ISSN 1070-4280, Russian Journal of Organic Chemistry, 2016, Vol. 52, No. 3, pp. 397–403. © Pleiades Publishing, Ltd., 2016.
Original Russian Text © S.S. Mochalov, A.N. Fedotov, E.V. Trofimova, R.A. Gazzaeva, N.S. Zefirov, 2016, published in Zhurnal Organicheskoi Khimii, 2016, Vol. 52, No. 3, pp. 417–423.

Isomerization of 3-Unsubstituted 4,5-dihydroisoxazoles over Alumina. A New Synthesis of β-Hydroxy Nitriles

S. S. Mochalov[a], A. N. Fedotov[a], E. V. Trofimova[a], R. A. Gazzaeva[b], and N. S. Zefirov[a]

[a] *Faculty of Chemistry, Moscow State University, Leninskie gory 1, Moscow, 119991 Russia*
e-mail: fed@org.chem.msu.ru

[b] *Khetagurov North Ossetian State University, ul. Vatutina 44–46, Vladikavkaz, 362025 Russia*

Received November 9, 2015

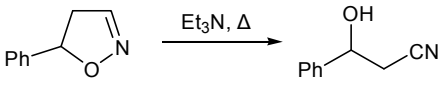
Abstract—3-Unsubstituted 4,5-dihydroisoxazoles obtained by nitrosation of arylcyclopropanes are capable of undergoing efficient isomerization into 3-aryl-3-hydroxypropanenitriles during chromatography on alumina.

DOI: 10.1134/S1070428016030179

Five-membered heterocyclic 4,5-dihydroisoxazole systems, which may be regarded as cyclic form of *O*-alkyl oximes, are structural units of many biologically active molecules [1], including natural alkaloids [2–5]. Therefore, systematic studies are performed with the goal of obtaining medicinal agents on the basis of dihydroisoxazole substrates. However, apart from medical purposes, the possibility of using dihydroisoxazole derivatives in synthetic organic chemistry is equally important. Due to the ability of 4,5-dihydroisoxazole structures to be converted into β-hydroxy nitriles, β-hydroxy ketones, γ-amino alcohols, and α,β-unsaturated ketones and acids, these compounds were referred to as those possessing latent bifunctionality [6–8].

From the viewpoint of synthetic potential, the transformation of 4,5-dihydroisoxazoles into β-hydroxy nitriles seems to be the most important, since these transformation products are quite useful building blocks for the synthesis of β-hydroxy carboxylic acids and their derivatives and γ-amino alcohols and are often used to assemble complex biologically active molecules [7, 9]. Up to now, syntheses of β-hydroxy nitriles from 3-bromo- [10, 11], 3-carboxy- [12], 3-trimethylsilyl- [13], and 3-(benzenesulfonyl)-4,5-dihydroisoxazoles [14, 15] have been well documented; in these reactions, the formation of cyano group is initiated through elimination of the 3-substituent. On the other hand, Huisgen and Christl [16] showed that β-hydroxy nitriles can readily be obtained by treatment of 3-unsubstituted 4,5-dihydroisoxazoles with triethylamine on heating (Scheme 1).

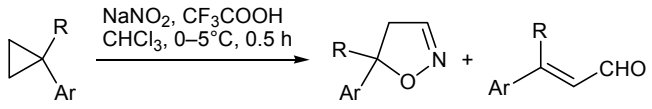
Scheme 1.



It is quite obvious that the synthesis of β-hydroxy nitriles from 3-unsubstituted 4,5-dihydroisoxazoles is more advantageous than their synthesis from 3-substituted analogs. However, no due attention has been paid for a long time to the Huisgen synthesis of β-hydroxy nitriles, presumably because of the lack of efficient procedures for preparation of 3-unsubstituted 4,5-dihydroisoxazoles. In recent years, extensive studies have been performed on the synthesis of 3-unsubstituted 4,5-dihydroisoxazoles, and reliable and efficient methods for their synthesis have been developed [8, 17–30]. The possibility for synthesizing β-hydroxy nitriles in moderate to high yields according to Huisgen was subsequently confirmed in [31–33]. While continuing studies on the base-catalyzed isomerization of 3-unsubstituted 4,5-dihydroisoxazoles into β-hydroxy nitriles, it was shown that, apart from triethylamine, this reaction can be initiated by other bases, such as sodium methoxide, potassium *tert*-butoxide, and 1,8-diazabicycloundec-7-ene (DBU) [8, 34].

In this study we have shown that the isomerization of 3-unsubstituted 4,5-dihydroisoxazoles into β-hydroxy nitriles can be efficiently catalyzed by alumina. The process can be performed in a one-pot mode; it includes reaction of arylcyclopropanes with nitrous acid (synthesis of 3-unsubstituted 4,5-dihydroisoxa-

Scheme 2.



1a–1k **2a–2k** **3a–3f**, **3h**, **3i**

R = H, Ar = Ph (**a**), 4-BrC_6H_4 (**b**), 3-BrC_6H_4 (**c**), 5,6,7,8-tetrahydronaphthalen-2-yl (**d**), fluoren-2-yl (**e**), 4-$AllC_6H_4$ (**f**), 4-(cyclopropylmethyl)phenyl (**g**), 4-(2,2-dichlorocyclopropylmethyl)phenyl (**h**), 3-(2,2-dichlorocyclopropylmethyl)phenyl (**i**), $PhCH_2$ (**j**); R = Me, Ar = 4-*i*-PrC_6H_4 (**k**).

zoles) and subsequent isomerization of the resulting heterocyclic compounds into β-hydroxy nitriles by the action of Al_2O_3.

According to the ^{1}H NMR data, the reaction mixtures obtained by reactions of arylcyclopropanes **1a**–**1k** with an equimolar amount of sodium nitrite in acid medium contained the corresponding 3-unsubstituted 4,5-dihydroisoxazoles **2a**–**2k** and cinnamaldehydes **3a**–**3h** together with unreacted initial compounds (Table 1, Scheme 2). The data in Table 1 show that each arylcyclopropane **1a**–**1k** gives rise mainly to 3-unsubstituted dihydroisoxazole and that cinnamaldehydes either are not formed (run nos. 7, 8, 11, 12) or are formed as minor products. An exception was the reaction with *m*-bromophenylcyclopropane (run no. 3). Under the nitrosation conditions, arylcyclopropanes having no electron-withdrawing substituents are converted into 3-unsubstituted dihydroisoxazoles in higher yields (run nos. 1, 4, 5, 11, 12) than are those containing even weakly acceptor groups, namely a bromine atom (run nos. 2, 3) or 2,2-dichlorocyclopropyl substituent (run nos. 8, 10). Despite the use of 2 equiv of $NaNO_2$, complete conversion of **1h** was not attained, and a considerable amount of the initial arylcyclopropane remained unchanged (run no. 9). Analogous relation between the nature of substituents in arylcyclopropanes and the yield of 4,5-dihydroisoxazoles was noted in [30] where the behavior of arylcyclopropanes with electron-donating and electron-withdrawing substituents in the benzene ring was studied in the reaction with nitrosyl chloride in the presence of sulfur(VI) oxide.

It should be emphasized that substrates **1f** and **1g** containing allyl or cyclopropylmethyl group capable of competing with the conjugated cyclopropyl substituent in the electrophilic addition reaction reacted with nitrous acid only through the cyclopropane fragment conjugated with the benzene ring.

By chromatographic separation of the reaction mixtures from run nos. 1–8 and 10–12 on alumina

Table 1. Composition of the reaction mixtures in the reactions of arylcyclopropanes **1a**–**1k** with an equimolar amount of nitrous acid

Run no.	Initial arylcyclopropane	Composition of the reaction mixture,[a] %		
		dihydroisoxazole	cinnamaldehyde	unreacted arylcyclopropane
1	**1a**	**2a** (79.5)	**3a** (8.3)	**1a** (12.5)
2	**1b**	**2b** (70.5)	**3b** (8.1)	**1b** (21.3)
3	**1c**	**2c** (42.2)	**3c** (20.3)	**1c** (36.6)
4	**1d**	**2d** (91.5)	**3d** (~2.0)	**1d** (6.5)
5	**1e**	**2e** (94.0)	**3e** (~3.0)	**1e** (4.0)
6	**1f**	**2f** (68.1)	**3f** (4.6)	**1f** (26.5)
7	**1g**	**2g** (55.5)	–	**1g** (44.3)
8	**1h**	**2h** (50.2)	–	**1h** (49.3)
9	**1h**[b]	**2h** (75.1)	**3g** (2.1)	**1h** (22.7)
10	**1i**	**2i** (56.3)	**3h** (~2.0)	**1i** (41.5)
11	**1j**	**2j** (72.2)	–	**1j** (26.3)
12	**1k**	**2k** (93.0)	–	**1k** (~3.0)

[a] According to the ^{1}H NMR data.
[b] 2 equiv of HNO_2.

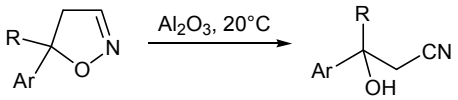
Table 2. Yields of compounds **1**–**4** (%) after chromatographic separation on Al_2O_3 of the reaction mixtures obtained in run nos. 1–8 and 10–12

Run no.	Dihydroisoxazole[a]	Cinnamaldehyde	Unreacted arylcyclopropane	β-Hydroxy nitrile[a]
1	**2a**, 10.5 (7.5)	**3a**, 6.5	**1a**, 10.4	**4a**, 69.0 (82.5)
2	**2b**, 9.5 (12.7)	**3b**, 8.3	**1b**, 18.2	**4b**, 67.1 (87.5)
3	**2c**, 6.8 (15.8)	**3c**, 10.2	**1c**, 36.7	**4c**, 46.1 (84.2)
4	**2d**, 21.8 (20.7)	**3d**, 1.6	**1d**, 3.9	**4d**, 66.8 (71.5)
5	**2e**, 9.4 (11.5)	**3e**, 4.3	**1e**, 5.5	**4e**, 71.0 (88.5)
6	**2f**, 14.5 (20.4)	**3f**, 5.1	**1f**, 17.5	**4f**, 56.7 (79.3)
7	**2g**, 19.5 (30.8)	–	**1g**, 35.5	**4g**, 45.4 (69.2)
8	**2h**, 5.3 (11.2)	–	**1h**, 52.2	**4h**, 42.5 (88.8)
10	**2i**, 8.7 (16.3)	–	**1i**, 46.7	**4i**, 44.5 (83.7)
11	**2j**, 17.5 (24.1)	–	**1j**, 27.5	**4j**, 55.0 (75.9)
12	**2k**, 53.0	–	**1k**, –	**4k**, 47

[a] In parentheses are given the concentrations (%) of **2a**–**2k** and **4a**–**4k** after a single chromatographic separation, which indicate the degree of isomerization of **2** over Al_2O_3.

(Table 2) we isolated both components of the initial mixture and (major products) β-hydroxy nitriles **4a**–**4k** resulting from isomerization of 3-unsubstituted 4,5-dihydroisoxazoles **2a**–**2k** (Scheme 3).

Scheme 3.



2a–2k **4a–4k**

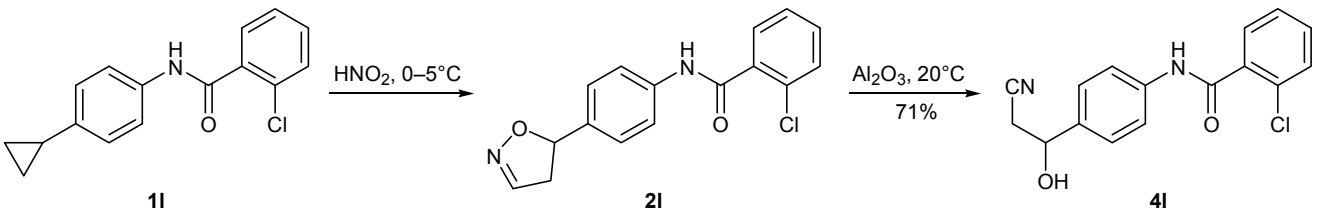
The efficiency of the Al_2O_3-catalyzed isomerization may be estimated by comparing the amounts of dihydroisoxazoles **2a**–**2k** isolated by chromatography and the corresponding β-hydroxy nitriles **4a**–**4k** (Table 2, in parentheses), calculated on **2a**–**2k** taken for chromatography.

In order to demonstrate that the presence of unreacted initial arylcyclopropanes **1a**–**1k** and cinnamaldehydes (by-products) in the reaction mixtures does not affect the isomerization process, 5-aryldihydroisoxazole **2l** was specially isolated by crystallization from the reaction mixture obtained in the nitrosation of **1l** and subjected to isomerization upon chromatography on Al_2O_3; as a result, β-hydroxy nitrile **4l** was obtained in high yield (Scheme 4). These findings allow us to believe that 3-unsubstituted 4,5-dihydroisoxazoles synthesized by any other method (not only by reaction of **1** with HNO_2) should undergo efficient Al_2O_3-catalyzed isomerization into the corresponding 3-hydroxyalkanenitriles. The transformation sequence including nitrosation of arylcyclopropanes followed by chromatography of the resulting 3-unsubstituted 4,5-dihydroisoxazoles on Al_2O_3 may be regarded as a one-pot synthesis of β-hydroxy nitriles from arylcyclopropanes.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded from solutions in $CDCl_3$ on a Varian VXR-400 spectrometer (400 MHz) using the residual proton signal of the solvent as reference. The IR spectra were measured on a UR-20 spectrometer from samples prepared as thin films or Nujol mulls (solids). The mass spectrum of **4i** (electron impact, 70 eV) was obtained on a Finnigan SSQ 7000 GC/MS instrument (DB-1 capillary column, 30 m×0.2 mm; carrier gas helium; oven temperature programming from 50 to 300°C at a rate of 10 deg ×

Scheme 4.



1l **2l** **4l**

min^{-1}). The elemental compositions were determined using a Vario-11 CHN analyzer. The melting points were measured on an Electrothermal 1A9100 digital melting point apparatus.

The products were isolated from the reactions mixtures by column chromatography on Al_2O_3 (Brockmann activity grade II) using diethyl ether, diethyl ether–chloroform (1:3, 1:2), and chloroform–methanol (1:1) as eluents.

Arylcyclopropanes **1a**, **1b** [35], **1c** [36], **1e** [37], **1f** [38], **1j** [39], and **1l** [28] were synthesized according to known procedures.

2-Cyclopropyl-5,6,7,8-tetrahydronaphthalene (1d) was synthesized by catalytic decomposition of 3-(5,6,7,8-tetrahydronaphthalen-2-yl)-4,5-dihydro-1*H*-pyrazole according to Kischner. Yield 69%, bp 173–174°C (45 mm), n_D^{20} = 1.5544. ^{1}H NMR spectrum, δ, ppm: 0.73 m (2H), 0.99 m (2H), and 1.92 m (1H, C_3H_5), 1.82 m (4H, 6-H, 7-H), 2.82 m (4H, 5-H, 8-H), 6.88–6.91 m (2H) and 7.05 d (1H, J = 8.1 Hz) (1-H, 3-H, 4-H). Found, %: C 90.28, 90.37; H 9.12, 9.19. $C_{13}H_{16}$. Calculated, %: C 90.64; H 9.36.

1-Cyclopropyl-4-(cyclopropylmethyl)benzene (1g) was synthesized by reduction of 1-cyclopropyl-4-(2,2-dichlorocyclopropylmethyl)benzene as described in [40]. Yield 72%, bp 151–153°C (20 mm), n_D^{20} = 1.5395. ^{1}H NMR spectrum, δ, ppm: 0.27 m (2H), 0.58 m (2H), and 1.06 m (1H) ($C_3\mathbf{H}_5CH_2$); 0.75 m (2H), 1.01 m (2H), and 1.95 m (1H) (1-C_3H_5); 2.58 d (2H, 4-CH_2, J = 6.2 Hz), 7.08 d and 7.23 d (2H each, H_{arom}, J = 8.0 Hz). Found, %: C 90.31, 90.46; H 9.14, 9.22. $C_{13}H_{16}$. Calculated, %: C 90.64; H 9.36.

1-Cyclopropyl-4-(2,2-dichlorocyclopropylmethyl)benzene (1h) was synthesized by dichlorocyclopropanation of 1-allyl-4-cyclopropylbenzene as described in [40]. Yield 81%, bp 199–201°C (12 mm), n_D^{20} = 1.5522. ^{1}H NMR spectrum, δ, ppm: 0.73 m (2H) and 1.01 m (2H, CH_2) (C_3H_5), 1.26 m (1H) and 1.71 m (1H, CH_2, $Cl_2C_3H_3$), 1.93 m (2H, CH), 2.79 d.d (1H, J = 6.6, 14.7 Hz) and 3.01 d.d (1H, J = 7.8, 14.7 Hz) (4-CH_2), 7.09 d and 7.21 d (2H each, H_{arom}, J = 8.1 Hz). Found, %: C 64.31, 64.52; H 5.63, 5.73. $C_{13}H_{14}Cl_2$. Calculated, %: C 64.75; H 5.85.

1-Cyclopropyl-3-(2,2-dichlorocyclopropylmethyl)benzene (1i) was synthesized in a similar way. Yield 64%, bp 214–215°C (23 mm), n_D^{20} = 1.5541. ^{1}H NMR spectrum, δ, ppm: 0.75 m (2H) and 1.01 m (2H, CH_2) (C_3H_5), 1.25 m (1H) and 1.72 m (1H, CH_2) ($Cl_2C_3H_3$), 1.94 m (2H, CH in C_3H_5, $Cl_2C_3H_3$), 2.78 d.d (1H, J = 6.8, 15.4 Hz) and 3.02 d.d (1H, J = 7.6, 15.4 Hz) (3-CH_2), 6.99 d (1H, H_{arom}, J = 7.6 Hz), 7.05 s (1H, H_{arom}), 7.11 d (1H, H_{arom}, J = 7.6 Hz), 7.26 t (1H, H_{arom}). Found, %: C 64.22, 64.41; H 5.68, 5.77. $C_{13}H_{14}Cl_2$. Calculated, %: C 64.75; H 5.85.

1-(1-Methylcyclopropyl)-4-(propan-2-yl)benzene (1k) was synthesized by reduction of 1-(2,2-dichloro-1-methylcyclopropyl)-4-(propan-2-yl)benzene according to [40]. Yield 69%, bp 126–127°C (30 mm), n_D^{20} = 1.5082. ^{1}H NMR spectrum, δ, ppm: 0.78 m (2H) and 0.93 m (2H, CH_2) (C_3H_4), 1.32 d [6H, CH(C$\mathbf{H}_3$)$_2$, J = 7.4 Hz], 1.48 s (3H, CH_3), 2.96 sept [1H, C$\mathbf{H}$(CH_3)$_2$], 7.22 d and 7.26 d (2H each, H_{arom}, J = 7.8 Hz). Found, %: C 89.21, 89.32; H 10.14, 10.21. $C_{13}H_{18}$. Calculated, %: C 89.59; H 10.41.

Reaction of arylcyclopropanes 1a–1l with nitrous acid generated *in situ* (*general procedure*). Sodium nitrite, 0.69 g (0.01 mol), was added in portions over a period of 10–15 min to a mixture of 0.01 mol of arylcyclopropane **1a**–**1l**, 5.2 g of trifluoroacetic acid, and 15 mL of chloroform, cooled to 0–5°C. The mixture was allowed to warm up to 20°C, kept for 1 h at that temperature, and poured into 100 mL of cold water. The organic phase was separated, the aqueous phase was extracted with chloroform (2×10 mL), the extracts were combined with the organic phase, washed with water (2×30 mL), and dried over $MgSO_4$, the solvent was removed, and the residue was analyzed by ^{1}H NMR. Compound **2l** was isolated by crystallization. The compositions of the reaction mixtures are given in Table 1. The physical constants and spectral characteristics of **2a** [16], **2b** [30], and **2l** [28] coincided with published data.

5-(3-Bromophenyl)-4,5-dihydro-1,2-oxazole (2c). Viscous oily material. ^{1}H NMR spectrum, δ, ppm: 2.98 d.d.d (1H, 4-H, J = 2.0, 7.4, 17.8 Hz) and 3.46 d.d.d (1H, 4-H, J = 2.0, 10.5, 17.8 Hz), 5.51 d.d (1H, 5-H, J = 7.4, 10.5 Hz), 7.23 s (1H, 3-H), 7.23–7.28 m (3H, H_{arom}), 7.49 m (1H, H_{arom}). Found, %: C 47.33, 47.51; H 3.36, 3.42; N 5.91, 6.02. C_9H_8BrNO. Calculated, %: C 47.82; H 3.57; N 6.20.

5-(5,6,7,8-Tetrahydronaphthalen-2-yl)-4,5-dihydro-1,2-oxazole (2d). Viscous oily material. ^{1}H NMR spectrum, δ, ppm: 1.82 m (4H, 6′-H, 7′-H), 2.78 m (4H, 5′-H, 8′-H), 3.02 d.d (1H, 4-H, J = 8.0, 17.2), 3.41 d.d (1H, 4-H, J = 11.2, 17.2 Hz), 5.56 d.d (1H, 5-H, J = 7.8, 11.2 Hz), 7.05–7.10 m (3H, H_{arom}), 7.24 s (1H, 3-H). Found, %: C 77.43, 77.61; H 7.41, 7.56; N 7.04, 7.12. $C_{13}H_{15}NO$. Calculated, %: C 77.58; H 7.51; N 6.96.

5-(9*H*-Fluoren-2-yl)-4,5-dihydro-1,2-oxazole (2e). mp 111–112°C (from Et_2O). ^{1}H NMR spectrum, δ, ppm: 3.07 d.d.d (1H, 4-H, *J* = 1.7, 8.2, 17.6 Hz), 3.50 d.d.d (1H, 4-H, *J* = 1.7, 11.2, 17.6 Hz), 3.91 s (2H, 9′-H), 5.62 d.d (1H, 5-H, *J* = 8.2, 11.2 Hz), 7.28 s (1H, 3-H), 7.31–7.42 m (3H, H_{arom}), 7.55 m (2H, H_{arom}), 7.79 t (2H, H_{arom}, ^3J = 7.8 Hz). Found, %: C 81.16, 81.37; H 5.35, 5.60; N 5.88, 6.01. $C_{16}H_{13}NO$. Calculated, %: C 81.68; H 5.57; N 5.95.

5-[4-(2-Prop-2-en-1-yl)phenyl]-4,5-dihydro-1,2-oxazole (2f). Viscous oily material. ^{1}H NMR spectrum, δ, ppm: 2.98 d.d.d (1H, 4-H, *J* = 1.8, 8.4, 17.7 Hz), 3.43 d.d.d (1H, 4-H, *J* = 1.8, 10.6, 17.7 Hz), 3.40 d (2H, 4′-CH_2, *J* = 7.1 Hz), 5.08–5.12 m (2H, CH=C**H**$_2$), 5.52 d.d (1H, 5-H, *J* = 8.4, 10.6 Hz), 5.92–6.02 m (1H, C**H**=CH_2), 7.20 s (1H, 3-H), 7.21 d (2H, H_{arom}, ^3J = 8.0 Hz), 7.28 d (2H, H_{arom}, ^3J = 8.0 Hz). Found, %: C 76.62, 76.73; H 6.76, 6.82; N 7.16, 7.31. $C_{12}H_{13}NO$. Calculated, %: C 76.98; H 7.00; N 7.48.

5-[4-(Cyclopropylmethyl)phenyl]-4,5-dihydro-1,2-oxazole (2g). Viscous oily material. ^{1}H NMR spectrum, δ, ppm: 0.21 m (2H), 0.53 m (2H), and 0.99 m (1H) (C_3H_5); 2.56 d (2H, 4′-CH_2, *J* = 6.4 Hz), 2.99 d.d (1H, 4-H, *J* = 8.2, 17.6 Hz), 3.42 d.d (1H, 4-H, *J* = 11.6, 17.6 Hz), 5.51 d.d (1H, 5-H, *J* = 8.2, 11.6 Hz), 7.21 s (1H, 3-H), 7.30 d (2H, H_{arom}, ^3J = 7.8 Hz), 7.33 d (2H, H_{arom}, ^3J = 7.8 Hz). Found, %: C 77.21, 77.38; H 7.27, 7.39; N 6.93, 7.06. $C_{13}H_{15}NO$. Calculated, %: C 77.58; H 7.51; N 6.96.

5-{4-[(2,2-Dichlorocyclopropyl)methyl]phenyl}-4,5-dihydro-1,2-oxazole (2h). Viscous oily material. ^{1}H NMR spectrum, δ, ppm: 1.26 m (1H), 1.71 m (1H), and 1.88 m (1H) ($Cl_2C_3H_3$); 2.82 d.d (1H, *J* = 6.7, 15.6 Hz) and 2.98 d.d (1H, *J* = 7.8, 15.6 Hz) (4′-CH_2), 3.03 d.d.d (1H, 4-H, *J* = 1.4, 8.0, 17.6 Hz), 3.45 d.d.d (1H, 4-H, *J* = 1.4, 10.7, 17.6 Hz), 5.55 d.d (1H, 5-H, *J* = 8.0, 10.7 Hz), 7.24 d (1H, 3-H, *J* = 1.4 Hz), 7.31 s (4H, H_{arom}). Found, %: C 57.23, 57.36; H 4.56, 4.62; N 5.26, 5.31. $C_{13}H_{13}Cl_2NO$. Calculated, %: C 57.80; H 4.85; N 5.19.

5-{3-[(2,2-Dichlorocyclopropyl)methyl]phenyl}-4,5-dihydro-1,2-oxazole (2i). Viscous oily material. ^{1}H NMR spectrum, δ, ppm: 1.26 m (1H), 1.70 m (1H), and 1.91 m (1H) ($Cl_2C_3H_3$); 2.84 d.d (1H, *J* = 6.6, 15.4 Hz) and 2.98 d.d (1H, *J* = 7.4, 15.4 Hz) (3′-CH_2), 3.05 d.d.d (1H, 4-H, *J* = 1.4, 8.2, 17.6 Hz), 3.46 d.d.d (1H, 4-H, *J* = 1.4, 10.7, 17.6 Hz), 5.54 d.d (1H, 5-H, *J* = 8.2, 10.7 Hz), 7.22 s (1H, 3-H), 7.23–7.29 m (4H, H_{arom}). Found, %: C 57.31, 57.53; H 4.61, 4.73; N 4.88, 5.01. $C_{13}H_{13}Cl_2NO$. Calculated, %: C 57.80; H 4.85; N 5.19.

5-Benzyl-4,5-dihydro-1,2-oxazole (2j). Oily material. ^{1}H NMR spectrum, δ, ppm: 2.73 d.d.d (1H, 4-H, *J* = 1.9, 7.4, 17.5 Hz), 2.99 d.d.d (1H, 4-H, *J* = 1.9, 10.4, 17.5 Hz), 2.82 d.d (1H, *J* = 7.2, 13.6 Hz) and 3.06 d.d (1H, *J* = 6.4, 13.6 Hz) (5-CH_2), 4.82 m (1H, 5-H), 7.12 s (1H, 3-H), 7.22–7.35 m (5H, H_{arom}). Found, %: C 74.42, 74.56; H 6.56, 6.71; N 8.71, 8.78. $C_{10}H_{11}NO$. Calculated, %: C 74.51; H 6.88; N 8.69.

5-Methyl-5-[4-(propan-2-yl)phenyl]-4,5-dihydro-1,2-oxazole (2k). Oily material. ^{1}H NMR spectrum, δ, ppm: 1.26 d [6H, CH(C**H**$_3$)$_2$, *J* = 6.4 Hz], 1.73 s (3H, CH_3), 2.93 sept [1H, C**H**$(CH_3)_2$], 3.14 d and 3.17 d (1H each, 4-H, *J* = 15.2 Hz), 7.19 s (1H, 3-H), 7.23 d (2H, H_{arom}, *J* = 8.2 Hz), 7.35 d (2H, H_{arom}, *J* = 8.2 Hz). Found, %: C 76.27, 76.45; H 8.11, 8.20; N 6.92, 7.02. $C_{13}H_{17}NO$. Calculated, %: C 76.81; H 8.43; N 6.89.

Chromatographic separation of the reaction mixtures on Al_2O_3. A column, 2.5 cm in diameter and 18 cm in height, was charged with 25–30 g of Al_2O_3 (Brockmann activity grade II) and wetted with petroleum ether (40–70°C), 0.5–0.6 g of the reaction mixture obtained by nitrosation of **1a**–**1l** was applied on the top, and the column was eluted in succession with diethyl ether, diethyl ether–chloroform (1:3, 1:2), and chloroform–methanol (1:1). The product yields are given in Table 2.

3-Hydroxy-3-phenylpropanenitrile (4a). Viscous oily material. IR spectrum, ν, cm^{-1} (film): 3465 (OH), 2278 (CN). ^{1}H NMR spectrum, δ, ppm: 2.78 d (2H, CH_2CN, *J* = 5.9 Hz), 2.95 br.s (1H, OH), 5.05 t (1H, C**H**OH, *J* = 5.9 Hz), 7.35–7.39 m (5H, H_{arom}). Found, %: C 73.24, 73.31; H 5.98, 6.07; N 9.31, 9.42. C_9H_9NO. Calculated, %: C 73.45; H 6.16; N 9.52.

3-(4-Bromophenyl)-3-hydroxypropanenitrile (4b). Viscous oily material. IR spectrum, ν, cm^{-1}: 3450 (OH), 2276 (CN). ^{1}H NMR spectrum, δ, ppm: 2.51 br.s (1H, OH), 2.75 d (2H, CH_2CN, *J* = 6.2 Hz), 5.02 t (1H, C**H**OH, *J* = 6.2 Hz), 7.29 d (2H, H_{arom}, ^3J = 8.2 Hz), 7.54 d (2H, H_{arom}, ^3J = 8.2 Hz). Found, %: C 47.53, 47.69; H 3.28, 3.41; N 5.93, 6.03. C_9H_8BrNO. Calculated, %: C 47.82; H 3.57; N 6.20.

3-(3-Bromophenyl)-3-hydroxypropanenitrile (4c). Viscous oily material. IR spectrum, ν, cm^{-1}: 3450 (OH), 2270 (CN). ^{1}H NMR spectrum, δ, ppm: 2.73 d (2H, CH_2CN, *J* = 5.6 Hz), 3.78 br.s (1H, OH), 4.98 t (1H, C**H**OH, *J* = 5.6 Hz), 7.25 t (1H, H_{arom}, ^3J = 7.8 Hz), 7.31 d (1H, H_{arom}, ^3J = 7.8 Hz), 7.45 d.d (1H, H_{arom}, ^4J = 1.1, ^3J = 7.8 Hz), 7.54 s (1H, H_{arom}). Found, %: C 47.38, 47.51; H 3.33, 3.44; N 6.17, 6.34. C_9H_8BrNO. Calculated, %: C 47.82; H 3.57; N 6.20.

3-Hydroxy-3-(5,6,7,8-tetrahydronaphthalen-2-yl)propanenitrile (4d). Viscous oily material. IR spectrum, ν, cm^{-1}: 3465 (OH), 2273 (CN). ^1H NMR spectrum, δ, ppm: 1.81 m (4H, 6′-H, 7′-H), 2.65 br.s (1H, OH), 2.76 d (2H, CH_2CN, J = 6.2 Hz), 2.78 m (4H, 5′-H, 8′-H), 4.98 t (1H, C**H**OH, J = 6.2 Hz), 7.08–7.13 m (3H, H_{arom}). Found, %: C 77.21, 77.36; H 7.19, 7.31; N 6.68, 6.87. $C_{13}H_{15}NO$. Calculated, %: C 77.58; H 7.51; N 6.96.

3-(9*H*-Fluoren-2-yl)-3-hydroxypropanenitrile (4e). mp 118–119°C. IR spectrum, ν, cm^{-1}: 3440 (OH), 2280 (CN). ^1H NMR spectrum, δ, ppm: 2.54 br.s (1H, OH), 2.82 d.d (1H, J = 5.8, 11.2 Hz) and 2.84 d.d (1H, J = 5.8, 11.2 Hz) (CH_2CN), 3.92 s (2H, 9′-H), 5.13 t (1H, C**H**OH, J = 5.8 Hz), 7.34 d.t (1H, H_{arom}, ^4J = 1.2, ^3J = 7.8 Hz), 7.41 t (2H, H_{arom}, ^3J = 8.0 Hz), 7.57 d (1H, H_{arom}, ^3J = 7.8 Hz), 7.60 s (1H, H_{arom}), 7.80 d (2H, H_{arom}, ^3J = 8.0 Hz). Found, %: C 81.11, 81.32; H 5.24, 5.34; N 5.52, 5.69. $C_{16}H_{13}NO$. Calculated, %: C 81.68; H 5.57; N 5.95.

3-Hydroxy-3-[4-(prop-2-en-1-yl)phenyl]propanenitrile (4f). Viscous oily material. IR spectrum, ν, cm^{-1}: 3460 (OH), 2276 (CN). ^1H NMR spectrum, δ, ppm: 2.58 br.s (1H, OH), 2.77 d (2H, CH_2CN, J = 5.8 Hz), 3.41 d (2H, C**H**$_2$CH=CH_2, J = 6.8 Hz), 5.03 t (1H, C**H**OH, J = 5.8 Hz), 5.12 m (2H, CH=C**H**$_2$), 5.91–6.01 m (1H, C**H**=CH_2), 7.23 d (2H, H_{arom}, ^3J = 8.0 Hz), 7.34 d (2H, H_{arom}, ^3J = 8.0 Hz). Found, %: C 76.63, 76.77; H 6.78, 6.83; N 7.19, 7.31. $C_{12}H_{13}NO$. Calculated, %: C 76.98; H 7.00; N 7.48.

3-[4-(Cyclopropylmethyl)phenyl]-3-hydroxypropanenitrile (4g). Viscous oily material. IR spectrum, ν, cm^{-1}: 3470 (OH), 2275 (CN). ^1H NMR spectrum, δ, ppm: 0.22 m (2H), 0.54 m (2H), and 0.99 m (1H) (C_3H_5); 2.56 d (2H, 4′-CH_2, J = 6.8 Hz), 2.67 br.s (1H, OH), 2.75 d (1H, J = 6.2 Hz) and 2.77 d (1H, J = 6.6 Hz) (CH_2CN), 5.02 d.d (1H, C**H**OH, J = 6.2, 6.6 Hz), 7.30 d (2H, H_{arom}, ^3J = 8.0 Hz), 7.32 d (2H, H_{arom}, ^3J = 8.0 Hz). Found, %: C 77.24, 77.33; H 7.22, 7.44; N 6.58, 6.76. $C_{13}H_{15}NO$. Calculated, %: C 77.58; H 7.51; N 6.96.

3-{4-[(2,2-Dichlorocyclopropyl)methyl]phenyl}-3-hydroxypropanenitrile (4h). Viscous oily material. IR spectrum (film), ν, cm^{-1}: 3437 (OH), 2253 (CN). ^1H NMR spectrum, δ, ppm: 1.27 m (1H), 1.71 m (1H), and 1.88 m (1H) ($Cl_2C_3H_3$); 2.59 br.s (1H, OH), 2.77 d (2H, CH_2CN, J = 6.2 Hz), 2.84 d.d (1H, J = 6.2, 15.6 Hz) and 2.98 d.d (1H, J = 7.6, 15.6 Hz) (4′-CH_2), 5.04 t (1H, C**H**OH, J = 6.2 Hz), 7.34 d (2H, H_{arom}, ^3J = 8.2 Hz), 7.38 d (2H, H_{arom}, ^3J = 8.2 Hz). ^{13}C NMR spectrum, δ_C, ppm: 26.7, 27.9, 31.2, 35.6, 61.5, 69.9, 117.1, 125.9, 128.8, 139.3, 141.2. Found, %: C 57.48, 57.57; H 4.61, 4.75; N 4.92, 5.03. $C_{13}H_{13}Cl_2NO$. Calculated, %: C 57.80; H 4.85; N 5.19.

3-{3-[(2,2-Dichlorocyclopropyl)methyl]phenyl}-3-hydroxypropanenitrile (4i). Viscous oily material. IR spectrum, ν, cm^{-1}: 3455 (OH), 2278 (CN). ^1H NMR spectrum, δ, ppm: 1.28 m (1H), 1.71 m (1H), and 1.91 m (1H) ($Cl_2C_3H_3$); 2.75 br.s (1H, OH), 2.77 d (2H, CH_2CN, J = 6.2 Hz), 2.84 d.d (1H, J = 6.6, 15.4 Hz) and 3.01 d.d (1H, J = 7.7, 15.4 Hz) (3′-CH_2), 5.04 t (1H, C**H**OH, J = 6.2 Hz), 7.28 d (1H, H_{arom}, ^3J = 7.6 Hz), 7.30 d (1H, H_{arom}, ^3J = 7.6 Hz), 7.33 s (1H, H_{arom}), 7.38 t (1H, H_{arom}, ^3J = 7.8 Hz). Mass spectrum, m/z (I_{rel}, %): 229 (4) [270 – CH_3CN], 160 (84), 133 (100), 129 (32), 105 (67), 77 (34), 51 (26). $C_{13}H_{13}Cl_2NO$. Calculated: M 270.15.

3-Hydroxy-4-phenylbutanenitrile (4j). Viscous oily material. IR spectrum, ν, cm^{-1}: 3450 (OH), 2275 (CN). ^1H NMR spectrum, δ, ppm: 2.48 d.d (1H, J = 6.3, 16.6 Hz) and 2.54 d.d (1H, J = 4.9, 16.6 Hz) (CH_2CN), 2.70 br.s (1H, OH), 2.89 d (2H, C**H**$_2$Ph, J = 6.7 Hz), 4.14 m (1H, C**H**OH), 7.23 d (2H, H_{arom}, ^3J = 8.2 Hz), 7.26 m (1H, H_{arom}), 7.34 m (2H, H_{arom}). Found, %: C 74.23, 74.34; H 6.69, 6.75; N 8.28, 8.44. $C_{10}H_{11}NO$. Calculated, %: C 74.51; H 6.88; N 8.69.

3-Hydroxy-3-[4-(propan-2-yl)phenyl]butanenitrile (4k). Viscous oily material. IR spectrum, ν, cm^{-1}: 3470 (OH), 2276 (CN). ^1H NMR spectrum, δ, ppm: 1.25 d [6H, CH(C**H**$_3$)$_2$, J = 7.2 Hz], 1.75 s (3H, CH_3), 2.28 br.s (1H, OH), 2.78 d and 2.83 d (1H each, CH_2CN, J = 12.6 Hz), 2.91 sept [1H, C**H**$(CH_3)_2$], 7.24 d (2H, H_{arom}, ^3J = 7.8 Hz), 7.39 d (2H, H_{arom}, ^3J = 7.8 Hz). Found, %: C 76.48, 76.57; H 8.18, 8.31; N 6.57, 6.81. $C_{13}H_{17}NO$. Calculated, %: C 76.81; H 8.43; N 6.89.

2-Chloro-*N*-[4-(2-cyano-1-hydroxyethyl)phenyl]-benzamide (4l). mp 116–118°C (from EtOH). IR spectrum, ν, cm^{-1}: 3470 (OH), 2281 (CN). ^1H NMR spectrum, δ, ppm: 2.60 br.s (1H, OH), 2.79 d (2H, CH_2CN, J = 4.7 Hz), 5.06 t (1H, C**H**OH, J = 4.7 Hz), 7.41–7.48 m (5H, H_{arom}), 7.68 d (2H, H_{arom}, ^3J = 8.1 Hz), 7.76 d (1H, H_{arom}, ^3J = 7.8 Hz), 8.01 br.s (1H, NH). Found, %: C 64.21, 64.30; H 4.51, 4.54; N 9.25, 9.40. $C_{16}H_{13}ClN_2O_2$. Calculated, %: C 63.90; H 4.36; N 9.31.

REFERENCES

1. Pozharskii, A.F., Soldatenkov, A.T., and Katritzky, A.R., *Heterocycles in Life and Society: An Introduction to Heterocyclic Chemistry and Biochemistry and the Role of Heterocycles in Science, Technology, Medicine, and Agriculture*, Chichester: Wiley, 1997.

2. Martin, D.G., Duchamp, D.J., and Chidester, C.G., *Tetrahedron Lett*., 1973, vol. 14, p. 2549.
3. Hanka, L.J., Gerpheide, P.R., Martin, D.G., Belter, B.A., Coleman, T.A., and Meyer, H.F., *Antimicrob. Agents Chemother*., 1975, vol. 7, p. 807.
4. Martin, D.G., Chidester, C.G., Mizak, S.A., Duchamp, D.J., Baczynskyi, L., Krueger, W.C., Wunk, R.J., and Menlman, P.A., *J. Antibiot*., 1975, vol. 28, p. 91.
5. Peng, J., Li, J., and Hamann, M.T., *The Alkaloids: Chemistry and Biology*, Cordell, G.A., Ed., New York: Academic, 2005, vol. 61, p. 59.
6. Akhrem, A.A., Lakhvich, F.A., and Khripach, V.A., *Chem. Heterocycl. Compd*., 1981, vol. 17, p. 853.
7. Lakhvich, F.A., Koroleva, E.V., and Akhrem, A.A., *Chem. Heterocycl. Compd*., 1989, vol. 25, p. 359.
8. Pohjakallio, A., *Doctoral Dissertation*, Aalto University, 2011.
9. Fukuda, Y. and Okamoto, Y., *Tetrahedron*, 2009, vol. 58, p. 2513.
10. Kociolek, M.G. and Kalbarczyk, K.P., *Synth. Commun*., 2004, vol. 34, p. 4387.
11. Seo, M.H., Lee, Y.Y., and Goo, Y.M., *Synth. Commun*., 1994, vol. 24, p. 1433.
12. Kozikowski, A.P. and Adamezyk, M., *J. Org. Chem*., 1983, vol. 48, p. 366.
13. Brandi, A., Desarlo, F., Guarna, A., and Speroni, G., *Synthesis*, 1982, no. 9, p. 719.
14. Wade, P.A. and Bereznak, J.F.B., *J. Org. Chem*., 1987, vol. 52, p. 2973.
15. Wade, P.A. and Hinney, H.R., *J. Am. Chem. Soc*., 1979, vol. 101, p. 1319.
16. Huisgen, R. and Christl, M., *Chem. Ber*., 1973, vol. 106, p. 3291.
17. De Sarlo, F., Brandi, A., Guarna, A., Goti, A., and Corezzi, S., *Tetrahedron Lett*., 1983, vol. 24, p. 1815.
18. De Sarlo, F., Guarna, A., Brandi, A., Guana, A., and Goti, A., *Tetrahedron*, 1985, vol. 41, p. 5181.
19. Wartrup, C., Gerecht, B., and Briehl, H., *Angew. Chem*., 1979, vol. 91, p. 503.
20. Torssell, K. and Zenthen, O., *Acta Chem. Scand., Ser. B*, 1978, vol. 32, p. 118.
21. Galley, G., Jones, P.G., and Patzel, M., *Tetrahedron: Asymmetry*, 1996, vol. 7, p. 2073.
22. Kim, B.H. and Lee, J.Y., *Tetrahedron: Asymmetry*, 1991, vol. 2, p. 1359.
23. Gefflaut, T., Martin, C., Delor, S., Besse, P., Veschambre, H., and Bolte, J., *J. Org. Chem*., 2001, vol. 66, p. 2296.
24. Shabarov, Yu.S., Saginova, L.G., and Gazzaeva, R.A., *Chem. Heterocycl. Compd*., 1983, vol. 19, no. 6, p. 589.
25. Bondarenko, O.B., Gavrilova, A.Yu., Saginova, L.G., and Zyk, N.V., *Russ. J. Org. Chem*., 2003, vol. 39, p. 1021.
26. Gazzaeva, R.A., Mochalov, S.S., Archegov, B.P., and Zefirov, N.S., *Chem. Heterocycl. Compd*., 2005, vol. 41, p. 272.
27. Gazzaeva, R.A., Shabarov, Yu.S., and Saginova, L.G., *Chem. Heterocycl. Compd*., 1984, vol. 20, p. 246.
28. Mochalov, S.S., Gazzaeva, R.A., Kadzhaeva, A.Z., Fedotov, A.N., and Trofimova, E.V., *Chem. Heterocycl. Compd*., 2011, vol. 47, no. 11, p. 1415.
29. Bondarenko, O.B., Gavrilova, A.Yu., Saginova, L.G., Zyk, N.V., and Zefirov, N.S., *Russ. Chem. Bull., Int. Ed*., 2003, vol. 52, p. 778.
30. Bondarenko, O.B., Gavrilova, A.Yu., Kazantseva, M.A., Tikhanushkina, V.N., Nifant'ev, E.E., Saginova, L.G., and Zyk, N.V., *Russ. J. Org. Chem*., 2006, vol. 42, p. 249.
31. Lukevics, E., Dimens, V., Kemme, A., and Popelis, J., *J. Organomet. Chem*., 1996, vol. 521, p. 235.
32. Imgartinger, H. and Weber, A., *Tetrahedron Lett*., 1997, vol. 38, p. 2075.
33. Ogamino, T. and Nichiyama, S., *Tetrahedron*, 2003, vol. 59, p. 9419.
34. Yashiro, A., Nishida, Y., Kobayashi, K., and Ohno, M., *Synlett*, 2000, no. 3, p. 361.
35. Levina, R.Ya., Gembitskii, P.A., and Treshchova, E.G., *Zh. Obshch. Khim*., 1963, vol. 33, p. 371.
36. Mochalov, S.S., Pogodin, S.S., Gazzaeva, R.A., Shabarov, Yu.S., and Zefirov, N.S., *Vestn. Mosk. Gos. Univ., Ser. 2: Khim*., 2001, vol. 42, p. 381.
37. Mochalov, S.S., Novokreshchennykh, V.D., and Shabarov, Yu.S., *Zh. Org. Khim*., 1976, vol. 12, p. 1008.
38. Mochalov, S.S., Gazzaeva, R.A., Fedotov, A.N., Archegov, B.P., Trofimova, E.V., Shabarov, Yu.S., and Zefirov, N.S., *Russ. J. Org. Chem*., 2005, vol. 41, p. 406.
39. Tishchenko, I.G., Kulinkovich, O.G., and Glazkov, Yu.V., *Zh. Org. Khim*., 1975, vol. 11, p. 581.
40. Mochalov, S.S., Gazzaeva, R.A., Fedotov, A.N., Trofimova, E.V., Trushkov, I.V., and Zefirov, N.S., *Russ. J. Org. Chem*., 2004, vol. 40, p. 1098.