Chemistry of Heterocyclic Compounds, Vol. 46, No. 6, 2010

SYNTHESIS OF 2-[2-ISOPROPYL-4-(*o*-METHOXYPHENYL)-TETRAHYDROPYRAN-4-YL]AMINE AND ITS REACTION WITH AROMATIC ALDEHYDES

N. S. Arutjunyan[1], L. A. Hakobyan[1], N. Z. Hakobyan[1], G. A. Gevorgyan[1]*, and H. A. Panosyan[2]

A preparative method was developed for the synthesis of 2-isopropyltetrahydropyran-4-one, which was then transformed by the action of ethyl cyanoacetate into ethyl (2-isopropyl-4-tetrahydropyranylidene)cyanoacetate. Reaction of the latter with o-methoxyphenylmagnesium bromide followed by saponification and reduction with $LiAlH_4$ led to 4-(2-aminoethyl)-2-isopropyl-4-(o-methoxyphenyl)tetrahydropyran. A series of new azomethines, which are reduced to the corresponding amines by the action of $NaBH_4$, were synthesized by the reaction of the above-mentioned amine with aromatic aldehydes.

Keywords: [2-isopropyl-4-(*o*-methoxyphenyltetrahydropyran-4-yl)]acetonitrile, 2-isopropyltetrahydropyran-4-one, derivatives of 2-[2-isopropyl-4-(*o*-methoxyphenyl)tetrahydropyran-4-yl]ethylamine, ethyl (2-isopropyl-4-tetrahydropyranylidene)cyanoacetate, reduction, deethoxycarbonylation.

Earlier it was shown that certain amides and amines, based on 2,2-dimethyl- and 2-ethyl-2-methyl-4-phenyl(benzyl)-4-tetrahydropyran-4-ylacetic acid, exhibit appreciable anticonvulsive activity [1]. In a continuation of the search for new biologically active compounds in the present work we synthesized a series of derivatives of 2-isopropyl-4-(*o*-methoxyphenyl)tetrahydropyran-4-ylacetic acid starting from 2-isopropyl-tetrahydropyran-4-one (**1**). A method for the production of the latter with a yield of not more than 10% is known [2]. We have developed a preparative method for the synthesis of the ketone **1** with a yield of 73.8% by the isomerization and hydration of isopropylvinylcarbinol in the presence of 5% aqueous sulfuric acid and mercury sulfate.

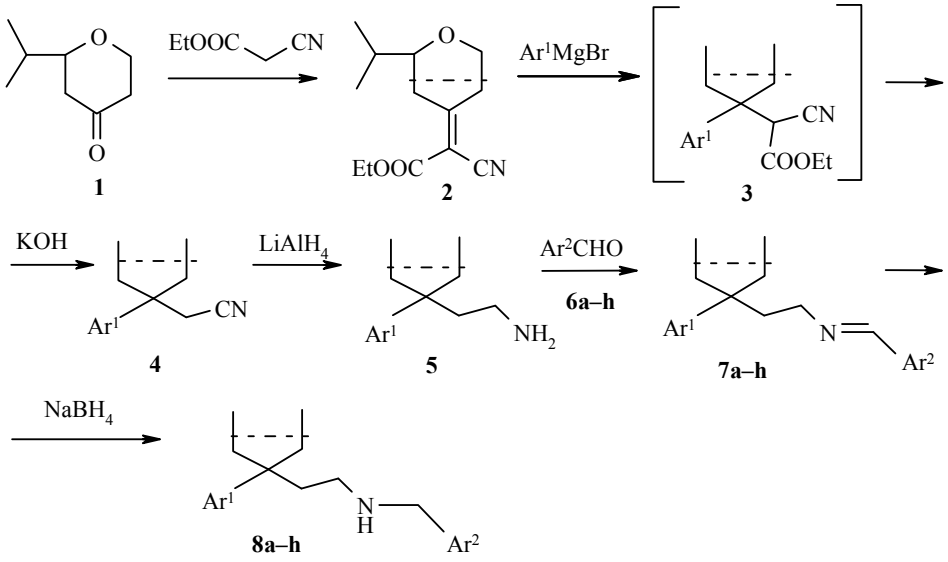
The reaction of the ketone **1** with ethyl cyanoacetate gave the corresponding tetrahydropyranylidene-substituted ester **2**, which was converted without previous purification (it resinifies during distillation) into (*o*-methoxyphenyl)tetrahydropyran-4-ylcyanoacetic ester **3** by treatment with *o*-methoxyphenylmagnesium

* To whom correspondence should be addressed, e-mail: gyulgev@gmail.com.

[1]A. L. Mndzhoyan Institute of Fine Organic Chemistry, Scientific Technological Center of Organic and Pharmaceutical Chemistry of the National Academy of Sciences of the Republic of Armenia, Erevan 0014, Armenia.
[2]Center of Research on the Structure of Molecules, National Academy of Sciences of the Republic of Armenia, Erevan 0014, Armenia.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 838-842, June, 2010. Original article submitted May 12, 2008. Revision submitted November 10, 2009. Second revision submitted January 30, 2010.

bromide. Deethoxycarbonylation of the ester **3** (without purification) by the action of KOH in ethylene glycol led to the corresponding nitrile **4**, the reduction of which with lithium aluminum hydride gave the amine **5**. Reaction of the latter with aromatic aldehydes gave the corresponding azomethines **7a-h**, which were then reduced with sodium borohydride without isolation to the amines **8a-h**.



3–8 Ar^1= *o*-$MeOC_6H_4$; **6–8 a** Ar^2 = Ph, **b** Ar^2 = *p*-$MeOC_6H_4$, **c** Ar^2 = *p*-(*i*-PrO)C_6H_4, **d** Ar^2 = *p*-$(Me_2N)C_6H_4$, **e** Ar^2 = *o*-FC_6H_4, **f** Ar^2 = 3,4-$(MeO)_2C_6H_3$, **g** Ar^2 = 3,4-methylenedioxyphenyl, **h** Ar^2 = α-furyl

The composition and structure of the synthesized compounds were confirmed by the data from elemental analysis (Table 1) and ^{1}H NMR spectra (Table 2).

TABLE 1. The Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %			bp, °C (mm Hg)	Yield, %
		C	H	N		
4	$C_{17}H_{23}NO_2$	74.60 / 74.69	8.39 / 8.47	5.21 / 5.12	174-176 (2)	80
5	$C_{17}H_{27}NO_2$	73.71 / 73.60	10.01 / 9.93	5.20 / 5.13	153-155 (2)	85
8a	$C_{24}H_{33}NO_2$	78.34 / 78.43	9.15 / 9.04	3.70 / 3.81	225-229 (3)	81
8b	$C_{25}H_{35}NO_3$	75.58 / 75.53	9.13 / 8.87	3.85 / 3.52	225-230 (1.5)	85
8c	$C_{27}H_{39}NO_3$	76.08 / 76.19	9.32 / 9.23	3.20 / 3.29	229-231 (2)	80
8d	$C_{26}H_{38}N_2O_2$	75.93 / 76.05	9.29 / 9.32	6.71 / 6.82	240-244 (2)	82
8e	$C_{24}H_{32}FNO_2$	74.85 / 74.77	8.47 / 8.36	3.56 / 3.63	205-208 (2)	90
8f	$C_{26}H_{37}NO_4$	73.15 / 73.03	8.63 / 8.72	3.18 / 3.27	235-238 (2)	78
8g	$C_{25}H_{33}NO_4$	72.85 / 72.96	8.19 / 8.08	3.50 / 3.40	230-233 (2)	80
8h	$C_{22}H_{31}NO_3$	74.02 / 73.91	8.60 / 8.73	3.80 / 3.91	195-199 (2)	83

TABLE 2. The ^{1}H NMR Spectra of Compounds **4**, **5**, and **8a-h**

Compound	Chemical shifts, δ, ppm (*J*, Hz)
4	0.95 and 0.96 (3H, d, *J* = 6.7 and 3H, d, *J* = 6.7, CH(C<u>H</u>$_3$)$_2$); 1.54 (1H, m, 2-CH); 1.66 and 1.84 (1H, m and 1H, m, H-5); 2.28 (2H, m, H-3); 3.23 (2H, s, CH_2CN); 3.24 (1H, m, H-2); 3.66 and 3.92 (1H, m and 1H, m, H-6); 3.88 (3H, s, OCH_3); 6.96 and 7.25 (2H, m and 2H, m, H Ar^1)
5	0.93 (6H, d, *J* = 6.8, CH(C<u>H</u>$_3$)$_2$); 1.32 (1H, m, 2-CH); 1.54-1.72 (2H, m, H-3); 1.96 (2H, br. s, NH_2); 2.14 (4H, m, 4-CH_2CH_2); 2.18 and 2.25 (1H, m, and 1H, m, H-5); 3.32 (1H, m, H-2); 3.71-3.82 (2H, m, H-6); 3.83 (3H, s, OCH_3); 6.85 and 7.11 (2H, m and 2H, m, H Ar^1)
8a	0.92 and 0.93 (3H, d, *J* = 6.8 and 3H, d, *J* = 6.8, CH(C<u>H</u>$_3$)$_2$); 1.35 and 1.69 (1H, m, and 1H, m, H-5); 1.60 (1H, m, 2-CH); 2.11-2.28 (6H, m, H-3, 4-CH_2CH_2); 2.25 (1H, br. s, NH); 3.32 (1H, m, H-2); 3.55 (2H, s, C<u>H</u>$_2$Ar^2); 3.72-3.84 (2H, m, H-6); 3.84 (3H, s, OCH_3); 6.84 and 7.14 (2H, m and 7H, m, H Ar^1, Ar^2)
8b	0.91 (6H, d, *J* = 6.7, CH(C<u>H</u>$_3$)$_2$); 1.33 and 1.67 (1H, m and 1H, m, H-5); 1.59 (1H, m, 2-CH); 1.60 (1H, br. s, NH); 2.07-2.26 (6H, m, H-3, 4-CH_2CH_2); 3.30 (1H, m, H-2); 3.46 (2H, s, C<u>H</u>$_2$Ar^2); 3.75 (3H, s, OCH_3); 3.78 (2H, m, H-6); 3.82 (3H, s, OCH_3); 6.72 and 7.04 (4H, m and 4H, m, H Ar^1, Ar^2)
8c	0.92 and 0.93 (3H, d, *J* = 6.8 and 3H, d, *J* = 6.8, CH(C<u>H</u>$_3$)$_2$); 1.30 (6H, d, *J* = 6.0, OCH(C<u>H</u>$_3$)$_2$); 1.34 and 1.68 (1H, m and 1H, m, H-5); 1.60 (1H, m, 2-CH); 2.15 (1H, br. s, NH); 2.08-2.27 (6H, m, H-3, 4-CH_2CH_2); 3.31 (1H, m, H-2); 3.46 (2H, s, C<u>H</u>$_2$Ar^2); 3.71-3.85 (2H, m, H-6); 3.82 (3H, s, OCH_3); 4.48 (1H, m, OC<u>H</u>$(CH_3)_2$); 6.84 and 7.11 (2H, m and 2H, m, H Ar^1); 6.88 and 7.02 (2H, m and 2H, m, H Ar^2)
8d	0.93 (6H, d, *J* = 6.8, CH(C<u>H</u>$_3$)$_2$); 1.35 and 1.69 (1H, m and 1H, m, H-5); 1.61 (1H, m, 2-CH); 1.89 (1H, br. s, NH); 2.09-2.28 (6H, m, H-3, 4-CH_2CH_2); 2.90 (6H, s, N$(CH_3)_2$); 3.32 (1H, m, H-2); 3.43 (2H, s, C<u>H</u>$_2$Ar^2); 3.72-3.86 (2H, m, H-6); 3.83 (3H, s, OCH_3); 6.56 and 6.97 (2H, m and 2H, m, H Ar^2); 6.85 and 7.11 (2H, m and 2H, m, H Ar^1)
8e	0.91 and 0.92 (3H, d, *J* = 6.7 and 3H, d, *J* = 6.7, CH(C<u>H</u>$_3$)$_2$); 1.34 and 1.68 (1H, m and 1H, m, H-5); 1.59 (1H, m, 2-CH); 1.95 (1H, br. s, NH); 2.09-2.27 (6H, m, H-3, 4-CH_2CH_2); 3.31 (1H, m, H-2); 3.59 (2H, s, C<u>H</u>$_2$Ar^2); 3.71-3.85 (2H, m, H-6); 3.82 (3H, s, OCH_3); 6.80-7.23 (8H, m, H Ar^1, Ar^2)
8f	0.92 (6H, d, *J* = 6.8, CH(C<u>H</u>$_3$)$_2$); 1.34 and 1.69 (1H, m and 1H, m, H-5); 1.60 (1H, m, 2-CH); 2.08-2.28 (6H, m, H-3, 4-CH_2CH_2); 2.23 (1H, br. s, NH); 3.32 (1H, m, H-2); 3.46 (2H, s, C<u>H</u>$_2$Ar); 3.75 and 3.76 (6H, s, OCH_3); 3.80 (2H, m, H-6); 3.82 (3H, s, OCH_3); 6.21-6.88 and 7.11 (2H, m and 2H, m, H Ar^1); 6.62 (1H, dd, J_1 = 8.1, J_2 = 1.9, H-6 Ar^2); 6.68 (1H, d, *J* = 8.1, H-5 Ar^2); 6.75 (1H, d, *J* = 1.9, H-2 Ar^2)
8g	0.92 (6H, d, *J* = 6.8, CH(C<u>H</u>$_3$)$_2$); 1.34 and 1.68 (1H, m, and 1H, m, H-5); 1.59 (1H, m, 2-CH); 2.06-2.26 (6H, m, H-3, 4-CH_2CH_2); 2.25 (1H, br. s, NH); 3.30 (1H, m, H-2); 3.44 (2H, s, C<u>H</u>$_2$Ar^2); 3.71-3.85 (2H, m, H-6); 3.83 (3H, s, OCH_3); 5.89 (2H, s, OCH_2O); 6.56 (1H, dd, J_1 = 7.9, J_2 =1.6, H-2 Ar^2); 6.62 (1H, d, *J* =7.9, H-5 Ar^2); 6.68 (1H, d, *J* = 1.6, H-2 Ar^2); 6.84 and 7.11 (2H, m and 2H, m, H Ar^1)
8h	0.92 (6H, d, *J* = 6.8, CH(C<u>H</u>$_3$)$_2$); 1.34 and 1.68 (1H, m and 1H, m, H-5); 1.60 (1H, m, 2-CH); 2.07-2.27 (6H, m, H-3, 4-CH_2CH_2); 2.15 (1H, br. s, NH); 3.31 (1H, m, 2-CH); 3.52 (2H, s, C<u>H</u>$_2$Ar^2); 3.71-3.85 (2H, m, H-6); 3.83 (3H, s, OCH_3); 5.96 (1H, d, *J* =3.2, H-3 furyl); 6.20 (1H, d. d, J_1 = 3.2, J_2 = 2.0, H-4 furyl); 6.84 and 7.11 (2H, m and 2H, m, H Ar^1); 7.26 (1H, d, *J* = 2.0, H-5 furyl)

EXPERIMENTAL

The IR spectra were recorded on a Specord IR-75 spectrometer. The ^{1}H NMR spectra were recorded on a Varian-Mercury-300 instrument (300 MHz) for solutions in 1:3 DMSO-d_6–CCl_4 with TMS as internal standard.

2-Isopropyltetrahydropyran-4-one (1). A mixture of 20% aqueous sulfuric acid (400 ml), isopropylvinylethynylcarbinol (400.0 g, 3.2 mol), mercury sulfate (15.0 g), and acetone (1100 ml) was stirred vigorously at 62°C for 20 h while a further mercury sulfate (30.0 g) was added in portions. After distillation of the greater part of the acetone an excess of K_2CO_3 was added to the reaction mixture, and the product was extracted with ether. The extract was dried, and the residue after distillation of the solvent was distilled under vacuum. We obtained 338.3 g (73.8%) of the pyranone **1**; bp 67-69°C (4 mm Hg), n_D^{15} = 1.4510, n_D^{19} = 1.4540 (n_D^{20} = 1.4612 [2]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.92 and 0.95 (3H, d, *J* = 6.8 and 3H, d, *J* = 6.8, $CH(C\underline{H}_3)_2$); 1.75 (1H, m, 2-CH); 2.18 and 2.51 (1H, m and 1H, m, H-5); 2.22-2.25 (2H, m, H-3); 3.26 (1H, m, H-2); 3.57 and 4.22 (1H, ddd, J_1 = 12.4, J_2 = 11.3, J_3 = 2.8 and 1H, ddd, J_1 = 11.3, J_2 = 7.4, J_3 = 1.4, H-6). ^{13}C NMR spectrum, δ, ppm: 17.46 and 17.55 (CH_3); 32.45 ($C\underline{H}CH_3$); 41.53 and 44.63 (C-3,5); 65.67 (C-6); 81.83 (C-2); 204.71 (CO) (assigned by DEPT). Found, %: C 67.55; H 9.93. $C_8H_{14}O_2$. Calculated, %: C 67.57; H 9.92.

Ethyl (2-Isopropyltetrahydropyran-4-ylidene)cyanoacetate (2). A mixture of ethyl cyanoacetate (170.0 g, 1.5 mol), ketone **1** (213 g, 1.5 mol), ammonium acetate (10.0 g), and benzene (200 ml) was boiled for 7 h in a flask with a Dean–Stark tube until the water had been completely removed. After cooling the liquid mixture was decanted, washed with water, and extracted with benzene. The extract was dried, and the residue after distillation of the benzene was distilled under vacuum. We obtained 263.0 g (74%) of the ester **2**; bp 120-124°C (2 mm Hg). IR spectrum, ν, cm^{-1}: 1610 (C=C), 1720 (C=O), 2225 (CN).

[2-Isopropyl-4-(*o*-methoxyphenyl)tetrahydropyran-4-yl]acetonitrile (4). To an ether solution of the Grignard reagent obtained from magnesium filings (31.9 g, 1.33 mol) and *o*-bromoanisole (248.7 g, 1.33 mol) with gentle boiling and stirring we added a solution of ester **2** (261.0 g, 1.1 mol) in benzene (270 ml). The reaction mixture was stirred at 42-44°C for 1.5 h, kept at room temperature for 16 h, cooled, acidified with 20% HCl, and extracted with ether. The extract was washed with water and dried. After distillation of the solvent the residue of compound **3** (233.0 g) was used in the next stage without purification (it decomposes during distillation). While heating KOH (59.5 g, 1.06 mol) was dissolved in ethylene glycol (300 ml), and the obtained solution was added to the unpurified compound **3**. The mixture was boiled with a reflux condenser for 3 h, 300 ml of water was added, and the product was extracted with benzene. The extract was washed with water and dried, and the residue after distillation of the benzene was distilled under vacuum. We obtained 147.3 g of the nitrile **4** (80% on the ester **2**). IR spectrum, ν, cm^{-1}: 1595, 1610 (C=C arom.), 2225 (CN).

2-[2-Isopropyl-4-(*o*-methoxyphenyl)tetrahydropyran-4-yl]ethylamine (5). To a cooled solution of $LiAlH_4$ (1.6 g, 0.28 mol) in dry ether (80 ml) we added dropwise an ether solution of the nitrile **4** (38.8 g, 0.14 mol) while keeping the temperature of the reaction mass in the range of 0 ± 2°C. The stirring was continued at the same temperature for a further 1 h, the mixture was then cooled to −10°C (with ice and salt), and water (10 ml), 15% solution of sodium hydroxide (10 ml), and water (32 ml) were added successively. The reaction mass was filtered, and the inorganic precipitate was washed with ether, which was then combined with the organic layer of the filtrate. The combined ether solution was dried, and the residue after evaporation of the solvent was distilled under vacuum. We obtained 35.0 g (90.3%) of the amine **5**. IR spectrum, ν, cm^{-1}: 1590, 1610 (C=C arom.), 3300 (NH_2).

Arylmethyl-{2-[2-isopropyl-4-(*o*-methoxyphenyl)tetrahydropyran-4-yl]ethyl}amines 8a-h (General Method). A mixture of equimolar amounts of the amine **5** and the aldehyde **6a-h** in benzene was boiled for 4 h in a flask with Dean–Stark trap until the water had completely separated. The solvent was then removed, the residue with the product **7a-h** was dissolved in methanol, and an equimolar amount of $NaBH_4$ was added in portions with stirring and cooling so that the temperature of the reaction mixture did not exceed 20°C. The reaction mixture was stirred at room temperature for a further 1 h, the methanol was distilled, the residue was made alkaline with 20% sodium hydroxide solution, and the product was extracted with ether. The extract was dried, the ether was distilled, and the amine **8a-h** was isolated by distillation of the residue.

REFERENCES

1. N. S. Arytunyan, L. A. Akopyan, R. G. Paronikyan, and N. E. Akopyan, *Khim.-Farm. Zh.*, **24**, No. 5, 29 (1990).
2. N. N. Nazarov, I. V. Torgov, and L. N. Terekhova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, No. 1, 50 (1943).