Study of reactions of lactim ethers with cyanoacetohydrazide

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Main pathways in reactions of lactim ethers with cyanoacetic acid hydrazide depend on the ring size of the starting lactim ether. Five-membered *O*-methylbutyrolactim produces predominantly 3-amino-4-(pyrrolidin-2-ylidene)-4,5-dihydropyrazol-5-one, whereas condensation of six- and seven-membered lactim ethers (*O*-methylvalero- and *O*-methylcaprolactim, respectively) affords the corresponding polymethylenetriazoles as the major products.

Key words: *O*-methylbutyrolactim, *O*-methylvalerolactim, *O*-methylcaprolactim, cyanoacetohydrazide, lactim ethers, enamines, triazoles, pyrazolone.

Earlier, it has been demonstrated[1] that the reaction of *O*-methylbutyrolactim (**1a**) with cyanoacetic acid *N*-acetylhydrazide (**2**) occurs at the active methylene group followed by cyclization of the resulting enamine **3** to give 3-amino-4-(pyrrolidin-2-ylidene)-4,5-dihydropyrazol-5-one (**4**) (Scheme 1).

The aim of the present study was to investigate the reactions of lactim ethers with *N*-unsubstituted cyanoacetohydrazide (**5**) and reveal the dependence of the reaction pathway on the ring size of the starting lactim ethers. We studied the reactions with *O*-methylbutyro- (**1a**), *O*-methylvalero- (**1b**), and *O*-methylcaprolactims (**1c**). It should be noted that the chemistry of lactim ethers is characterized as an important line of investigation associated with the synthesis of various types of organic, primarily heterocyclic, compounds, and consequently, the development of new approaches to investigation of the reactions of lactim ethers is a topical problem.[2]

It is known that condensation of lactim ethers with compounds containing the active methylene group generally affords enamines, whereas condensation with compounds containing the primary amino group produces amidines.[2,3] It is also known that many properties of enamines and amidines produced in these reactions are to a great extent determined by the ring size of lactim ether (five-, six-, or seven-membered) used in condensation.[4]

Heating of lactim ether **1a** with hydrazide **5** in DMF gave rise to the final product, *viz.*, pyrazolone **4**, which was also isolated in the reaction of **1a** with *N*-acetyl derivative **2**. However, this reaction performed under milder conditions (heating at 35—40 °C for 2—3 min) afforded the condensation product not at the active methylene group but at the primary amino group. The structure of the resulting cyclic amidrazone **6a** (which was isolated as a mixture of the *syn* and *anti* isomers in a ratio of approximately 1 : 1) was unambiguously established by NMR spectroscopy, mass spectrometry, and elemental analysis.

The ^{1}H NMR spectrum of compound **6a** shows two sets of signals. For example, the protons of the NH groups give signals at δ 6.80 and 9.75 along with strongly broadened signals at lower field (approximately at δ 7.25 and 10.10). A singlet for the methylene protons of the CH_2CN groups exists as a standard signal (at δ 3.84) and a broadened signal (at δ 3.44). The signals for the methylene protons at position 3 of the pyrrolidine ring at δ 2.34 (a triplet) and 2.48 (a broadened triplet) can also be identified. The signals for the methylene protons at positions 4 and 5 of both isomers appear as multiplets at δ 1.19 and 3.44, respectively.

The signals for the methylene carbon atoms of the pyrrolidine ring belonging to different isomers at δ 21.7 and 21.8 (position 4), 28.5 and 29.0 (position 3), and 45.0 and 45.1 (position 5) and the signals for the methylene carbon atoms at the cyano group (at δ 23.1 and 24.3) can be identified from the ^{13}C NMR, HSQC, and HMBC spectra. The signals for the carbon atoms of the nitrile group are observed at δ 116.4 and 117.0; of the C=N group, at δ 154.9 and 160.7; and of the carbonyl group, at δ 158.0 and 162.9.

Based on the structure of amidrazone **6a**, heating of this compound would be expected to give 3-cyanomethyl-4,5-trimethylene-1,2,4-triazole (**7a**). However, refluxing of a solution of compound **6a** in DMF leads to considerable resinification. Nevertheless, only compound **4** was

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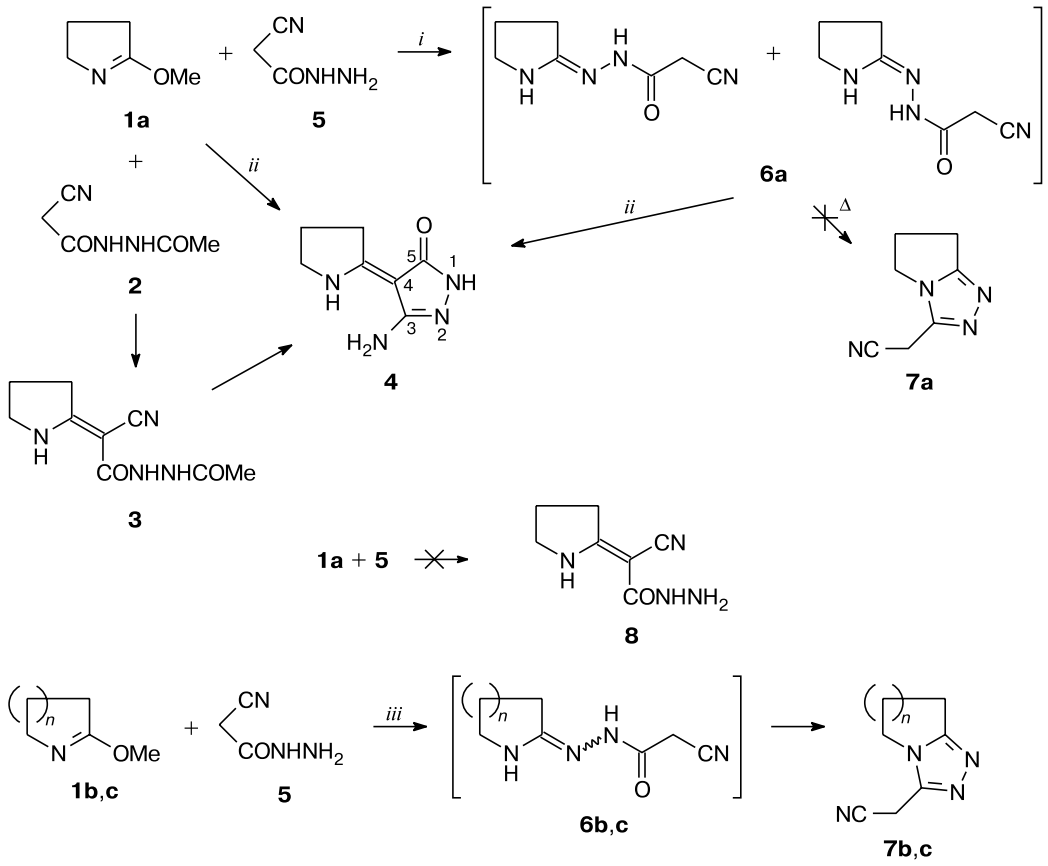
Scheme 1



n = 2 (**b**), 3 (**c**)

Reagents and conditions: *i*. DMF, 40 °C, *ii*. DMF, refluxing, *iii*. DMF, heating.

isolated from the solution, although in low yield. All characteristics, including the spectroscopic parameters, of this compound are completely identical to those of the product prepared by condensation of *O*-methylbutyrolactim (**1a**) with *N*-acetyl derivative **2**.

Intermediates **6b**,**c** were not isolated when other lactim ethers **1b**,**c** were used in condensation with hydrazide **5**. Both these reactions afforded polymethylenetriazoles **7b**,**c** in high yields.

It should be noted that direct cyclization of a mixture of isomers **6a** giving rise to pyrazole derivative **4** cannot be performed, and enamine **8** would be required for this reaction. However, acylamidrazones **6a** were prepared in high yield, and the reaction of *O*-methylbutyrolactim **1a** with hydrazide **5** did not produce noticeable amounts of enamine **8**. In our opinion, the differences observed in condensation of lactim ethers with cyanoacetohydrazide are associated with the ratio of the reaction rates of the triazole cyclization and the amidine-enamine rearrangement during heating for intermediates containing a five-membered saturated ring. Possible steps of this rearrangement, including the presumed transition state (TS), are presented in Scheme 2.

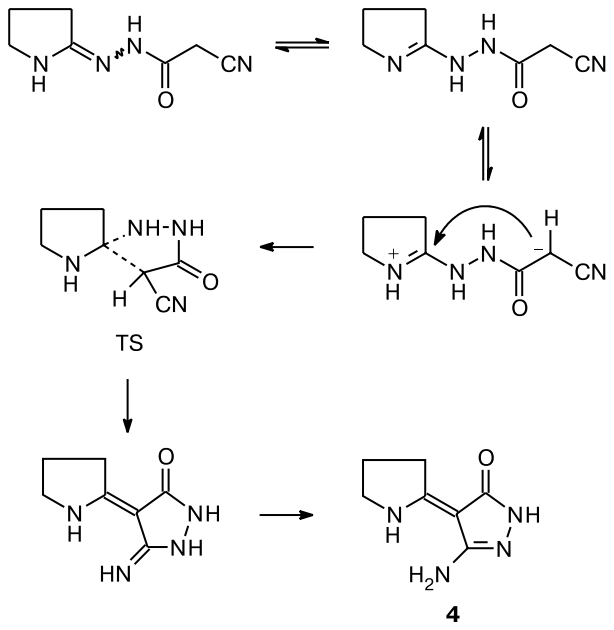
To our knowledge, such transformations in reactions involving activated forms of lactams, among which are lactim ethers,[2] were not described in the literature.

As mentioned above, the main pathway in the reactions of six- and seven-membered lactim ethers **1b**,**c** with hydrazide **5** (Scheme 3) gives rise to triazole derivatives.[5]

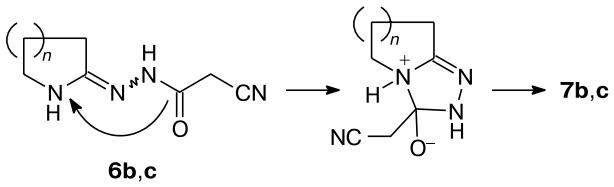
Presumably, the construction of fused systems involving five- and six-membered (or seven-membered) rings is energetically more favorable than the construction of systems involving two five-membered rings and occurs more rapidly, resulting in the predominant formation of triazole bicyclic compounds **7b**,**c**. By contrast, the reaction involving *O*-methylbutyrolactim produces nonannulated pyrazole derivative **4**.

Study of solutions of the reactions mixtures in acetonitrile by LC-mass spectrometry demonstrated that similar reaction pathways are observed for all lactim ethers, although occurring to a different extent.

Scheme 2

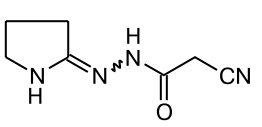


Scheme 3

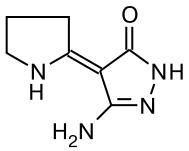


n = 2 (**b**), 3 (**c**)

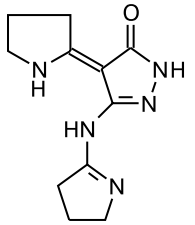
For *O*-methylbutyrolactim, the chromatogram of the reaction mixture shows two dominating peaks. One peak includes primarily compounds with masses 166 and 233 (which account for a total of 59% of the substance). Apparently, structure **6a** or **4** should be assigned to the former mass; structure **9** or supposedly **10a**, to the latter mass. Presumably, compounds **9** and **10a** are generated through condensation of *O*-methylbutyrolactim at the primary amino group of pyrazole derivative **4** and at the active methylene group of compounds **6a**, respectively (regardless of whether the *cis* or *trans* isomer is involved in this reaction).



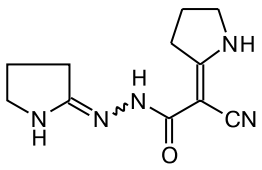
6a
M^+ 166



4
M^+ 166

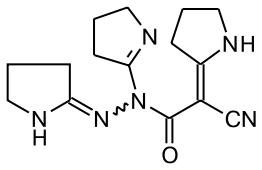


9
M^+ 233

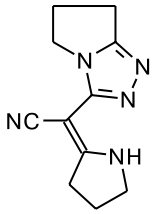


10a
M^+ 233

The second peak involves compounds with masses 215 and 300 (which account for a total of 29% of the substance), which, presumably, have structures **12a** and **11a**, respectively. Compound **12a** is of interest because it is a trimethylenetriazole derivative, *i.e.*, has a bicyclic structure generated in the reactions with six- and seven-membered lactim ethers. Although we failed to preparatively isolate compound **12a** in the reaction with *O*-methylbutyrolactim, the fact of its formation is essential, because this is evidence for the similarity of the general scheme for the reactions of all lactim ethers with cyanoacetic acid hydrazide.



11a
M^+ 300



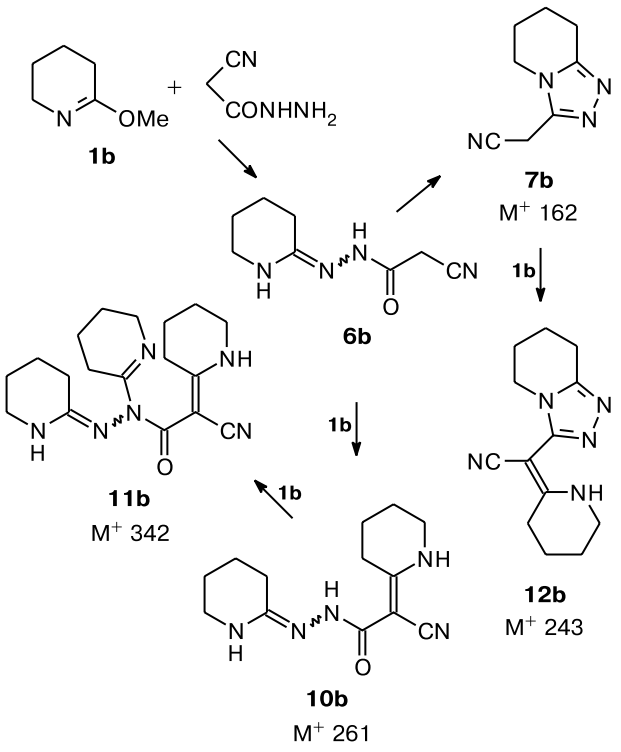
12a
M^+ 215

The above conclusion is confirmed by analysis of the chromatogram of the reaction mixture obtained by the reaction of *O*-methylvalerolactim with cyanoacetohydrazide, the reaction products being detected by mass spectrometry. This reaction produces triazole **7b** (M^+ 162) as the major product, but the chromatogram contains also impurity peaks with a mass 243 (**12b**) and with masses 261 and 342, which, apparently, belong respectively to compounds **10b** and **11b**, (Scheme 4) containing no triazole rings.

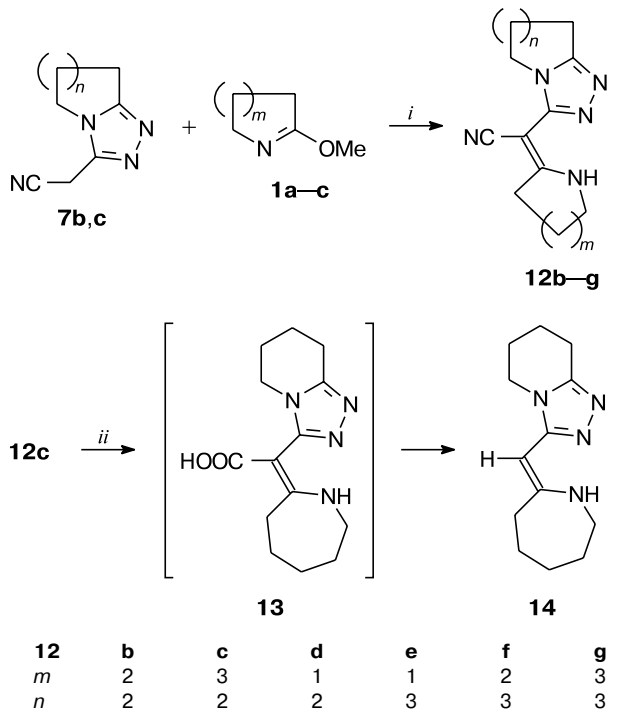
In conclusion, it should be noted that compounds **7b**,**c** are characterized by very high CH acidity of the methylene group due to the electron-withdrawing properties of the nitrile group and the triazolyl fragment. Heating of these compounds with lactim ethers **1a**—**c** gave rise to the corresponding enaminonitriles **12b**—**g** in high yields (Scheme 5).

Using compound **12c** as an example, it was demonstrated that brief heating in 25% sulfuric acid leads to saponification of the cyano group to form the corresponding carboxylic acid (**13**), which under these conditions undergoes decarboxylation giving rise to 3-[(azepan-2-ylidene)methyl]-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyridine (**14**). On the whole, this behavior is not

Scheme 4



Scheme 5



Reagents and conditions: *i.* DMF, refluxing; *ii.* 50% H_2SO_4, refluxing.

typical of usual enaminonitriles and is, apparently, attributed to the strong electron-withdrawing effect of the triazolyl group (see Scheme 5).

It should be noted that compounds **12** can be prepared also by refluxing of twofold excesses of lactim ethers **1b**,**c** with hydrazide **5** in DMF.

To conclude, it should be noted that the pathway in the reactions of lactim ethers with *N*-unsubstituted cyanoacetohydrazide substantially depends on the lactam ring size. New polymethylenetriazoles were synthesized based on the above-described processes.

Experimental

The ^{1}H NMR spectra were recorded on Varian Unity+400, Bruker DRX500, and Bruker AM360 spectrometers in DMSO-d_6 with Me_4Si as the internal standard. The mass spectra were obtained on a Finnigan SSQ-710 instrument using a direct inlet system; the ionization chamber temperature was 180 °C; the ionizing electron energy was 70 eV. The LC-mass spectra (LC/MS) were recorded on an Agilent Technologies 1100 instrument. The IR spectra were measured on a Perkin-Elmer 599 spectrometer as Nujol mulls and on a Specord M82 spectrometer in KBr pellets (1 mg/200 mg of KBr). The course of the reactions was monitored and the purity of the compounds was checked by chromatography on Silufol UV-254 plates; the spots in the chromatograms were visualized with UV light. The melting points were determined on a Boetius hot-stage apparatus.

The physicochemical characteristics, elemental analysis data, and ^{1}H NMR spectroscopic data are given in Table 1.

3-Amino-4-(pyrrolidin-2-ylidene)-4,5-dihydro-1*H*-pyrazol-5-one (4). A mixture of *O*-methylbutyrolactim (**1a**) (5.0 g, 50 mmol), cyanoacetohydrazide (**5**) (5.0 g, 50 mmol), and DMF (5 ml) were refluxed with stirring for 2 h. Then the reaction mixture was cooled, washed with diethyl ether, triturated with Pr^iOH, and filtered off. The yield of **4** was 3.0 g (36%). The physicochemical properties of the product are identical to those of the authentic sample.[1]

2-(Pyrrolidin-2-ylidene)cyanoacetohydrazide (6a). A mixture of *O*-methylbutyrolactim (**1a**) (1.0 g, 10 mmol) and cyanoacetohydrazide (**5**) (1.0 g, 10 mmol) was thoroughly ground and slightly warmed on a water bath (at 40 °C). The reaction mixture first became liquid and then rapidly solidified. The solid mixture was triturated with diethyl ether and filtered. Compound **6a** was obtained in a yield of 1.61 g (99%).

3-Cyanomethyl-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]-pyridine (7b). A mixture of *O*-methylvalerolactim (**1b**) (2.5 g, 22 mmol) and cyanoacetohydrazide (**5**) (2.2 g, 22 mmol) in DMF (2 mL) was refluxed for 1.5 h, cooled, triturated with diethyl ether, filtered, and successively washed with a 5 : 1 ethyl acetate—isopropanol mixture and diethyl ether. Compound **7b** was obtained in a yield of 2.75 g (77%).

3-Cyanomethyl-6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*a*]azepine (7c). A mixture of *O*-methylcaprolactim (**1c**) (6.4 g, 50 mmol) and cyanoacetohydrazide (**5**) (5.0 g, 50 mmol) in DMF (3 mL) was slightly warmed until dissolution of the hydrazide started and then kept at room temperature for 12 h. The mixture was concentrated, and the residue was triturated with diethyl ether and filtered. Compound **7c** was obtained in a

Table 1. Selected physicochemical characteristics and elemental analysis data for the compounds synthesized

Compound	Yield (%) (method)	M.p./°C (solvent)	Found / Calculated (%)			Molecular formula	^{1}H NMR (δ, (*J*/Hz))	MS, *m/z*
			C	H	N			
4	36	—	—	—	—	$C_7H_{10}N_4O$	—	166[M]$^+$
6a*	99	153—163 (decomp.) (H_2O)	—	—	—	$C_7H_{10}N_4O$	—	166[M]$^+$
7b	77	136—139 (PhH)	59.27 59.24	6.23 6.22	35.15 34.55	$C_8H_{10}N_4$	1.80 (m, 2 H, CH_2); 1.90 (m, 2 H, CH_2); 2.81 (t, 2 H, CH_2, *J* = 6.41); 3.89 (t, 2 H, CH_2, *J* = 6.10); 4.29 (s, 2 H, CH_2CN)	162[M]$^+$
7c	89	107—109 (PhH)	61.06 61.34	7.16 6.86	31.80 31.80	$C_9H_{12}N_4$	1.58 (m, 2 H, CH_2); 1.68 (m, 2 H, CH_2); 1.80 (m, 2 H, CH_2); 2.88 (t, 2 H, CH_2, *J* = 5.75); 3.92 (t, 2 H, CH_2, *J* = 5.09); 4.32 (s, 2 H, CH_2CN)	176[M]$^+$
12b	59(A) 66(B)	160—163 (PhMe)	63.89 64.17	7.06 7.04	28.52 28.79	$C_{13}H_{17}N_5$	1.77 (m, 6 H, CH_2); 1.91 (m, 2 H, CH_2); 2.69 (m, 2 H, CH_2); 2.80 (t, 2 H, CH_2, *J* = 6.41); 3.40 (m, 2 H, CH_2); 4.05 (t, 2 H, CH_2, *J* = 5.97); 10.30 (br.s, 1 H, NH)	243[M]$^+$
12c	93(B)	213—215 (AcOEt—Pr^iOH, 5 : 1)	65.38 65.34	7.31 7.44	27.26 27.22	$C_{14}H_{19}N_5$	1.60 (m, 2 H, CH_2); 1.67 (m, 2 H, CH_2); 1.74 (m, 4 H, CH_2); 1.80 (m, 2 H, CH_2); 2.70 (m, 2 H, CH_2); 2.89 (t, 2 H, CH_2, *J* = 6.11); 3.35 (m, 2 H, CH_2); 4.22 (t, 2 H, CH_2, *J* = 4.58); 9.76 (br.s, 1 H, NH)	—
12d	98(B)	252—255 (AcOEt—Pr^iOH, 3 : 1)	62.69 62.86	6.73 6.60	30.53 30.55	$C_{12}H_{15}N_5$	1.80 (m, 2 H, CH_2); 1.93 (m, 2 H, CH_2); 2.05 (m, 2 H, CH_2); 2.81 (t, 2 H, CH_2, *J* = 6.41); 3.63 (t, 2 H, CH_2, *J* = 7.02); 4.06 (t, 2 H, CH_2, *J* = 6.10); 9.46 (br.s, 1 H, NH)	—
12e	98(B)	199—201 (AcOEt—Pr^iOH, 3 : 1)	64.35 64.17	7.39 7.04	29.00 28.79	$C_{13}H_{17}N_5$	1.60 (m, 2 H, CH_2); 1.68 (m, 2 H, CH_2); 1.80 (m, 2 H, CH_2); 2.04 (m, 2 H, CH_2); 2.90 (m, 4 H, CH_2); 3.59 (t, 2 H, CH_2, *J* = 7.02); 4.21 (t, 2 H, CH_2, *J* = 4.58); 9.15 (br.s, 1 H, NH)	—
12f	58(B)	208—210 (AcOEt—Pr^iOH, 5 : 1)	65.33 65.34	7.51 7.44	27.23 27.22	$C_{14}H_{19}N_5$	1.54 (m, 2 H, CH_2); 1.66 (m, 2 H, CH_2); 1.73 (m, 2 H, CH_2); 1.80 (m, 2 H, CH_2); 1.92 (m, 2 H, CH_2); 2.83 (m, 2 H, CH_2); 3.52 (m, 2 H, CH_2); 4.08 (t, 2 H, CH_2, *J* = 6.10); 10.29 (br.s, 1 H, NH)	—
12g	48(A) 92(B)	184—187 (PhMe)	66.29 66.39	7.95 7.80	26.25 25.81	$C_{15}H_{21}N_5$	1.67 (m, 6 H, CH_2); 2.80 (t, 2 H, CH_2, *J* = 5.20); 2.88 (t, 2 H, CH_2, *J* = 5.61); 3.42 (m, 2 H, CH_2); 4.15 (t, 2 H, CH_2, *J* = 4.80); 9.42 (br.t, 1 H, NH)	—
14*	55	190—193 (AcOEt—Pr^iOH, 1 : 1)	—	—	—	$C_{13}H_{20}N_4$	1.51 (m, 2 H, CH_2); 1.61 (m, 2 H, CH_2); 1.77 (m, 2 H, CH_2); 1.87 (m, 2 H, CH_2); 2.40 (m, 2 H, CH_2); 2.74 (t, 2 H, CH_2, *J* = 6.64); 3.67 (t, 2 H, CH_2, *J* = 6.19); 4.60 (s, 1 H, CH); 8.2 (br.t, 1 H, NH)	232[M]$^+$

* The structure was established by IR and NMR spectroscopy and mass spectrometry.

yield of 7.9 g (89%). ^{13}C NMR (DMSO-d_6), δ: 19.8, 30.4, 31.0, 33.1, and 34.9 (2 C each, cyclic CH_2); 49.9 (2C, $\underline{C}H_2CN$); 121.3, 150.7, and 163.0 (1 C each).

3-[(Piperidin-2-ylidene)cyanomethyl]-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyridine (12b). Method *A*. A mixture of cyanoacetohydrazide (**5**) (1.0 g, 10 mmol), *O*-methylvalerolactim (**1b**) (2.6 g, 23 mmol), and DMF (3 mL) was refluxed for 4 h, the solvent was evaporated, and the residue was triturated with benzene and filtered off. Compound **12b** was obtained in a yield of 1.44 g (59%).

Method ***B***. Compound **12b** was synthesized analogously to compound **12d** (see below) from **7b** (0.81 g, 5 mmol) and *O*-methylvalerolactim (**1b**) (0.85 g, 7.5 mmol) in a yield of 0.8 g (66%).

3-[(Azepan-2-ylidene)cyanomethyl]-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyridine (12c) was synthesized analogously to compound **12d** (see below) from polymethylenetriazole **7b** and *O*-methylcaprolactim (**1c**). The yield was 93%.

3-[(Pyrrolidin-2-ylidene)cyanomethyl]-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyridine (12d). A mixture of compound **7b** (0.5 g, 5 mmol), *O*-methylbutyrolactim (**1a**) (0.85 g, 7.5 mmol), and DMF (1 mL) was refluxed with stirring for 1.5 h and then cooled. The residue was triturated with diethyl ether and filtered off. Compound **12d** was obtained in a yield of 0.69 g (98%).

3-[(Pyrrolidin-2-ylidene)cyanomethyl]-6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*a*]azepine (12e) was synthesized analogously to compound **12d** from polymethylenetriazole **7c** and *O*-methylbutyrolactim (**1a**). The yield was 98%.

3-[(Piperidin-2-ylidene)cyanomethyl]-6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*a*]azepine (12f) was synthesized analogously to compound **12d** from polymethylenetriazole **7c** and *O*-methylvalerolactim (**1b**). The yield was 58%.

3-[(Azepan-2-ylidene)cyanomethyl]-6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*a*]azepine (12g). Method ***A***. Compound **12g** was synthesized analogously to compound **12b** (method ***A***) from cyanoacetohydrazide (8.3 g, 84 mmol) and *O*-methylcaprolactim (**1c**) (21.3 g, 168 mmol) in a yield of 11.0 g (48%).

Method ***B***. Compound **12g** was synthesized analogously to compound **12d** from polymethylenetriazole **7c** (0.88 g, 5 mmol) and *O*-methylcaprolactim (**1c**) (0.95 g, 7.5 mmol) in a yield of 1.25 g (92%).

3-[(Azepan-2-ylidene)methyl]-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyridine (14). A mixture of compound **12c** (0.4 g, 1.6 mmol) and 50% sulfuric acid (3 mL) was refluxed for 15 min, diluted with water (30 mL), and cooled. Then a concentrated KOH solution was added dropwise with cooling to pH 12—13. The precipitate that formed was filtered off and thoroughly washed with water to remove inorganic impurities. Compound **14** was obtained in a yield of 0.2 g (55%). IR (KBr), ν/cm^{-1}: 3280, 3224 (NH); 1632 (C=N).

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