct **7** (containing a cyano group) gives the amidine **8** in good yield (46%) (Scheme 3). In this case the yield of the reaction product does not differ from that using KCN [14] but the reaction time is decreased eightfold.

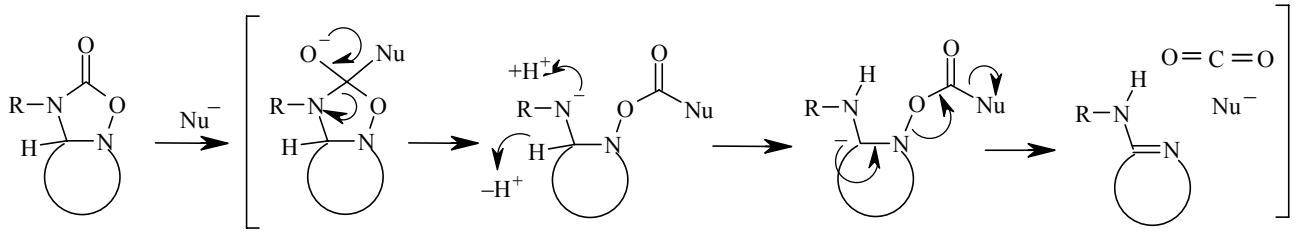
Scheme 3



7 **8**

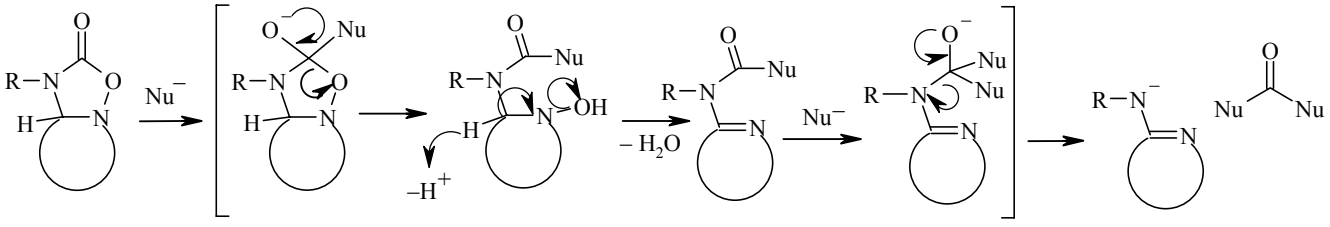
One of the possible schemes of conversion of the oxadiazolone to the amidine under nucleophilic reagent conditions has been discussed by us before [14]. The scheme is based on heterolytic cleavage of the C–N bond of the oxadiazolone fragment and it implies a recovery of the nucleophile in the reaction (Scheme 4A).

Scheme 4A



Another scheme involving heterolytic cleavage of the C–O bond and using two equivalents of the nucleophilic reagent also seems possible (Scheme 4B). This sequence of reaction can be realized, in particular, in conditions of opening of the oxadiazolone ring of the heterocycle by an excess of sodium methylate. In this case one of the reaction products should be the stable dimethylcarbonate which could be identified in the reaction mixture by spectroscopic methods.

Scheme 4B



We have studied the solvolysis of cycloadduct **1** (R = Ph) using MeONa solution in MeOH by chromatomass-spectrometric analysis of the initial and final reaction stages. The presence of the dimethylcarbonate was not recorded in the reaction mixture. Instead, there was observed an increase in the amount of CO_2 in the reaction mixture over time (an exact quantitative measurement was not carried out) and this supports Scheme 4A [14] (see Experimental section).

It should be noted that all of the experiments reported above (with the exception of the solvolysis in the system MeONa/MeOH) used not less than one equivalent of the nucleophilic reagent. However, we also found that a preparative opening of the oxadiazolone ring can be achieved with less than an equimolar amount of the

nucleophile. We have studied the cleavage reaction of the oxadiazolone ring in the cycloadduct **4** with 0.75, 0.5, and 0.25 equivalents of NaCN. The ratio of amidine **5** to starting cycloadduct **4** was determined by HPLC at the moment when the reaction with one equivalent of the nucleophile had been achieved and for the indicated amounts of the nucleophile came to 31, 19, and 16 respectively. In each of these examples the reaction can reach completion using less than an equivalent amount of the nucleophile just by increasing the reaction time. The results of the experiments reported fully agree with our previously proposed scheme of nucleophilic opening of an oxadiazolone ring which implies a recovery of the nucleophile in the reaction [14].

Hence we have shown for the first time that the reaction of 1-ethoxycarbonylmethyl-5,5,7,7-tetramethyl-2-oxotetrahydroimidazo[1,5-*b*][1,2,4]oxadiazol-6-oxyl (**4**) with the weakly basic nucleophiles NaN_3, NaCN, KF, KBr, KCl, and $NaNO_2$ (as in the reaction with NaOH and MeONa) leads to opening of the oxadiazolone ring and to the formation of *exo*-N-substituted amidines. Clear advantages of this method compared with those reported in the literature are the use of mild reaction conditions (DMSO, 55ºC) and its application to substrates which contain substituents sensitive to attack by nucleophiles like NaOH or MeONa. We have studied the effect of the nature of the nucleophiles on the course of the opening of the oxadiazolone ring.

It was found that the reactivity of the nucleophiles in DMSO changes in the order $F^- > CN^- > N_3^- > NO_2^- > Cl^- > Br^-$ and correlates qualitatively with their basicity in this solvent (the pK_a of the conjugated acid).

The use of fluoride ion is more convenient for the viewpoint of the preparative synthesis of amidines from oxadiazolones. We have also studied the effect of the ratio of the reagents on the degree of conversion of the starting oxadiazolone. It was found that an amount of nucleophile less than one equivalent can also lead to complete cleavage of the oxadiazolone ring by just increasing the reaction time. This observation and also the results of a study of the solvolysis reaction of an oxadiazolone heterocycle in the system MeONa/MeOH *via* chromato-mass spectrometric analysis supports the reaction scheme proposed by us in [14] and implies a recovery of the nucleophile in the reaction.

EXPERIMENTAL

IR spectra were taken on a Bruker Vector 22 FT-IR spectrometer for KBr tablets (concentration 0.25%, tablet thickness 1 mm). UV spectra were recorded in EtOH solution using an HP 8453 spectrometer and chromato mass spectra on a GSD HP 1800A spectrometer. EPR spectra were measured on a Bruker ER 200D-SRC instrument (9.5 GHz) and HPLC data was obtained on a MilliChrom A-02 (EcoNova) liquid chromatograph. The mobile phase was 70% water–30% MeOH. A Corning 345 pH meter was used for pH measurement. The spectroscopic characteristics for compound **5, 7, 8** agreed with those reported before [14]. The halides were initially heated in a roaster furnace at 400ºC for 4 h and $NaNO_2$ was dried at 120ºC for 1 h. The water content of the DMSO used in the reactions was determined by Fischer titration and was found to be 0.035%

Reactions of 1-Ethoxycarbonylmethyl-5,5,7,7-tetramethyl-2-oxotetrahydroimidazo[1,5-*b*][1,2,4]oxadiazol-6-oxyl (4) with Nucleophiles (General Method). The nucleophile (NaN_3, NaCN, KF, KBr, KCl, or $NaNO_2$, 0.18 mmol, 1 equivalent) was added to a solution of the cycloadduct **4** (0.05 g, 0.18 mmol) in dry DMSO (2 ml) (or DMSO+5 vol. % water). The reaction mixture was held on an oil bath at 55ºC. Monitoring of the reaction course was carried out by TLC (SiO_2, $CHCl_3$–MeOH, 15:1). At the end of the reaction the mixture was diluted with water (2 ml) and extracted with chloroform (4×3 ml). The chloroform extract was washed with saturated NaCl solution (7×5 ml) and dried over anhydrous Na_2SO_4. Distillation of the solvent at reduced pressure gave the amidine **5** as orange crystals.

(2,2,5,5-Tetramethyl-1-oxyl-2,5-dihydro-1H-imidazol-4-ylamino)acetic Acid Hydrochloride (6). NaOH (0.4 g, 10 mmol) was added to a solution of ester **5** (0.15 g, 0.6 mmol) in a mixture of ethanol and water (1:1, 15 ml). The reaction course was followed by TLC (SiO_2, $CHCl_3$–MeOH, 15:1). The amidine acid was purified by ion exchange chromatography on Dowex 1-X8 100-200 resin.

The commercially available resin in the Cl^- form was washed with acetone (3×50 ml), ethanol (3×50 ml), and deionized water (3×50 ml). The resin was held for 10 min in 2 M HCl and filtered (this procedure was repeated five times) and then washed with deionized water to neutral pH of the water washings [23].

The pH of the reaction mixture was taken to 10 and it was transferred to a column filled with ion exchange resin (resin thickness 3 x 15 cm), washed with deionized water to neutral pH of the water washings, and the amidine acid **6** was eluted with 3% HCl. Lyophylization of the aqueous solution gave orange crystals of the acid hydrochloride **6** (0.07 g, 45%) with mp 203-206ºC (decomp., EtOAc–MeOH, 7:6). IR spectrum, ν, cm^{-1}: 1759 (C=O); 1690 (C=N); 1577 (COO^-). Found, %: C 42.60; H 7.24; Cl 14.16; N 16.52. $C_9H_{16}N_3O_3 \cdot HCl$. Calculated, %: C 43.11; H 6.79; Cl 14.17; N 16.77.

Titration of Amidine Acid 6 Using EPR Spectroscopy (9.5 GHz). The titration is carried out using a published method [24]. A solution of the amidine acid was prepared in 10 mM buffered sodium phosphate solution with a nitroxyl radical concentration of approximately 0.1 mM. A sample was titrated with solutions of HCl or NaOH to the desired pH value which was determined using a pH meter with an accuracy of 0.05 pH units and a_N was measured as the distance between the low field and central components in the EPR spectrum. $pK_a = 6.21$; a_N ($R^{\bullet}H^+$) = 15.00 G, a_N (R•) = 15.85 G; $\Delta a_N = 0.85$ G.

Investigation of the Solvolysis of the Cycloadduct 1 (R = Ph) Using Chromato-mass Spectrometry. A solution of cycloadduct **1** (R = Ph) (0.15 g, 0.5 mmol) in MeOH (2 ml) was used as the vaseline CO_2 content of the reaction mixture. A 2N solution of MeONa in MeOH (0.5 ml) was added to the indicated solution, the reaction mixture was held for 15 min at room temperature, and an aliquot was removed for analysis. A further aliquot was taken 95 min after the start of the reaction. The relative intensity of the CO_2 peak with *m/z* 44 increases eightfold in the first 15 min of the experiment and a further 1.3 times in the subsequent 80 min.

Effect of the Concentration of Reagents on the Degree of Reaction of Cycloadduct 4. Sodium cyanide 12.8 mg (0.14 mmol), 8.5 mg (0.09 mmol), or 4.3 mg (0.05 mmol) (corresponding to 0.75, 0.5, and 0.25 equivalents respectively) was added to a solution of the cycloadduct **4** (0.05 g, 0.18 mmol) in dry DMSO (2 ml). The reaction mixture was held for 12 h at 55ºC (under these conditions the reaction of cycloadduct in the presence of 1 equivalent of the nucleophiles reaches 100%). The ratio of the starting compound to product at this moment is determined by HPLC from the ratio of peak areas for the corresponding components. The conditions for the chromatography were: Diaspher-110-C16 column (BioChemMak, Russia) (4.6×150 mm, mean particle size 5 μm). The retention times were: cycloadduct **4** = 3.8 and amidine **5** = 9.8 min. UV spectrum (EtOH), λ_{max} (log ε): **4** = 201 (0.4); **5** = 206 (1.0).

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REFERENCES

1. D. S. C. Black, R. F. Crozier, and V. C. Davis, *Synthesis*, **4**, 205 (1975).
2. N. Coskun and A. Parlar, *Synth. Commun.*, **36**, 997 (2006).
3 H. Seidl, R. Huisgen, and R. Grashey, *Chem. Ber.* **102**, 926 (1969).
4. T. Hisano, S. Yoshikawa, and K. Muraoka, *Chem. Pharm. Bull.*, **22**, 1611 (1974).
5. J. Goerdeler and R. Schimpf, *Chem. Ber.*, **106**, 1496 (1973).
6. C. J. Wilkerson and F. D. Green, *J. Org. Chem.*, **40**, 3112 (1975).
7. V. G. Granik, *Usp. Khim.*, **52**, 669 (1983).
8. V. A. Dorokhov and M. A. Prezent, *Izv. Akad Nauk, Ser. Khim.*, 888 (1994).

9. S. Dagorne, I. A. Guzei, M. P. Coles, and R. F. J. Jordan, *J. Amer. Chem. Soc.*, **122**, 274 (2000).
10. J. Barker and M. Kilner, *Coord. Chem. Rev.*, **133**, 219 (1994).
11. J. A. Tucker, T. L. Clyton, C. G. Chidester, M. W. Schulz, L. E. Harrington, S. J. Conrad, Y. Yagi, N. L. Oien. D. Yurek, and M.-S. Kuo, *Bioorg. Med. Chem.*, **8**, 601 (2001).
12. V. V. Khramtsov and L. B. Volodarsky in L. J. Berliner (editor), *Spin Labelling: The Next Millennium: Biological Magnetic Resonance*, Vol. 14, Plenum Press, New York (1998), p.109.
13. T. A. Berezina, V. V. Martin, L. B. Volodarsky, V. V. Khramtsov, and L. M. Vainer, *Bioorg. Khim.*, **16**, 262 (1990).
14. J. F. Polienko, T. Schanding, Y. V. Gatilov, I. A. Grigor'ev, and M. A. Voinov, *J. Org. Chem.*, **73**, 502 (2008).
15. T. A. Berezina, V. A. Reznikov, and L. B. Volodarsky, *Tetrahedron*, **49**, 10693 (1993).
16. F. G. Bordwell, *Acc. Chem. Res.*, **21**, 456 (1988).
17. J. O. Edwards and R. G. Pearson, *J. Am. Chem. Soc.*, **84**, 16 (1962).
18. R. G. Parr and R. G. Pearson, *J. Am. Chem. Soc.*, **105**, 7512 (1983).
19. S. A. Shevelev, *Usp. Khim.*, **39**, 1773 (1970).
20. E. A. S. Cavell, *J. Chem. Soc.*, 4217 (1958).
21. S. Winstein, L. G. Savedoff, S. Smith, I. D. R. Stevens, and J. S. Gall, *Tetrahedron Lett.*, **1**, 24 (1960).
22. R. F. Rodewald, K. Mahendran, J. L. Bear, and R. Fuchs, *J. Amer. Chem. Soc.*, **90**, 6698 (1968).
23. J. Korkisch, *Handbook of Ion Exchange Resins: Their Application to Inorganic Analytical Chemistry,* Vol. 1, CRC Press Inc., Boca Raton, Florida (1989).
24. M. Balakirev, V. V. Khramtsov, T. A. Berezina, V. V. Martin, and L. B. Volodarsky, *Synthesis*, **12**, 1223 (1992).