Reactions of cyclic enhydrazinoketones with arylidene derivatives of malononitrile. Synthesis of fused *N*-substituted 1,4-dihydropyridines

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A new method for the synthesis of fused *N*-amino-1,4-dihydropyridines was proposed. The method is based on the addition of cyclic enhydrazinoketones to arylidenemalononitriles. The structures of the compounds synthesized were studied using ^{1}H NMR spectroscopy.

Key words: cyclic enhydrazinoketones, arylidenemalononitriles, fused 1,4-dihydropyridines, Michael reaction.

Interest in the synthesis of 1,4-dihydropyridines is due to the broad spectrum of their biological activity. 4-Aryl-1,4-dihydropyridines are used to treat cardiovascular diseases.[1] Of considerable practical interest also are fused 1,4-dihydropyridines.[2,3] However, compounds of this type with different substituents at the ring nitrogen atom are scarcely studied. The published methods for the synthesis of fused *N*-substituted 1,4-dihydropyridines[4,5] are not general and allow only restricted variation of substituents at the skeletal N atom.

Among the ways of synthesizing fused 1,4-dihydropyridines, an approach involving cyclic enaminoketones is of particular interest. This method allows one to attach substituents to the N atom at the stage of preparation of enaminoketones. For example, it is known that heating of 3-anilino-5,5-dimethylcyclohex-2-en-1-one (**1**) with arylidene derivatives of malononitrile in alcohol in the presence of a catalytic amount of a base yields substituted hexahydroquinolines **2** (Scheme 1).[5]

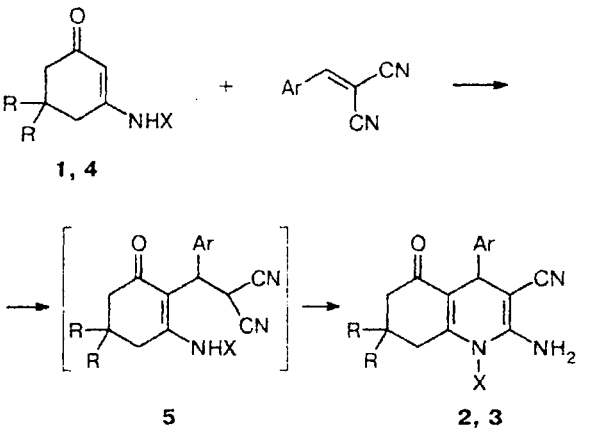
The use of enhydrazinoketones instead of enaminoketones would allow one to obtain unknown fused *N*-amino-1,4-dihydropyridines.

The goal of this work is to study the addition of enhydrazinoketones **4** to arylidenemalononitriles and synthesize fused *N*-amino-1,4-dihydropyridines **3**. The starting enhydrazinoketones **4** are prepared by the reaction of the corresponding hydrazines with cyclic 1,3-diketones.[6,7]

We showed that enhydrazinoketones **4** react with arylidene derivatives of malononitrile in ethanol at elevated temperature to give hexahydroquinolines **3** in 58–84% yields (Table 1). However, note that, unlike the aforesaid reaction,[5] the course of this reaction remains unchanged in the presence of piperidine as a base catalyst.

According to a plausible scheme of transformation, enhydrazinoketone **4** initially adds to arylidenemalononitrile following the Michael reaction to give intermediate **5** (Scheme 1). Subsequent intramolecular nucleophilic addition of the amino group to the nitrile one yields final hexahydroquinoline **3**.

Scheme 1



1, 2: X = Ph, R = H; **3:** R = H, Me

4	R	X
a	Me	NMe_2
b	H	NMe_2
c	Me	NHPh
d	H	NHPh
e	H	4-MeC_6H_4NH

Note. For particular R, X, and Ar substituents in compounds **3** see Table 1.

Both the Michael addition and final cyclization occur without base catalysis. This suggests that enhydrazinoketones **4** are more active analogs of enaminoketone **1**. Arylidene derivatives with electron-acceptor substitu-

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Table 1. Melting points, yields, reaction conditions, and elemental analysis data for compounds **3**

Compound	Substituents X	Ar	R	M.p. /°C	Yield (%)	Heating time	Found / Calculated (%) C	H	N	Cl	Br	Molecular formula
3a	NMe_2	Ph	Me	221—223	72	5 h	71.27 71.40	7.14 7.19	16.81 16.65	—	—	$C_{20}H_{24}N_4O$
3b	NMe_2	$4\text{-}ClC_6H_4$	Me	268—269	81	2 h	64.95 64.77	6.33 6.25	14.90 15.11	9.38 9.56	—	$C_{20}H_{23}ClN_4O$
3c	NMe_2	$4\text{-}ClC_6H_4$	H	227—228	78	2 h	63.30 63.06	5.43 5.59	16.52 16.34	10.21 10.34	—	$C_{18}H_{19}ClN_4O$
3d	NMe_2	$3\text{-}NO_2C_6H_4$	Me	263—264	84	1 h	62.79 62.98	6.22 6.08	18.49 18.36	—	—	$C_{20}H_{23}N_5O_3$
3e	NMe_2	$4\text{-}MeOC_6H_4$	Me	234—235	58	8 h	69.10 68.83	7.06 7.15	15.08 15.29	—	—	$C_{21}H_{26}N_4O_2$
3f	NMe_2	$4\text{-}BrC_6H_4$	H	237—238	71	3 h	55.59 55.83	5.09 4.95	14.32 14.47	—	20.79 20.63	$C_{18}H_{19}BrN_4O$
3g	PhNH	$4\text{-}ClC_6H_4$	Me	243—245	65	15 min	68.65 68.81	5.66 5.53	13.51 13.37	8.59 8.46	—	$C_{24}H_{23}ClN_4O$
3h	PhNH	$4\text{-}NO_2C_6H_4$	H	232—233	70	5 min	65.61 65.83	4.60 4.77	17.68 17.45	—	—	$C_{22}H_{19}N_5O_3$
3i	PhNH	$3\text{-}NO_2C_6H_4$	Me	268—269	73	15 min	66.95 67.12	5.23 5.40	16.45 16.31	—	—	$C_{24}H_{23}N_5O_3$
3j	$4\text{-}MeC_6H_4NH$	$4\text{-}BrC_6H_4$	H	218—219	61	5 min	61.23 61.48	4.55 4.71	12.57 12.47	—	17.56 17.78	$C_{23}H_{21}BrN_4O$
3k	$4\text{-}MeC_6H_4NH$	$4\text{-}ClC_6H_4$	H	221—223	67	5 min	68.05 68.23	5.37 5.23	14.01 13.84	8.93 8.76	—	$C_{23}H_{21}ClN_4O$

ents in the aromatic ring and electron-donor analogs can be smoothly involved in the reaction. However, the synthesis of hexahydroquinolines **3** containing electron-donor substituents requires longer heating (see Table 1).

The structures of the compounds obtained correlate well with ^1H NMR and elemental analysis data (Tables 1—3). Examination of ^1H NMR spectra revealed a series of interesting structural features in compounds **3**. Apparently, they all exist in the boat conformation typical of 4-aryl-1,4-dihydropyridines.[1] In the ^1H NMR spectra of hexahydroquinolines **3a—f**, derivatives of *N,N*-dimethylhydrazine, the signals for the methyl protons of the dimethylamino group differ by 0.05 ppm, thus indicating that the methyl groups are nonequivalent. For example, the ^1H NMR spectrum of compound **3a** shows two equally intense signals at δ 2.85 and 2.90 corre-

Table 2. ^1H NMR spectra (DMSO-d_6, δ, *J*/Hz) for compounds **3a—f**

Compound	CMe_2	CH_2	NMe_2	CH	NH_2	Ar
3a	0.90 (s, 3 H); 1.10 (s, 3 H)	2.00 (d, 1 H, *J* = 18); 2.20 (d, 1 H, *J* = 18); 2.55—2.70 (m, 2 H)	2.85 (s, 3 H); 2.90 (s, 3 H)	4.30 (s, 1 H)	6.15 (s, 2 H)	7.05—7.30 (m, 5 H)
3b	0.90 (s, 3 H); 1.10 (s, 3 H)	2.05 (d, 1 H, *J* = 18); 2.20 (d, 1 H, *J* = 18); 2.55—2.65 (m, 2 H)	2.85 (s, 3 H); 2.90 (s, 3 H)	4.35 (s, 1 H)	6.25 (s, 2 H)	7.10 (d, 2 H, *J* = 8); 7.30 (d, 2 H, *J* = 8)
3c	—	1.60—2.30 (m, 4 H); 2.60—2.75 (m, 2 H)	2.85 (s, 3 H); 2.90 (s, 3 H)	4.35 (s, 1 H)	6.30 (s, 2 H)	7.10 (d, 2 H, *J* = 8); 7.30 (d, 2 H, *J* = 8)
3d	0.90 (s, 3 H); 1.10 (s, 3 H)	2.00 (d, 1 H, *J* = 18); 2.25 (d, 1 H, *J* = 18); 2.55—2.65 (m, 2 H)	2.85 (s, 3 H); 2.90 (s, 3 H)	4.45 (s, 1 H)	6.45 (s, 2 H)	7.60 (m, 2 H); 7.90—8.10 (m, 2 H)
3e	0.90 (s, 3 H); 1.10 (s, 3 H)	2.00 (d, 1 H, *J* = 18); 2.20 (d, 1 H, *J* = 18); 2.60—2.65 (m, 2 H)	2.85 (s, 3 H); 2.90 (s, 3 H)	4.25 (s, 1 H)	6.15 (s, 2 H)	6.80 (d, 2 H, *J* = 8); 7.05 (d, 2 H, *J* = 8); 3.80 (s, 3 H, OCH_3)
3f	—	1.60—2.30 (m, 4 H); 2.60—2.75 (m, 2 H)	2.85 (s, 3 H); 2.90 (s, 3 H)	4.30 (s, 1 H)	6.35 (s, 2 H)	7.05 (d, 2 H, *J* = 8); 7.45 (d, 2 H, *J* = 8)

Table 3. ^{1}H NMR spectra (DMSO-d_6, δ, *J*/Hz) for compounds **3g—k**

Compound*	CMe_2	CH_2	CH	NH_2	Ar	NH
3g	0.70 (A); 0.85 (A); 1.00 (B) (all s, 6 H)	2.00—2.25 (m, 3 H); 2.70 (d, 1 H, *J* = 18)	4.50 (A); 4.45 (B) (both s, 1 H)	6.45 (A); 6.25 (B) (both s, 2 H)	6.65 (m, 2 H); 6.85 (m, 1 H); 7.20—7.50 (m, 6 H)	8.60 (A); 8.80 (B) (both s, 1 H)
3h	—	1.60—2.40 (m, 5 H); 2.70—2.90 (m, 1 H)	4.70 (A); 4.65 (B) (both s, 1 H)	6.45 (A); 6.25 (B) (both s, 2 H)	6.70 (m, 2 H); 6.90 (m, 1 H); 7.30 (m, 2 H); 7.50 (m, 2 H); 8.25 (m, 2 H)	8.60 (A); 8.75 (B) (both s, 1 H)
3i	0.70 (A); 0.85 (A); 1.00 (B) (all s, 6 H)	1.95—2.25 (m, 3 H); 2.70 (d, 1 H, *J* = 18)	4.70 (A); 4.65 (B) (both s, 1 H)	6.45 (A); 6.25 (B) (both s, 2 H)	6.70 (m, 2 H); 6.90 (m, 1 H); 7.25 (m, 2 H); 7.70 (m, 2 H); 8.10 (m, 2 H)	8.65 (A); 8.85 (B) (both s, 1 H)
3j	—	1.60—2.40 (m, 5 H); 2.70—2.90 (m, 1 H)	4.50 (A); 4.40 (B) (both s, 1 H)	6.45 (A); 6.25 (B) (both s, 2 H)	6.55 (m, 2 H); 7.05 (m, 2 H); 7.20 (m, 2 H); 7.50 (m, 2 H); 2.20 (s, 3 H, CH_3)	8.50 (A); 8.65 (B) (both s, 1 H)
3k	—	1.60—2.40 (m, 5 H); 2.70—2.90 (m, 1 H)	4.50 (A); 4.45 (B) (both s, 1 H)	6.40 (A); 6.15 (B) (both s, 2 H)	6.55 (m, 2 H); 7.05 (m, 2 H); 7.25 (m, 2 H); 7.40 (m, 2 H); 2.20 (s, 3 H, CH_3)	8.50 (A); 8.65 (B) (both s, 1 H)

* The A : B ratio is ≈2 : 1.

sponding to the protons of two methyl groups of the dimethylamino group (see Table 2). The nonequivalence of the latter is associated with the presence of an asymmetric center in position 4 of the dihydropyridine ring and hindered rotation about the N—N bond. One could assume that the presence of two nonequivalent substituents at the nitrogen atom in arylhydrazine derivatives **3g—k** would give rise to a second element of asymmetry. Indeed, the ^{1}H NMR spectra suggest that hexahydroquinolines **3g—k** obtained from arylhydrazines exist as a mixture of diastereomers **3A** and **3B**.

Each diastereomer manifests itself by its own set of ^{1}H NMR signals, *i.e.*, the total number of signals is doubled. The largest difference in the chemical shifts for the pair of diastereomers is observed for the NH_2 protons and the C(4)-bound proton in the dihydropyridine ring (Δδ ≈ 0.1 ppm). For example, in the spectrum of compound **3g**, the signal from the NH_2 protons of the major diastereomer appears at δ 6.45, while those for the minor diastereomer are shifted to δ 6.25. The chemical shifts for the ring H(4) protons of the diastereomers differ less significantly (see Table 3). Thus, sterically hindered rotation about the single N—N bond gives rise to an additional element of asymmetry.

Hexahydroquinolines **3** are colorless or slightly colored high-melting crystalline substances. Their poor solubility in cold ethanol substantially facilitates the process of isolation and purification (see Table 1).

Experimental

^{1}H NMR spectra were recorded on Bruker AM-300 (300 MHz) and Bruker WM-250 instruments (250 MHz) in DMSO-d_6. Melting points were measured on a Boetius hot stage and are given uncorrected. All reaction mixtures were analyzed and the purity of the reaction products was checked by TLC on Silufol UV 254 plates with AcOEt—hexane (3 : 1) as the eluent.

3-(2,2-Dimethylhydrazino)-5,5-dimethylcyclohex-2-en-1-one (4a)[6]. Me_2NNH_2 (2.4 g, 0.04 mol) was added to a solution of dimedone (5.6 g, 0.04 mol) in 50 mL of benzene. The reaction mixture was refluxed with a Dean—Stark adapter for 4 h and then cooled. The precipitate that formed was filtered off and washed on the filter with a small amount of benzene to give enhydrazinoketone **4a** (5.85 g, 80%), m.p. 164—165 °C (Ref. 6: 164 °C).

3-(2,2-Dimethylhydrazino)cyclohex-2-en-1-one (4b)[6] was obtained by analogy with **4a** from cyclohexane-1,3-dione (4.48 g, 0.04 mol) and Me_2NNH_2 (2.4 g, 0.04 mol). Yield 5.28 g (86%), m.p. 141—142 °C (Ref. 6: 143 °C).

5,5-Dimethyl-3-(2-phenylhydrazino)cyclohex-2-en-1-one (4c)[7]. A solution of $NaOAc \cdot 3\ H_2O$ (2.72 g, 0.02 mol) in 20 mL of water was added to a suspension of dimedone (2.8 g, 0.02 mol) and $PhNHNH_2 \cdot HCl$ (2.89 g, 0.02 mol) in 50 mL of water. The reaction mixture was stirred at ~20 °C for 2 h. Then, the precipitate that formed was filtered off, washed on the filter with water, and recrystallized from aqueous ethanol to give enhydrazinoketone **4c** (3.36 g, 73%), m.p. 162—163 °C (Ref. 7: 163—164 °C).

3-(2-Phenylhydrazino)cyclohexen-2-one (4d)[7] was obtained by analogy with **4c** from cyclohexane-1,3-dione (2.24 g,

0.02 mol), $PhNHNH_2 \cdot HCl$ (2.89 g, 0.02 mol), and $AcONa \cdot 3\ H_2O$ (2.72 g, 0.02 mol). Yield 2.79 g (69%), m.p. 141—142 °C (Ref. 7: 143 °C).

3-[2-(4-Methylphenyl)hydrazino]cyclohexenone (4e) was obtained by analogy with **4c** from cyclohexane-1,3-dione (2.24 g, 0.02 mol), p-$TolNHNH_2 \cdot HCl$ (3.17 g, 0.02 mol), and $AcONa \cdot 3\ H_2O$ (2.72 g, 0.02 mol). Yield 3.33 g (77%), m.p. 117—118 °C. Found (%): C, 72.02; H, 7.39; N, 13.09. $C_{13}H_{16}N_2O$. Calculated (%): C, 72.19; H, 7.46; N, 12.95. ^1H NMR, δ: 1.85 (m, 2 H, CH_2); 2.15 (m, 2 H, CH_2); 2.20 (s, 3 H, CH_3); 2.40 (m, 2 H, CH_2); 5.05 (s, 1 H, CH); 6.60 (d, 2 H, CH_{Ar}, J = 8 Hz); 7.00 (d, 2 H, CH_{Ar}, J = 8 Hz); 7.70 (s, 1 H, NH); 8.75 (s, 1 H, NH).

2-Amino-4-aryl-1-(dimethylamino)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitriles (3a—f, X = NMe_2) (general procedure). A solution of enhydrazinoketone **4a—b** (0.002 mol) and the corresponding arylidenemalononitrile (0.002 mol) in 5 mL of ethanol was refluxed for several hours (see Table 1). Then the reaction mixture was cooled, and the precipitate that formed was filtered off and washed on the filter with a small amount of ethanol. The yields and melting points of compounds **3** are presented in Table 1.

2-Amino-4-aryl-1-(arylamino)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitriles (3g—k, X = NHAr) (general procedure). A solution of enhydrazinoketone **4c—e** (0.002 mol) and the corresponding arylidenemalononitrile (0.002 mol) in 5 mL of ethanol was refluxed for several minutes (see Table 1). Then the reaction mixture was cooled, and the precipitate that formed was filtered off and washed on the filter with a small amount of ethanol. The yields and melting points of compounds **3** are presented in Table 1.

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