Synthesis of 3-alkyl-4-aminofurazans*

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A "one-pot" method for the synthesis of 3-alkyl-4-aminofurazans from ethyl β-alkyl-β-oxopropionates was developed. The multistep process involves hydrolysis of the ester, nitrosation at the activated methylene group, and treatment of the resulting intermediate with an alkaline solution of hydroxylamine in the presence of urea.

Key words: alkylfurazans, aminofurazans, glyoximes, oximes, nitrosation, cyclization.

Aminofurazans (amino-1,2,5-oxadiazoles) have found a wide use in organic synthesis.[1,2] Although 3-amino-4-methylfurazan (**1a**)[3] was first obtained more than 80 years ago, its homologs with longer alkyl substituents have not been synthesized to date. Reactions affecting the methyl group of compound **1a** remain unknown so far. At the same time, the chemistry of its amino group have been studied in detail.[1,2]

Scheme 1 illustrates the strategy that was used for the first synthesis of amine **1a**.[3] The total yield of the product was ~3%. This multistep process started from commercially inaccessible 2-chloro-1-methylglyoxime (**2**). Acylation of glyoxime **3** gave *O*,*O*′-diacyl derivative **4**, which underwent cyclization into 1,2,4-oxadiazole **5**. When treated with HCl, oxadiazole **5** rearranged into *N*-acetyl derivative **6**, which was *in situ* deacylated to give the target amine **1** in low yield. Later versions of this process,[4,5] as well as direct cyclization of 1-amino-2-methylglyoxime (**3**) into furazan **1**,[6] did not increase its yield noticeably.

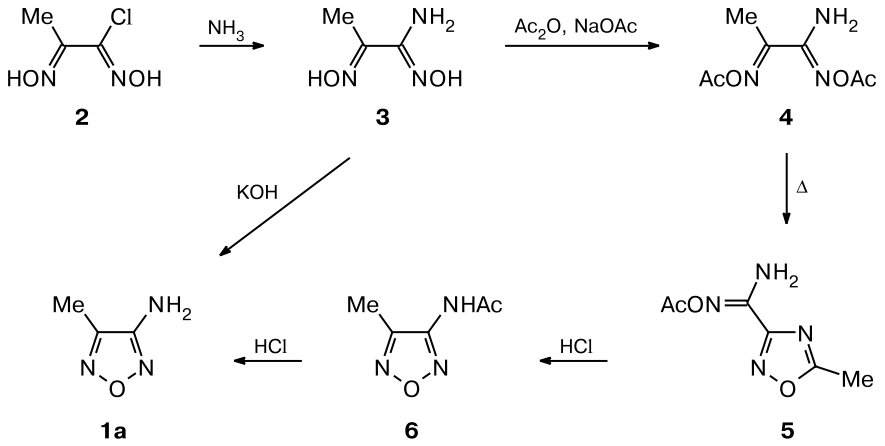
An original solution to the problem was a "one-pot" method[7] and its modified versions[8] for the conversion of isonitrosoacetone (**7a**) into furazan **1a**. According to the procedure, oxo oxime **7a** was treated with hydroxylamine in the presence of an alkali (Scheme 2) to give aminofurazan **1a** in 10% yield. Later,[9] its yield was increased to 63% by carrying out the reaction in the presence of urea.

The detailed mechanism of the transformation of compound **7a** into aminofurazan **1a** and the roles and effects of different factors on the reaction outcome have not been discussed hitherto.

The goal of the present study was to develop an efficient method for the synthesis of 3-alkyl-4-aminofurazans. Scheme 2 is obviously attractive as a basic route to this group of compounds. However, to extend the area of its

* Dedicated to Corresponding Member of the Russian Academy of Sciences E. P. Serebryakov on the occasion of his 70th birthday.

Scheme 1



Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 4, pp. 1007—1012, April, 2005.

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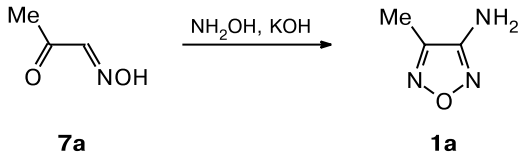
Scheme 2



7a **1a**

application, one should distinctly conceive of the chemism of the conversion **7a** → **1a** and the factors affecting the reaction at different steps. Analysis and detailing of these separate steps were essential parts of this study.

Obviously, this reaction involves a sequence of transformations, which can be described, by analogy with the literature data and our previous results,[10—13] by Scheme 3. Note that the feasibility of some of these transformations was mentioned earlier.[9,14]

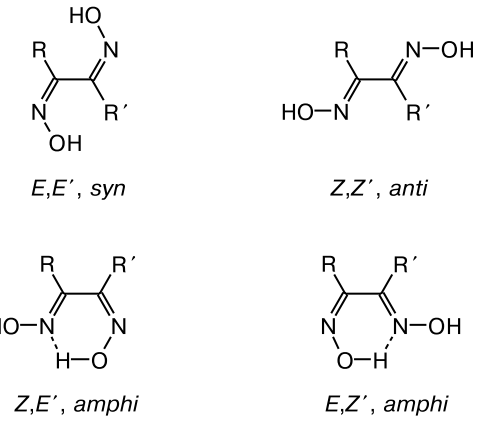
Previously,[10—13] in the study of one-pot syntheses of aminofurazans, we found that cyclization of glyoximes into the corresponding furazans is most difficult to occur in such processes as shown in Scheme 2. The ability of the oxime groups to participate in cyclization is determined by their configurations.

Unsymmetrically substituted glyoximes can exist as four geometrical isomers, depending on the configurations of the oxime groups.[15—17]

The intramolecular hydrogen bond in the *amphi*-form fixes both oxime groups on the same side of the C—C bond, which is favorable for cyclization.

Indeed, the formation of the furazan ring implies an intramolecular attack of an anionic center (formed in an alkaline medium at the O atom of one oxime group) on the N atom of the other oxime group (Scheme 4), which is possible only for the *amphi*-configuration of the glyoxime. Other conformers must be isomerized into the *amphi*-form before cyclization.

As a rule, the transition of one conformer into another is hindered.[15—17] To initiate it, high temperatures are required in some cases and base or acid catalysis, in others.

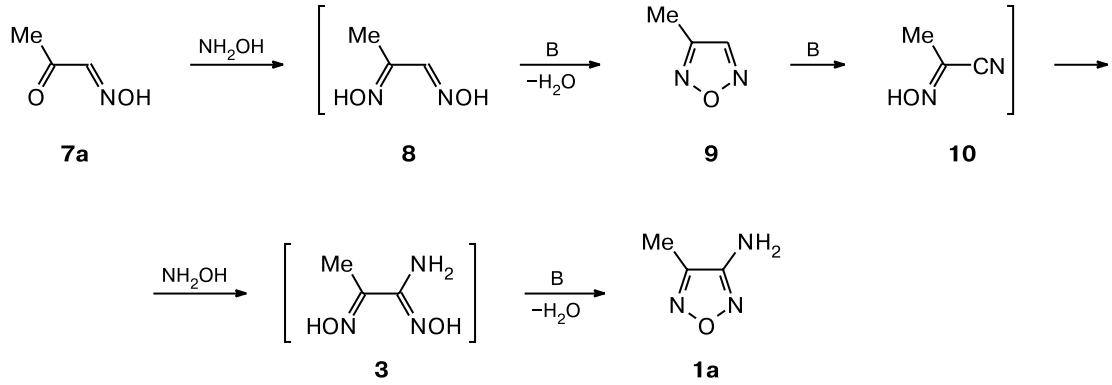


The configurations of both the glyoximes shown in Scheme 3 are known. For instance, glyoxime **8** exists in two sufficiently easily interconvertible isomers (*E*,*E*′ and *Z*,*E*′).[18] Because of this, glyoxime **8** is involved in subsequent transformations and is not detected in the final reaction mixture. Aminoglyoxime **3** exists exclusively as the unfavorable *Z*,*Z*′-form,[19,20] which necessitates its preisomerization.

According to the method proposed[8] (see Scheme 2), a mixture of α-hydroxyiminoacetone **7a**, KOH, and $NH_2OH \cdot HCl$ in the molar ratio 1 : 5 : 2.5 is refluxed for 6 h to give amine **1a** in 10% yield. We found that 1-amino-2-methylglyoxime **3**, which is a precursor of amine **1a** (see Scheme 3), is fairly resistant to dehydration/cyclization. A fourfold extension of the refluxing time (~24 h) increased the yield of amine **1** only to 15%. The reaction mixture always contained aminoglyoxime **3**, which could be isolated in 20 to 48% yield. It should be noted that heating in an alkaline medium causes reported[9] hydrolysis of important intermediates in Scheme 3. The major hydrolysis products **11**—**14** [21,22] are found in the reaction mixture as salts.

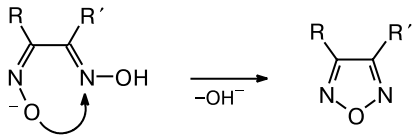
It turned out that the percentages of by-products increase with an increase in the reaction time.

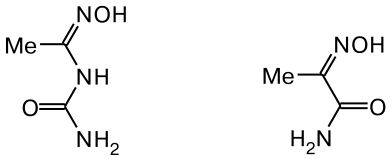
Scheme 3



7a **8** **9** **10** **3** **1a**

Scheme 4





11 **12**

13 **14**

We believed that the synthesis of aminofurazan **1a** could be intensified by optimization of the ratio of the reagents, as well as by addition of various additives.

For instance, according to Scheme 3, even catalytic amounts of an alkali are sufficient for the cyclization to occur since it is not consumed in this process. The presence of an alkali ensures intermediate generation of the oxime anion. Moreover, an alkali excess can give rise to a dianion[15] as the result of simultaneous deprotonation of both oxime groups of the glyoxime, which is not favorable for cyclization into the furazan ring. Indeed, a decrease in the alkali amount by one and a half (to 3 equiv.) provided a nearly doubled yield (up to 18%). Replacement of KOH by NaOH increased the yield to 21%.

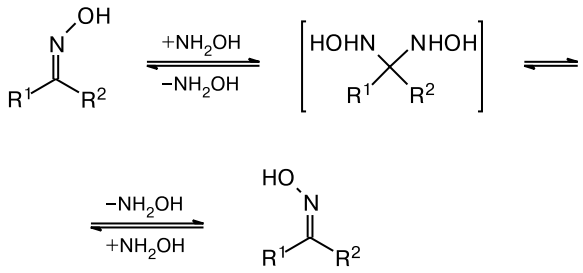
The formation of aminofurazan **1a** proved to be dependent on the hydroxylamine excess: the use of an 1.5—2 excess of NH_2OH made it possible to reduce the reaction time by half (3 h), the same yield being reached. However, a further increase in the amount of NH_2OH was ineffective.

Apparently, the presence of hydroxylamine facilitates the *E*/*Z*-isomerization of the oximes. We assumed that NH_2OH adds to the C=N bond of the oxime to form an intermediate with geminal hydroxyamino groups, which is converted into another oxime isomer by loss of a hydroxylamine molecule (Scheme 5). This process is obviously reversible.

Since the isomer involved in the formation of the furazan ring is consumed in subsequent cyclization, this equilibrium is shifted in the desired isomerization direction.

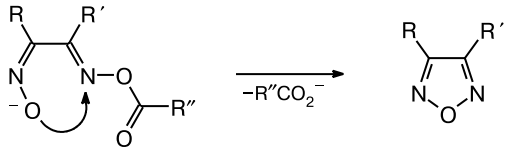
It has long been known that *O*-acyl derivatives of glyoximes undergo cyclization into furazans more easily

Scheme 5



than do glyoximes themselves.[1,2] According to Scheme 4, hydroxyl is a leaving group in intramolecular nucleophilic substitution resulting in ring formation. In *O*-acylglyoxime, the acyloxy group is displaced (Scheme 6). Here, requirements to the glyoxime conformation are also substantial.

Scheme 6



Because the electronic stabilization of the acyloxy anion is much higher than that of the hydroxide anion, detachment of the former should occur more easily, thus making ring closure more efficient. Clearly, a catalytic amount of an alkali is insufficient in this case, because the resulting carboxylate is brought out of the reaction cycle.

It should be noted that acylation of aminoglyoximes is often accompanied by cyclization of another type (see Scheme 1) that yields 1,2,4-oxadiazole derivatives. When heated with an acid or an alkali, they become rearranged into *N*-acylated aminofurazans;[3,23] subsequent deacylation is possible only in an acidic medium.

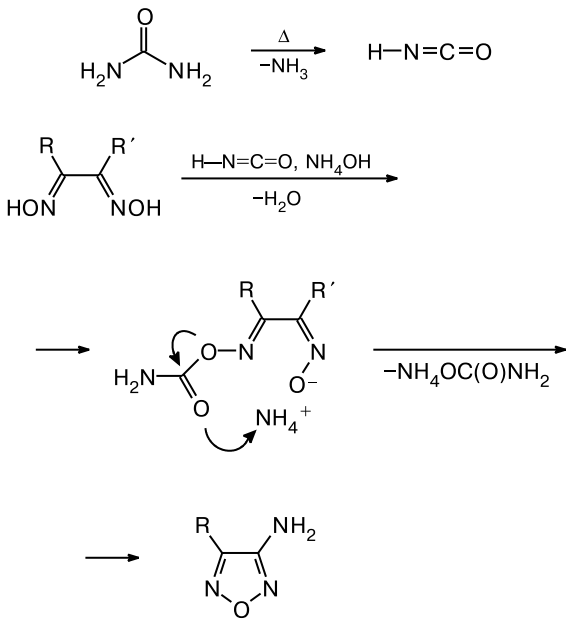
We found that addition of strong acylating reagents to the reaction mixture, which is a complex multicomponent system, is inefficient. For this reason, less reactive acylating reagents should be used (*e.g.*, isocyanic acid derivatives, which change oximes into *O*-carbamoyl derivatives[22,24—26]). Urea is most attractive in this group of reagents. Urea is known as a dehydrating agent that allows cyclization of glyoximes into furazans.[9,27] The plausible mechanism of the action of urea is shown in Scheme 7.

Thermal decomposition of urea produces two species necessary for the transformation of glyoxime into furazan: isocyanic acid acts as an acylating reagent, while ammonia provides the formation of an anionic center at the oxime group, thus promoting the cyclization. No less than

Table 1. Effects of the reaction conditions on the yield of aminofurazan **1a**

Entry	Ratio of the starting reagents (mol)				τ/h	Yield (%)
	Compound **7a**	$NH_2OH \cdot HCl$	NaOH	$OC(NH_2)_2$		
1	1	2	2	0.5	2	38
2	1	2	2	1	2	45
3	1	2	2	1	4	51
4	1	3	3	1	2	57
5	1	3	3	1	4	60
6	1	3.5	3.5	1	2	67
7	1	3.5	3.5	1	4	69
8	1	3.5	3.6	1	2	72
9	1	3.5	3.7	1	2	75
10	1	3.5	3.8	1	2	78
11	1	3.5	3.8	1	3	81
12	1	3.5	4.5	1	3	69

Scheme 7



an equimolar amount of urea is required for successful completion of the reaction.

We studied the effects of the ratio of reagents (**7a**/$NH_2OH \cdot HCl$/NaOH/urea) and the reaction time on the outcome of the process. A typical procedure involved slow addition of a solution of an alkali to an aqueous solution of compound **7a** and $NH_2OH \cdot HCl$, heating of the reaction mixture, addition of urea, and refluxing for a certain period of time. Selected data illustrating the observed trends are given in Table 1.

Apparently, the enhanced nucleophilicity of the oximate anion in the presence of a small alkali excess is due to an exchange reaction (replacement of the NH_4^+ cation by Na^+; see Scheme 7). This increases the yield of furazan **1a**. Finally, we attained an 81% yield of the target product.

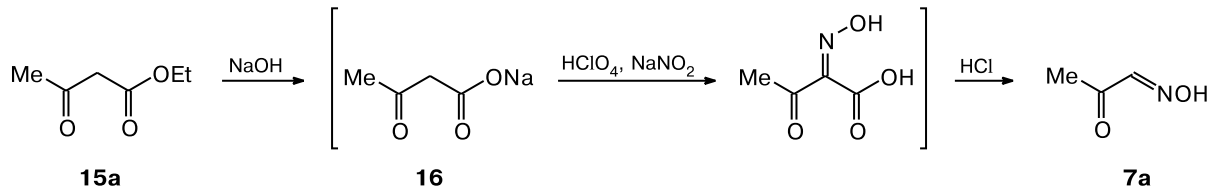
Thus, use of an excess of hydroxylamine and alkali in the presence of an equimolar amount of urea is efficient for the one-pot syntheses of aminofurazans.

The starting isonitrosoacetone **7a** in Scheme 2 was easily prepared from ethyl acetoacetate **15a** [28] by hydrolysis to sodium acetoacetate **16**, nitrosation at the methylene group, and decarboxylation in an acidic medium. The yield of compound **7a** was 80% (Scheme 8).

Treatment of the reaction mixture containing compound **7a** (without its isolation in the individual state) with an alkaline solution of hydroxylamine and urea in the aforementioned ratio allowed amine **1a** to be obtained in 50 to 55% total yield with respect to the starting ester **15a**. Thus, we developed a simple and efficient one-pot method for the synthesis of amine **1a**.

An analogous procedure was used to obtain for the first time homologs of compound **1a** with larger alkyl

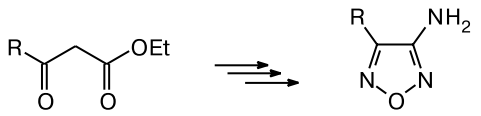
Scheme 8



15a **16** **7a**

substituents. As with compound **1a**, 3-alkyl-4-aminofurazans **1b—d** and 3-(adamant-1-yl)-4-aminofurazan (**1e**) were synthesized from the corresponding β-alkyl-β-oxo esters **15b—e** (Scheme 9) in ten sequential steps (see Schemes 3, 7, and 8). This methodology afforded alkylfurazans and adamantylfurazan in satisfactory yields.

Scheme 9



15b—e **1b—e**

R = Et (**b**), Pr (**c**), Bu^t (**d**), Ad (**e**)

Thus, 3-alkyl-4-aminofurazans can be obtained by the developed one-pot method from ethyl β-alkyl-β-oxopropionates. The process involves a sequence of steps such as hydrolysis of the ester, nitrosation at the activated methylene group, and treatment with an alkaline solution of hydroxylamine in the presence of urea. Apparently, this methodology is of the general character.

Experimental

Melting points were determined with a Gallenkamp unit (Sanyo Co.). Natural-isotope ^{1}H and ^{13}C NMR spectra were recorded on Bruker AM-300 (300.13 and 75.7 MHz, respectively) and Bruker DRX-500 spectrometers (500.13 and 125.7 MHz, respectively). Chemical shifts are given in the δ scale with a solvent as the internal standard. Mass spectra were recorded on Finnigan MAT INCOS-50 and Varian MAT CH-111 instruments (EI, 70 eV). IR spectra were recorded on a Specord IR75 spectrometer in pellets with KBr for solids and in a thin film for liquids. The course of the reaction was monitored and the purity of the products was checked by TLC on Silufol UV-254 plates; spots were visualized with UV irradiation. β-Alkyl-β-oxo esters were purchased from Reakhim Co.

One-pot synthesis of 3-alkyl-4-aminofurazans (general procedure). Freshly distilled ethyl acetoacetate (100 mL, 0.78 mol) was added at 10 °C to a solution of NaOH (35.6 g, 0.89 mol) in water (300 mL). The resulting emulsion was stirred for 12 h to homogenization and $NaNO_2$ (58.7 g, 0.85 mol) was dissolved. Then 20% $HClO_4$ (1.74 mol) was slowly added dropwise at 10 to 15 °C. The reaction mixture was stirred while warming it to room temperature and then left for ~14 h. Sodium hydroxide (1 g) was added; a solution of $NH_2OH \cdot HCl$ (166 g, 2.4 mol) in water (300 mL) was then added dropwise with vigorous stirring. After half the solution of hydroxylamine was added, a solution of NaOH (108 g, 2.7 mol) in water (200 mL) was simultaneously added dropwise from a second dropping funnel at a temperature no higher than 30 °C. The mixture was heated to 95 °C for 1.5 to 2 h and urea (40 g, 0.67 mol) was added in one portion. The resulting reaction mixture was refluxed for 3 h and cooled and the product was extracted with CH_2Cl_2 (5×200 mL). The combined extracts were washed with water (2×200 mL), 5% sodium carbonate (200 mL), and water (200 mL) and dried with $MgSO_4$. The solvent was removed and the residue was recrystallized from $CHCl_3$—light petroleum (3 : 1).

The yield of **3-amino-4-methylfurazan (1a)** was 39 g (51%), small colorless crystals, m.p. 72.8—73.8 °C (*cf.* Refs: m.p. 72 °C,[9] 72—73 °C[3]). Its IR[29] and NMR spectra[30] were identical with the published ones.

Compounds **1b—e** were synthesized analogously.

3-Amino-4-ethylfurazan (1b), yield 49%, m.p. 71.3—71.6 °C (hexane). Found (%): C, 42.51; H, 6.22; N, 37.09. $C_4H_7N_3O$. *M* = 113.12. Calculated (%): C, 42.47; H, 6.24; N, 37.15. IR (KBr), ν/cm^{-1}: 3408, 3368, 3344, 3288, 3264, 1648, 1600, 1536, 1448, 1216, 968, 872. MS, *m/z*: 113 $[M]^+$, 83 $[M - NO]^+$. ^{1}H NMR ($CDCl_3$), δ: 1.29 (t, 3 H, Me, *J* = 6.7 Hz); 2.59 (q, 2 H, CH_2, *J* = 6.7 Hz); 4.38 (br.s, 2 H, NH_2). ^{13}C NMR ($CDCl_3$), δ: 10.9 (Me); 16.1 (CH_2); 148.7 (N=C—CH_2); 154.8 (CNH_2).

3-Amino-4-propylfurazan (1c), yield 57%, m.p. 31.4—31.9 °C (light petroleum). Found (%): C, 47.30; H, 7.12; N, 33.01. $C_5H_9N_3O$. *M* = 127.15. Calculated (%): C, 47.23; H, 7.13; N, 33.05. IR (KBr), ν/cm^{-1}: 3428, 3332, 2964, 2936, 2876, 1632, 1532, 1468, 1452, 1380, 1212, 1096, 992, 876. MS, *m/z*: 127 $[M]^+$, 97 $[M - NO]^+$. ^{1}H NMR ($CDCl_3$), δ: 0.91 (t, 3 H, Me, *J* = 6.4 Hz); 1.67 (m, 2 H, CH_2Me); 2.53 (t, 2 H, N=C—CH_2, *J* = 5.7 Hz); 4.58 (br.s, 2 H, NH_2). ^{13}C NMR ($CDCl_3$), δ: 13.3 (Me); 19.8 (CH_2Me); 24.1 (N=C—CH_2); 147.5 (N=C—CH_2); 155.0 (CNH_2).

3-Amino-4-*tert*-butylfurazan (1d), yield 42%, m.p. 101—104 °C (light petroleum). Found (%): C, 51.11; H, 7.88; N, 29.71. $C_6H_{11}N_3O$. *M* = 141.17. Calculated (%): C, 51.05; H, 7.85; N, 29.77. IR (KBr), ν/cm^{-1}: 3452, 3348, 3252, 3216, 2972, 2968, 2940, 2908, 1640, 1516, 1468, 1424, 1376, 1300, 1148, 1028, 984, 888. MS, *m/z*: 141 $[M]^+$, 111 $[M - NO]^+$, 84 $[M - Bu^t]^+$. ^{1}H NMR (DMSO-d_6), δ: 1.32 (s, 9 H, Me); 5.93 (br.s, 2 H, NH_2). ^{13}C NMR (DMSO-d_6), δ: 27.5 (Me); 30.9 (CMe_3); 153.9 (CBu^t); 155.0 (CNH_2).

4-Adamant-1-yl-3-aminofurazan (1e), yield 31%, m.p. 158—159 °C (CCl_4). Found (%): C, 65.77; H 7.82; N, 19.14. $C_{12}H_{17}N_3O$. *M* = 219.29. Calculated (%): C, 65.73; H, 7.81; N, 19.16. IR (KBr), ν/cm^{-1}: 3468, 3324, 3232, 2904, 2852, 1624, 1508, 1456, 1344, 1272, 1100, 992. MS, *m/z*: 219 $[M]^+$. ^{1}H NMR ($CDCl_3$), δ: 1.70, 2.05 (both br.s, 6 H each, CH_2); 2.10 (br.s, 3 H, CH); 4.33 (br.s, 2 H, NH_2). ^{13}C NMR ($CDCl_3$), δ: 27.7 (CH); 36.4 (CH_2); 39.1 (N=C—C); 39.7 (N=C—C—CH_2), 153.4 (N=C—Ad), 154.2 (CNH_2).

This work was financially supported in part by the Russian Foundation for Basic Research (Project No. 01-03-32944a) and the Federal Target Program "Integration of Science and Higher Education in Russia for 2002 to 2006" (State Contract No. I0667).

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Received June 28, 2004;
in revised form February 2, 2005