Reaction of γ-nitroketones and methyl 4-nitrobutanoates with formaldehyde and primary amines

R. R. Shakirov,[a]★ L. I. Vlasova,[a] D. V. Shishkin,[a] N. N. Yarmukhamedov,[a] N. Z. Baybulatova,[a] D. G. Semesko,[a] V. A. Dokichev,[a] and Yu. V. Tomilov[b]

[a]Institute of Organic Chemistry, Ufa Research Center of the Russian Academy of Sciences, 71 prosp. Oktyabrya, 450054 Ufa, Russian Federation. Fax: +7 (347 2) 35 6066. E-mail: dokichev@anrb.ru
[b]N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky prosp., 119991 Moscow, Russian Federation. Fax: +7 (095) 135 6390. E-mail: tom@ioc.ac.ru

5-Nitropentan-2-one reacts with methylamine and formaldehyde according to the Mannich reaction pattern to give 5-hexahydropyrimidinylcarbonyl-substituted 1-nitro-3,7-diazabicyclo[3.3.1]nonane in one experimental stage. When methyl 3-R-4-nitrobutanoates are used, the reaction stops after the formation of substituted 5-nitrohexahydropyrimidines in 40—98% yields.

Key words: Mannich reaction, 5-nitropentan-2-one, 4-nitrobutanoates, 3,7-diazabicyclo[3.3.1]nonanes, 5-nitrohexahydropyrimidines.

The reaction of primary amines and formaldehyde with compounds having an mobile hydrogen atom at a carbon atom is widely used in organic synthesis as a convenient method for the preparation of tetrahydro-1,3-oxazines, hexahydropyrimidines,[1,2] and 3-aza-[3—6] and 3,7-diazabicyclo[3.3.1]nonanes.[3,7—13] Representatives of this class possess high biological activities and are used in medical practice as antimicrobial, antiviral, antitumor, and other drugs.[10—12,14] It is also known that nitro-substituted heterocyclic compounds exhibit an enhanced antibacterial activity[1] and function as nitrogen oxide sources[15] in the human body and, hence, they are of interest as chemotherapeutic means.

Previously,[13] we proposed a method for the synthesis of 1,5-dinitro-3,7-diazabicyclo[3.3.1]nonane by four successive condensations of 1,3-dinitro-2-phenylpropane with formaldehyde and methylamine or monoethanolamine under the Mannich reaction conditions. In order to extend the range of CH-acids able to undergo several one-pot condensations, we studied the reactions of primary amines and formaldehyde with γ-nitroketones and methyl γ-nitrocarboxylates.

Results and Discussion

The range of γ-nitroketone and methyl γ-nitrocarboxylates included 5-nitropentan-2-one (**1a**), 4-nitro-1,3-diphenylbutan-1-one (**1b**), 2,2-dimethyl-4-nitrocyclohexan-1-one (**1c**), methyl 4-nitrobutanoate (**1d**), and methyl 3-methyl-4-nitrobutanoate (**1e**). Methylamine (**2a**) and isopropylamine (**2b**) were used as amines.

To attain a higher degree of conversion, the experiments were usually carried out with refluxing in a MeOH—H_2O mixture for 15 h with a nitro compound : formaldehyde : amine molar ratio of 1 : 10 : 5. Thus the reaction of nitropentanone **1a** with a 26% solution of formaldehyde and methylamine hydrochloride yields substituted 5-(hexahydropyrimidinyl-5-carbonyl)-1-nitro-3,7-diazabicyclo[3.3.1]nonane **3** in 21% yield (Scheme 1). This one-pot process occurs as seven condensations involving three reaction centers, methyl and two activated methylene groups, of nitroketone **1a**. The process includes not only the formation of a 3,7-diazabicyclo[3.3.1]nonane structure, as in the case of 1,3-dinitropropanes,[13] but also the formation of the hexahydropyrimidine ring. It should be noted that despite the relatively low yield of compound **3**, no 1-acetyl-3,7-dimethyl-5-nitro-3,7-diazabicyclo[3.3.1]nonane and/or 5-(4-nitrobutanoyl)-1,3-dimethylhexahydropyrimidine, which are possible intermediates on the pathway to compound **3**, have been detected in any of the experiments. This apparently indicates that the reactivities of the activated methylene and methyl groups in the initial nitroketone **1a** and in all the successively formed products are commensurable and rather high. It is noteworthy that the use of an aqueous solution of methylamine or conducting the reaction in AcOH, $CHCl_3$, or MeCN does not result in compound **3**, but affords 1,3,5-trimethylhexahydro-1,3,5-triazine and a complex mixture of products, which might

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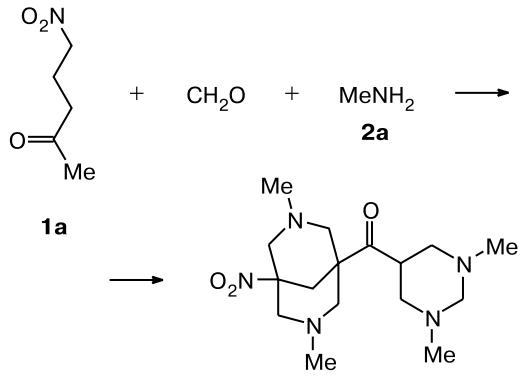
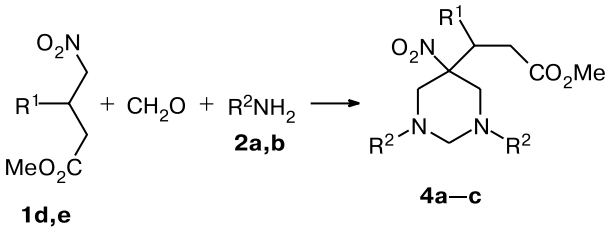
have formed *via* a smaller number of the Michael condensation steps. Under the conditions we chose (refluxing in a MeOH—H_2O mixture for 15 h), substituted nitroketones **1b,c** do not enter into the condensation.

Scheme 1



Unlike nitroketone **1a**, 4-nitrobutanoate **1d** reacts with methylamine hydrochloride and CH_2O under the same conditions (MeOH—H_2O, 15 h) to give 1,3-dimethyl-5-nitro-5-[2-(methoxycarbonyl)ethyl]hexahydropyrimidine (**4a**) in 40% yield. This product is formed with participation of only the CH_2NO_2 fragment of the starting nitrobutanoate (Scheme 2). The diazabicyclo[3.3.1]nonane structure is not formed under these conditions, apparently, due to the insufficient activating effect of the ester group. Note that in this reaction (unlike the synthesis of compound **3**), the use of an aqueous solution of methylamine in $CHCl_3$ or MeOH allows one decrease the reaction time from 15 to 4 h and markedly increases the yield of hexahydropyrimidine **4a** (to 83 and 98%, respectively). Similarly to condensation of methylamine, the condensation of isopropylamine (**2b**) with CH_2O and nitroester **1d** in MeOH does not change the reaction pattern, substituted hexahydropyrimidine **4b** being formed in 98% yield. Conversely, the introduction of a substituent into the aliphatic chain of nitroesters markedly decreases the yield of

Scheme 2



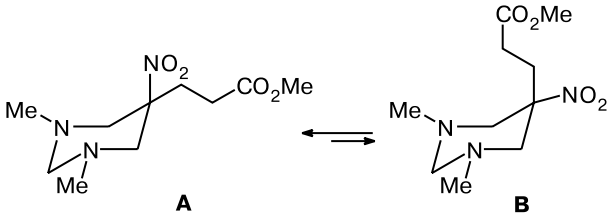
R^1 = H (**1d**, **4a,b**), Me (**1e**, **4c**)
R^2 = Me (**2a**, **4a,c**), Pr^i (**2b**, **4b**)

hexahydropyrimidines. For example, the reaction of 3-methyl-4-nitrobutanoate **1e** with $MeNH_2$ and CH_2O (MeOH, 4 h) results in 5-nitrohexahydropyrimidine **4c** in ~65% yield.

The structures of the compounds were determined using the 2D H—H- and C—H-correlated ^1H and ^{13}C NMR spectra. Analysis of the H—H COSY NMR spectrum of heterocyclic compound **3** showed that the signals with δ 2.32, 2.61, 2.69, and 2.98 belong to the methylene protons of the diazabicyclononane fragment, and the signals at δ 2.28, 2.82 and δ 2.64, 3.54 correspond to CH_2N and NCH_2N groups of the hexahydropyrimidine fragment. In the ^{13}C NMR spectrum, the highest-field signal at δ_C 32.3 is due to the bridging C atom of the bicyclic system; the signals at δ_C 84.2 and 49.4 correspond to the quaternary carbon atoms at the NO_2 and CO groups, respectively.

In the ^{13}C NMR spectrum of hexahydropyrimidine **4a**, recorded in the *J*-modulation mode, the carbon atoms of the NMe, OMe, CNO_2, and CO_2 functional groups are identified unambiguously from the CH constants; the corresponding chemical shifts are 42.3, 51.8, 86.5, and 172.0 ppm, respectively. The signal for the carbon atom of the NCH_2N group, typical of hexahydropyrimidines, occurs at δ_C 78.1. Note that the ^1H NMR spectrum of hexahydropyrimidine **4a** recorded at 20 °C shows the signals for the methylene protons as broad multiplets. The low resolution of the spectrum at room temperature is apparently related to the fact that compound **4a** can exist as several conformations under these conditions. According to published data,[16] this may be due to the existence of two chair conformations **A** and **B** with axial and equatorial nitro group (Scheme 3).

Scheme 3



Raising the temperature to 50 °C provides the possibility of unambiguous assignment of the ^1H NMR signals with δ 2.44, 3.20 (J = 12.2 Hz) and δ 2.79, 3.26 (J = 8.6 Hz) to the NCH_2 and NCH_2N groups, respectively.

The attachment of the carbon atoms to the corresponding protons was determined unambiguously from the 2D CH-correlated spectrum of hexahydropyrimidine **4c** . The low-field signal at δ_C 77.9 for the NCH_2N fragment is matched by the equatorial and axial protons with δ_H 3.38 and 3.42, respectively. These values differ

Table 1. Energy characteristics of conformers **4a,b**

Compound	Position of NO_2	E_{total}/Hartree ($CHCl_3$)	ZPE /kJ mol^{-1}	ZPE + TC (Hartree)	$H°_{298}$ (Hartree)	$\Delta H°_{298}$ /kJ mol^{-1}	Population
4a	ax	−857.574172 (−857.579584)	801.0	0.324206	−857.255378	0.0	0.65
	eq	−857.575764 (−857.579300)	802.1	0.324528	−857.254772	1.6	0.35
4b	ax [a]	−1014.839966 (−1014.840551)	1097.4	0.442772	−1014.397779	0.0	0.72 [b]
	eq [a]	−1014.840920 (−1014.839696)	1097.8	0.442911	−1014.396785	2.6	0.28 [b]

[a] Data are given for the most stable conformers for the rotation of isopropyl groups.
[b] Total population of the four conformers in which the methyl groups of the isopropyl fragments occur in the antiperiplanar position with respect to the nitrogen lone pairs.

little from each other but are markedly different from the chemical shifts of the corresponding protons of hexahydropyrimidine **4a**, which may be attributed to the substantial flattening of the six-membered heterocycle in the case of compound **4c**. A pair of protons (δ_H 2.05 and 2.62) resonates with the carbon atom (δ_C 35.6) located in the α-position relative to the CO_2 group. Attention is also attracted by the magnetic nonequivalence of the methyl protons in the ^{1}H NMR spectrum and the carbon atoms in positions 4 and 6 of the hexahydropyrimidine ring in ^{13}C NMR spectrum of compound **4c**.

The structures of compounds **4a,b** were studied by quantum-chemical calculations using the Gaussian 98 software.[17] The calculations showed that conformers with the axial or equatorial nitro group have nearly the same energy (Table 1). The total energies of the conformers of structure **4b** with equatorial and axial NO_2 groups are also affected by rotation of the isopropyl groups around the C—N bonds. The conformers with the antiperiplanar arrangement of one methyl group with respect to the lone electron pair of the N atom in the hexahydropyrimidine ring are the most stable (Scheme 4).

For estimating the possibility of free rotation of the isopropyl group, the transition states for the conformational rotation were calculated. It was found that the height of the barriers to rotation does not exceed 9.5 kJ mol^{-1}, *i.e.*, the rotation around the C—N bond is almost nonhindered. Hence, the populations of the stable conformers of these compounds correspond to the Boltzmann energy distribution.

The energies of the conformers of **4a,b** were calculated as follows. First, full optimization of the compound was carried out in the B3LYP/6-31G(d, p) approximation and the vibration problem was solved. For the structure thus found, the total energy in $CHCl_3$ was found using the COSMO polarized continuum model[18] in the same approximation. The enthalpies of the conformers were calculated as follows

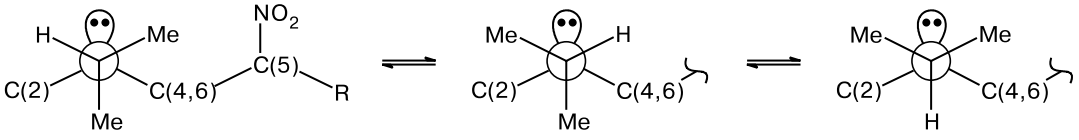
$$H°_{298} = E_{total}^{solv} + ZPE + TC, \quad (1)$$

where ZPE is the zero-point energy, TC is the thermal correction taking into account the transition of the intrinsic energy into enthalpy (*RT*) and the change in the substance enthalpy on heating to 298 K ($\Delta H_{0\to298K}$). The thermal correction was calculated using known statistical thermodynamic equations.[19]

It was found that at 300 K, the population of conformer **A** is 65%, *i.e.*, with allowance for the possible error of the quantum-chemical method, it can be stated that conformers **A** and **B** exist in $CHCl_3$ solutions in comparable amounts.

Of the nine possible stable states arising during the free rotation of both isopropyl groups in compound **4b**, the total population of the four most stable states is 85% for both the axial and equatorial NO_2 group. In each of these states (−*sc*, −*sc*; −*sc*, +*sc*; +*sc*, −*sc*; +*sc*, +*sc*), both antiperiplanar positions with respect to the nitrogen lone pair are occupied by the methyl groups. The conformers with the axial NO_2 group account for 72%, while those

Scheme 4



	−*sc*	+*sc*	*ap*
$H°_{298}$/kJ mol^{-1}:	0.0	3.7	11.7

Note. The conformers are designated based on the position of the H atom relative to the nitrogen lone pair.

with the equatorial NO_2 group make 28% of the total amount of **4b** conformers.

To verify the assignments for the experimental NMR spectra of compounds **4a,b**, the δ_H and δ_C values (relative to Me_4Si) of the most stable conformers **4a,b** were calculated by the CSGT method [20] in the MPW1PW91/6-311+G(2d,p) approximation. Comparison of the experimental and simulated ^{13}C NMR spectra shows almost complete coincidence: the δ_C values obey the linear dependence with a high correlation coefficient (for example, for **4a**, $r = 0.9996$)

$$\delta_{exp} = a \cdot \delta_{calc} + b, \qquad (2)$$

$a = 0.961 \pm 0.008$, $b = -0.1 \pm 0.8$ (**4a**); $a = 0.965 \pm 0.005$, $b = -1.5 \pm 0.5$ (**4b**).

The δ values corrected using Eq. (2) are listed in Tables 2 and 3. It can be seen from Table 3 that the calculated δ_C values for the C atoms in positions 2, 4, and 6 vary appreciably depending on the orientation of the isopropyl substituent. However, in view of the ease of free rotation of the $CHMe_2$ group, one should expect averaging of the experimental chemical shifts. Indeed, the range of calculated δ_C for C(2), C(4), and C(6) covers the chemical shifts found experimentally.

An even more interesting situation is observed for the methyl groups of the isopropyl fragment in compound **4b**, which are responsible for two doublets in the ^1H NMR spectrum, despite the possibility of free rotation of the $CHMe_2$ fragment and averaging of the observed signals. The nitrogen lone pair induces an upfield shift of the

Table 2. Experimental and simulated ^1H and ^{13}C NMR spectra of compound **4a** ($CDCl_3$, δ)

Group	^{13}C NMR			^1H NMR		
	Experiment	Simulation		Experiment	Simulation	
		NO_2(ax)	NO_2(eq)		NO_2(ax)	NO_2(eq)
OMe	51.76	51.26	51.07	3.65	3.20—3.48	3.18—3.48
$\underline{CH_2}CH_2CO_2$	31.29	33.58	32.33	2.20—2.36	1.57—2.14	1.83—2.75
CH_2CO_2	27.71	28.20	27.91	2.20—2.36	1.57—2.14	1.83—2.75
NMe	42.25	40.88; 40.88	41.17; 41.46	2.26	1.73—2.24	1.81—2.27
CH_2N	58.96	55.88; 59.53	55.49; 59.05	2.44 (H_{eq}); 3.26 (H_{ax})	1.53, 1.64 (H_{eq}); 3.53, 3.53 (H_{ax})	1.68, 1.80 (H_{eq}); 3.09, 3.13 (H_{ax})
NCH_2N	78.13	75.58	75.77	2.79 (H_{eq}); 3.20 (H_{ax})	2.07 (H_{eq}); 3.21 (H_{ax})	1.96 (H_{eq}); 3.19 (H_{ax})
CNO_2	86.48	87.50	86.15	—	—	—
CO_2	171.99	172.75	172.65	—	—	—

Table 3. Experimental and simulated ^1H and ^{13}C NMR spectra of compound **4b** ($CDCl_3$, δ)

Group	^{13}C NMR			^1H NMR		
	Experiment	Simulation		Experiment	Simulation	
		NO_2(ax)*	NO_2(eq)*		NO_2(ax)*	NO_2(eq)*
OMe	51.73	49.93	49.77	3.65	3.19—3.48	3.17—3.49
$\underline{CH_2}CH_2CO_2$	31.29	31.71—31.80	30.37—30.25	2.15—2.35	1.55—2.17	1.75—2.84
CH_2CO_2	27.95	26.87	26.60—26.70	2.15—2.35	1.55—2.17	1.75—2.84
$\underline{Me}CH$ (*ap*)	18.38	12.05—12.49	12.21—12.58	1.00	0.50—1.10	0.54—1.17
$\underline{Me}CH$ (±*sc*)	19.14	19.81—19.98	20.07—20.41	1.05	0.82—1.26	0.84—1.20
CHN	52.11	53.66—54.00	53.57—55.13	2.83	2.67—2.74	2.73—2.77
CH_2N	52.69	46.01—58.33	45.68—58.16	2.47 (H_{eq}); 3.33 (H_{ax})	1.85—2.37 (H_{eq}); 3.45—3.70 (H_{ax})	1.93—2.51 (H_{eq}); 3.01—3.27 (H_{ax})
NCH_2N	70.66	64.02—71.70	64.46—72.19	3.13 (H_{eq}); 3.44 (H_{ax})	2.97—3.07 (H_{eq}); 3.30—3.36 (H_{ax})	2.86—3.25 (H_{eq}); 3.04—3.27 (H_{ax})
CNO_2	86.86	86.62—87.05	85.36—85.70	—	—	—
CO_2	172.26	172.08	172.00	—	—	—

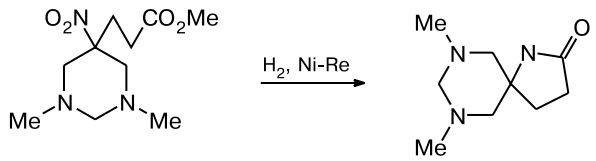
* The ranges of calculated chemical shifts are given for the three most stable conformers of rotation of the isopropyl groups.

signal from the antiperiplanar C atom (see Table 3). According to the conformational analysis presented above, this position is occupied in 85% of cases, suggesting that the temperature of recording the spectra is below the coalescence temperature.

Thus, quantum-chemical simulation of the structure and the ^1H and ^{13}C NMR spectra of compounds **4a,b** indicates, first, that the conformers with the equatorial and the axial NO_2 group coexist in solution, the latter somewhat predominating. Second, the magnetic nonequivalence of the C atoms of the methyl groups of the isopropyl fragment in **4b** is due to the high population of conformers in which one methyl group occurs in the antiperiplanar orientation relative to the nitrogen lone pair and resonates in a higher field than the C atom of the other methyl group.

The geminal position of the substituents in the hexahydropyrimidine ring was confirmed by the transformation of compound **4a** into a spirocyclic lactone upon the reduction of the NO_2 group to the amino group with its simultaneous intramolecular cyclocondensation with the ester fragment. Catalytic hydrogenation of nitro compound **4a** in MeOH in the presence of Raney Ni (70 bar, 50 °C, 5 h) gave 7,9-dimethyl-1,7,9-triazaspiro[4,5]decan-2-one (**5**) in 60% yield (Scheme 5).

Scheme 5



4a **5** (60%)

Thus, the condensation of sterically nonhindered 5-nitropentan-2-one with formaldehyde and methylamine allows one-pot formation of 5-nitro-3,7-diazabicyclo[3.3.1]nonane and hexahydropyrimidine fragments connected by a carbonyl group. In turn, the reaction of methyl 4-nitrocarboxylates with formaldehyde and methyl- or isopropylamine gives only substituted 5-nitrohexahydropyrimidines.

Experimental

^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer (300.13 and 75.47 MHz, respectively) in $CDCl_3$ using Me_4Si as the internal standard. IR spectra were measured on a Specord M-80 instrument in thin film or in mineral oil. The mass spectrum for compound **3** was run on a Thermo Finnigan MAT 95 XP high-resolution mass spectrometer at an ionizing voltage of 70 eV (temperature in the ionization chamber, 250 °C; direct injection temperature, 50—270 °C; heating rate, 10 °C min^{-1}). The mass spectra of compounds **4a—c** were recorded on an MX-1300 spectrometer with an inlet cylinder temperature of 100 °C and an ionizing voltage of 12 and 70 eV. GLC analysis was carried out on a Chrom-5 chromatograph (FID, a 1200×5 mm stainless-steel column, 5% SE-30 on Inerton N-AW DMCS (0.125—0.160 mm), helium as the carrier gas). TLC analysis was carried out on Silufol plates (Merck).

Quantum-chemical calculations were performed using the Gaussian 98 software.[17] The structures were optimized in the RB3LYP/6-31G(d,p) approximation. The search for all stable conformers of 1,3-dialkyl-5-[2-(methoxycarbonyl)ethyl]-5-nitrohexahydropyrimidines **4a,b** was carried out taking into account the possibility of free rotation around the C(5)—CH_2, CH_2—CH_2, and N—Alk bonds and inversion of the hexahydropyrimidine ring. The solvent ($CHCl_3$) effect on the relative stability of the conformers was determined in terms of the COSMO polarized continuum model.[18] The chemical shifts of the hydrogen and carbon atoms in compounds **4a,b** were calculated relative to Me_4Si by the CSGT method[20] in the MPW1PW91/6-311+G(2d,p) approximation using geometric parameters for the most stable conformers found by the B3LYP/6-31G(d,p) calculations. For all stationary points (stable compounds, transition states for the conformation transitions), the vibration problem was used and the zero-point vibration energy and the thermal correction for the standard $H°_{298}$ enthaplies were calculated. The height of the rotation barriers was calculated as the difference between $H°_{298}$ for the stable conformer (conformational potential minimum) and the transition state. The transition states were characterized based on the only imaginary vibration frequency.

5-Nitropentan-2-one (**1a**),[21] methyl 4-nitrobutanoate (**1d**),[22] and methyl 3-methyl-4-nitrobutanoate (**1e**)[22] were prepared by known procedures.

1-(1,3-Dimethylhexahydropyrimidinyl-5-carbonyl)-3,7-dimethyl-5-nitro-3,7-diazabicyclo[3.3.1]nonane (3). Methanol (4 mL), 26% formaldehyde (4.5 mL, ~42 mmol), and 5-nitropentan-2-one (**1a**) (0.55 g, 4.2 mmol) were added successively to a stirred solution of methylamine hydrochloride (1.42 g, 21 mmol) in H_2O (10 mL) A 20% aqueous solution of NaOH (2.6 mL) was added to pH 7—8 (this is accompanied by warming-up of the mixture and appearance of a yellow color). The reaction mixture was refluxed for 15 h, MeOH was evaporated *in vacuo*, water (5 mL) was added, and the reaction mixture was acidified to pH 5—6 and extracted with $CHCl_3$ (3×5 mL). A 20% aqueous solution of NaOH was added to the aqueous phase to pH 8—9, and the mixture was extracted with $CHCl_3$ (3×5 mL). The organic phase was washed with water and dried with anhydrous Na_2SO_4. After removal of the solvent *in vacuo,* the residue was chromatographed on a column with Al_2O_3 (elution with $CHCl_3$—MeOH, 9 : 1) to give 0.30 g (21%) of compound **3** as colorless crystals, m.p. 113—114 °C. Found (%): C, 57.05; H, 8.50; N, 21.02. $C_{16}H_{29}N_5O_3$. Calculated (%): C, 56.62; H, 8.61; N, 20.63. MS, *m/z*: 339.224 $[M]^+$. Calculated: M = 339.226. IR, ν/cm^{-1}: 1355, 1555 (NO_2), 1710 (C=O). ^1H NMR ($CDCl_3$), δ: 2.28 (dd, 2 H, CH_2N, ^2J = 12.1 Hz, ^3J = 10.8 Hz); 2.30 and 2.32 (both s, 6 H each, 4 MeN); 2.32 and 2.61 (both d, 2 H each, 2 CH_2N, ^2J = 11.2 Hz); 2.64 and 3.54 (both d, 1 H each, NCH_2N, ^2J = 9.5 Hz); 2.69 and 2.98 (both d, 2 H each, 2 CH_2N, ^2J = 11.0 Hz); 2.82 (dd, 2 H, CH_2N, ^2J = 12.1 Hz, ^3J = 3.7 Hz); 3.45 (tt, 1 H, CH, ^3J = 10.8, ^3J = 3.7). ^{13}C NMR ($CDCl_3$), δ: 32.3 (CH_2); 41.4 and 42.0 (MeN); 44.6

(CH); 49.4 (CCO); 55.9, 57.8 and 60.7 (CH_2N); 76.3 (NCH_2N); 84.2 (CNO_2); 209.0 (C=O).

1,3-Dimethyl-5-[2-(methoxycarbonyl)ethyl]-5-nitrohexahydropyrimidine (4a). A mixture of 26% formalin (2.33 mL, ~22 mmol of CH_2O) and a 24% aqueous solution of $MeNH_2$ (1.40 g, ~11 mmol) was added at 0—10 °C to a stirred solution of methyl 4-nitrobutanoate (**1d**) (0.32 g, 2.17 mmol) in MeOH (15 mL). The mixture was refluxed for 4 h, MeOH was evaporated under reduced pressure, and $CHCl_3$ (10 mL) was added. The reaction mixture was washed with water (3×5 mL) and dried with anhydrous Na_2SO_4, and the solvent was removed under reduced pressure to give 0.52 g (98%) of compound **4a** as an oil. For analytical purposes, the product was additionally chromatographed on SiO_2 ($CHCl_3$—Pr^iOH, 9 : 1). Found (%): C, 49.05; H, 7.74; N, 16.92. $C_{10}H_{19}N_3O_4$. Calculated (%): C, 48.97; H, 7.81; N, 17.13. MS, *m/z*: 245 [M^+]. ^{1}H NMR ($CDCl_3$), 50 °C, δ: 2.20—2.36 (m, 4 H, $CH_2CH_2CO_2$); 2.26 (s, 6 H, 2 NMe); 2.44 (d, 2 H_{eq}, CH_2N, ^2J = 12.2 Hz); 2.79 (d, 1 H_{eq}, NCH_2N, ^2J = 8.6 Hz); 3.20 (d, 2 H_{ax}, CH_2N, ^2J = 12.2 Hz); 3.26 (d, 1 H_{ax}, NCH_2N, ^2J = 8.6 Hz); 3.65 (s, 3 H, OMe). The ^{13}C NMR spectrum is presented in Table 3.

When the reaction was carried out in $CHCl_3$ (20 °C, 4 h), the yield of hexahydropyrimidine **4a** was 83%, and under conditions used to prepare **3** (refluxing for 15 h), the yield was 40%.

1,3-Diisopropyl-5-[2-(methoxycarbonyl)ethyl]-5-nitrohexahydropyrimidine (4b). A mixture of 33% formalin (2.83 mL, ~34 mmol of CH_2O) and isopropylamine (1.01 g, 17 mmol) was added at 0—10 °C to a stirred solution of 4-nitrobutanoate **1d** (0.50 g, 3.4 mmol) in MeOH (25 mL). The mixture was refluxed for 4 h, MeOH was evaporated at a reduced pressure, and $CHCl_3$ (15 mL) was added. The reaction mixture was washed with water (3×5 mL) and dried with anhydrous Na_2SO_4 and the solvent was removed at a reduced pressure to give 1.0 g (98%) of hexahydropyrimidine **4b** as an oil. The sample for analysis was prepared by chromatography on SiO_2 ($CHCl_3$—Pr^iOH, 9 : 1). Found (%): C, 55.50; H, 8.95; N, 14.04. $C_{14}H_{27}N_3O_4$. Calculated (%): C, 55.79; H, 9.03; N, 13.94. MS, *m/z*: 301 [M^+]. IR, ν/cm^{-1}: 1540 (NO_2), 1738 (C=O). ^{1}H NMR ($CDCl_3$), δ: 1.00 and 1.05, (both d, 6 H each, 4 Me, ^2J = 6.5 Hz); 2.15—2.35 (m, 4 H, ($CH_2CH_2CO_2$)); 2.47 (d, 2 H_{eq}, CH_2N, ^2J = 11.9 Hz); 2.83 (sept, 1 H, CHN, ^2J = 6.6 Hz); 3.13 (d, 1 H_{eq}, NCH_2N, ^2J = 8.4 Hz); 3.33 (d, 2 H_{ax}, CH_2N, ^2J = 11.9 Hz); 3.44 (d, 1 H_{ax}, NCH_2N, ^2J = 8.4 Hz); 3.65 (s, 3 H, OMe). The ^{13}C NMR spectrum is presented in Table 3.

1,3-Dimethyl-5-[1-methyl-2-(methoxycarbonyl)ethyl]-5-nitrohexahydropyrimidine (4c). A mixture of 26% formalin (6.7 mL, ~62 mmol of CH_2O) and a 24% aqueous solution of $MeNH_2$ (4.0 g, ~31 mmol) was added at 0—10 °C to a stirred solution of methyl 3-methyl-4-nitrobutanoate (**1e**) (1.00 g, 6.2 mmol) in $CHCl_3$ (43 mL). The mixture was stirred for 4 h at 20 °C, washed with water (3×10 mL), and dried with anhydrous Na_2SO_4, and the solvent was removed at a reduced pressure. The residue was chromatographed on a column with SiO_2 ($CHCl_3$—Pr^iOH, 9 : 1) to give 1.1 g (65%) of hexahydropyrimidine **4c** as an oil. Found (%): C, 51.12; H, 7.95; N, 16.04. $C_{11}H_{21}N_3O_4$. Calculated (%): C, 50.95; H, 8.16; N, 16.21. MS, *m/z*: 259 [$M]^+$. IR, ν/cm^{-1}: 1270, 1740 (CO_2); 1355, 1555 (NO_2); 2780 (CH_3N). ^{1}H NMR ($CDCl_3$), δ: 0.98 (d, 3 H, Me, ^3J = 6.8 Hz); 2.05 (dd, 1 H, $CHCO_2$, ^2J = 15.7 Hz, ^3J = 10.3 Hz); 2.25 (m, 2 H_{eq}, CH_2N); 2.26 and 2.28 (both s, 6 H, 2 MeN); 2.43 (m, 3 H, NCH_2N, CH); 2.61 (dd, 1 H, $CHCO_2$, ^2J = 15.7 Hz, ^3J = 9.0 Hz); 3.38 (d, 1 H_{eq}, NCH_2N, ^2J = 8.6 Hz); 3.42 (d, 1 H_{ax}, NCH_2N, ^2J = 8.6 Hz); 3.50 (m, 2 H_{ax}, CH_2N); 3.67 (s, 3 H, OMe). ^{13}C NMR ($CDCl_3$), δ: 14.2 (Me); 35.0 (CH); 35.6 (CH_2CO_2); 42.2 (NMe); 51.6 (OMe); 57.7 and 58.0 (CH_2N); 77.9 (NCH_2N); 89.5 (CNO_2); 171.9 (CO_2).

7,9-Dimethyl-1,7,9-triazaspiro[4,5]decan-2-one (5). Hexahydropyrimidine **4a** (0.52 g, 2.1 mmol), MeOH (50 mL), and freshly prepared Raney Ni (0.16 g) were placed in a 0.1-L steel autoclave. Hydrogenation was carried out for 5 h at an H_2 pressure of 70 bar and a temperature of 50 °C. The reaction mixture was filtered off, the solvent was evaporated, and the residue was chromatographed on a column with SiO_2 ($CHCl_3$—Pr^iOH, 7 : 3) to give 0.23 g (60%) of compound **5** as colorless crystals, m.p. 117—118 °C. Found (%): C, 58.55; H, 9.60; N, 22.85. $C_9H_{17}N_3O$. Calculated (%): C, 58.99; H, 9.35; N, 22.93. MS, *m/z*: 183 [M^+]. IR, ν/cm^{-1}: 808, 1366, 1384, 1426, 1462, 1654, 1684. ^{1}H NMR ($CDCl_3$), δ: 1.80—1.88 (m, 2 H, CCH_2); 1.94 (m, 2 H, CH_2N); 2.22 (s, 6 H, 2 MeN); 2.36—2.41 (m, 3 H, CH_2CO and one of NCH_2N); 2.52—2.63 (m, 2 H, CH_2N); 3.30—3.51 (m, 1 H, one of NCH_2N); 6.50 (s, 1 H, NH). ^{13}C NMR ($CDCl_3$), δ: 29.1 (CCH_2); 29.2 (CH_2CO); 42.6 (MeN); 57.1 (C); 64.0 (CH_2N); 78.9 (NCH_2N); 175.9 (CO).

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