Chemistry of Heterocyclic Compounds, Vol. 43, No. 10, 2007

SYNTHESIS OF 4-AMINO-4,8,9,10-TETRAHYDRO-PYRIMIDO[4',3':4,5]FURO-[2,3-*b*]QUINOLINES

V. V. Dabaeva, M. R. Bagdasaryan, and A. S. Noravyan

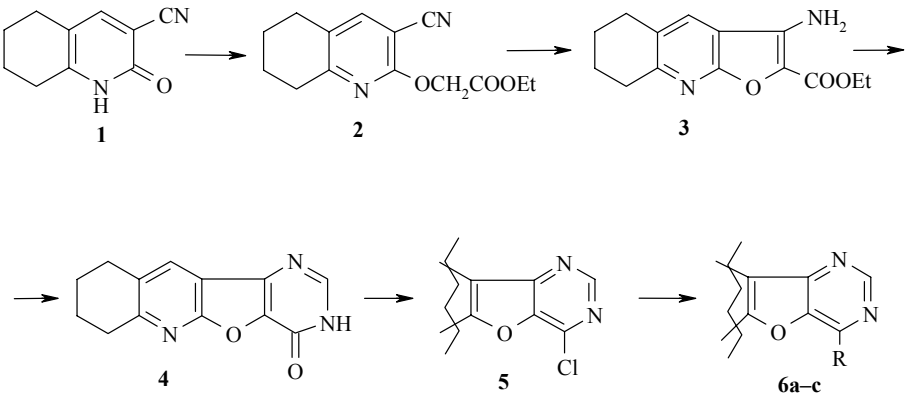
Previously unreported derivatives of 7,8,9,10-tetrahydropyrimido[4',3':4,5]furo[2,5-b]quinoline were synthesized starting with 3-cyanohexahydro-2-quinolone.

Keywords: hexahydroquinolone, pyridopyrimidine, pyrimidofuroquinoline.

Condensed derivatives of pyridopyrimidines with active functional groups hold interest since they may be starting materials for the synthesis of numerous new derivatives [1, 2] and biologically active compounds [3, 4].

3-Cyanohexahydro-2-quinolone (**1**) was used as a readily available starting compound for the synthesis of such derivatives containing a furan ring [5].

Heating **1** with chloroethyl acetate in alkaline medium gave cyano ester **2**, whose cyclization upon heating in the presence of sodium ethylate gave amino ester **3**. Heating **3** with formamide at 200-205°C led to 1-oxopyrimidofuroquinoline **4**, which reacts with $POCl_3$ in the presence of pyridine to give 1-chloro derivative **5**. The reaction of **5** with hydrazine hydrate, morpholine, or piperidine gave amino derivatives **6a-c** in high yield.



6 a R = $NHNH_2$, **b** R = morpholino, **c** R = piperidino

A. L. Mndzhoyan Institute of Fine Organic Chemistry, National Academy of Sciences of the Republic of Armenia, Yerevan 375014, Armenia; e-mail: amartirosyan@web.am. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1571-1573, October, 2007. Original article submitted March 9, 2007.

TABLE 1. Characteristics of Compounds **2-6**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	R_f*	Yield, %
		C	H	N			
2	$C_{14}H_{16}N_2O_3$	64.02 / 64.60	6.35 / 6.19	10.22 / 10.76	86-87	0.65	90
3	$C_{14}H_{16}N_2O_3$	64.34 / 64.60	6.12 / 6.19	10.56 / 10.76	229-230	0.55	54
4	$C_{13}H_{11}N_3O_2$	67.22 / 67.72	4.38 / 4.59	17.95 / 17.42	305-306	—	93
5	$C_{13}H_{10}ClN_3O$*[2]	64.48 / 64.07	4.23 / 4.14	17.12 / 17.24	204-205	0.57	56
6a	$C_{13}H_{13}N_5O$	61.42 / 61.16	5.25 / 5.13	27.38 / 27.43	287-288	0.62	65
6b	$C_{17}H_{18}N_4O_2$	65.87 / 65.79	5.28 / 5.85	18.39 / 18.05	197-198	0.69	75
6c	$C_{18}H_{20}N_4O$	70.38 / 70.11	6.24 / 6.54	18.28 / 18.17	175-176	0.66	79

* Solvent systems: 1:3 ethyl acetate–petroleum ether (compound **2)**, 1:1 ethyl acetate–petroleum ether (compound **3**, 3:1 ethyl acetate–petroleum ether for **6a-c**, and 2:1 chloroform–ether (compound **5)**.
*[2] Found, %: Cl 14.87. Calculated, %: Cl 14.55.

EXPERIMENTAL

The ^{1}H NMR spectra were taken on a Varian Mercury 300 spectrometer at 300 MHz in DMSO-d_6 using TMS as the internal standard. Thin-layer chromatography was carried out on Silufol UV-254 plates with development by iodine vapor.

The characteristics of these compounds are given in Table 1.

Ethyl 2-(3-cyano-5,6,7,8-tetrahydro-2-quinolinyloxy)acetate (2). A mixture of keto nitrile **1** (18.4 g, 100 mmol), ethyl chloroacetate (12.2 g, 100 mmol), and potassium carbonate (13.8 g, 100 mmol) in DMF (120 ml) was heated at 70°C for 1.5 h. The mixture was cooled and poured onto ice. The crystalline precipitate was filtered off and washed with water, a small amount of dilute alkali, and again with water until neutral. The crude product was recrystallized from absolute ethanol and dried. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.92 (1H, s, =CH); 4.72 (2H, s, O–CH_2); 4.20 (2H, q, *J* = 7, O$\underline{CH_2}CH_3$); 3.02 (4H, m, H-5,8); 1.94 (4H, m, H-6,7); 1.32 (3H, t, *J* = 7, CH_2–$\underline{CH_3}$).

Ethyl 3-amino-5,6,7,8-tetrahydrofuro[2,3-*b*]quinoline-2-carboxylate (3). Compound **2** (2.9 g, 10 mmol) was added to a solution of sodium (0.28 g, 12 mmol) in absolute ethanol (45 ml) and heated at reflux with stirring for 2-3 min. The solution obtained was left overnight at room temperature. The crystalline precipitate was filtered off and washed with water and a small amount of ethanol. The crude product was recrystallized from ethanol and dried. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.90 (1H, s, H-4); 6.15 (2H, br. s, NH_2); 4.32 (2H, q, *J* = 7, O$\underline{CH_2}CH_3$); 2.90 (4H, m, H-5,8); 1.92 (4H, m, H-6,7); 1.40 (3H, t, *J* = 7, CH_2–$\underline{CH_3}$).

4-Oxo-3,4,7,8,9,10-hexahydropyrimido[4',5':4,5]furo[2,3-*b*]quinoline (4). A mixture of amino ester **3** (2.9 g, 10 mmol) and formamide (30 ml) was heated at 200-205°C for 3 h. The crystalline precipitate formed upon cooling was filtered off, thoroughly washed with water and ethanol, and recrystallized from ethanol. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.85 (1H, br. s, NH); 8.10 (1H, s, N=CH); 7.95 (1H, s, =CH); 3.05 (4H, m, H-7,10); 1.95 (4H, m, H-8,9).

4-Chloro-7,8,9,10-tetrahydropyrimido[4',5':4,5]furo[2,3-*b*]quinoline (5). A mixture of pyrimidinone **4** (2.4 g, 10 mmol), $POCl_3$ (19.9 g, 130 mmol), and pyridine (2.0 g) was heated at 105°C for 3 h. Excess $POCl_3$ and pyridine were distilled off in vacuum created by a water pump. Ice water (20 ml) was added dropwise to the residue with cooling. The mixture was then neutralized by adding 25% aqueous ammonia. The crystalline precipitate was filtered off, washed with water and ethanol, and dried. The crude product was recrystallized from ethanol. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.11 (1H, s, N=CH); 8.05 (1H, s, =CH); 3.05 (4H, m, H-7,10); 1.95 (4H, m, H-8,9).

4-Substituted 7,8,9,10-tetrahydropyrimido[4',5':4,5]furo[2,3-*b*]quinolines 6. A mixture of chloride **5** (2.6 g, 10 mmol) and corresponding amine, morpholine, piperidine (or concentrated aqueous hydrazine hydrate) (20 ml) was heated at reflux for 6 h. After cooling, water was added. The crystalline precipitate was filtered off, washed with water, and recrystallized from ethanol. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): **6a:** 8.08 (1H, s, N=CH); 8.05 (1H, s, =CH); 3.59-3.38 (3H, br. s, NH–NH_2); 3.02 (4H, m, H-7,10); 1.95 (4H, m, H-8,9); **6b:** 8.09 (1H, s, N=CH); 8.07 (1H, s, =CH); 3.72 (4H, m, OCH_2); 3.55 (4H, m, NCH_2); 3.02 (4H, m, H-7,10); 1.95 (4H, m, H-8,9); **6c:** 8.10 (1H, s, N=CH); 8.07 (1H, s, =CH); 3.54 (4H, m, N-CH_2); 1.64-1.74 (6H, m, β-, γ-CH_2); 3.02 (4H, m, H-7,10); 1.92 (4H, m, H-8,9).

REFERENCES

1. A. Sh. Oganisyan, A. S. Noravyan, and M. Zh. Grigoryan, *Khim. Geterotsikl. Soedin.*, 1372 (2003). [*Chem. Heterocycl. Comp.*, **39**, 1203 (2003)].
2. E. G. Paronikyan, S. N. Sirakanyan, and A. S. Noravyan, *Khim. Geterotsikl. Soedin.*, 421 (2003). [*Chem. Heterocycl. Comp.*, **39**, 374 (2003)].
3. E. G. Paronikyan, A. Kh. Oganisyan, A. S. Noravyan, R. G. Paronikyan, and I. G. Dzhagatspanyan, *Khim.-Farm. Zh.*, **36**, No. 8, 17 (2002).
4. E. G. Paronikyan, A. S. Noravyan, I. G. Dzhagatspanyan, I. M. Nazaryan, and R. G. Paronikyan, *Khim.-Farm. Zh.*, **36**, No. 9, 8 (2002).
5. H. Kurihara and H. Mishima, *J. Heterocycl. Chem.*, **14**, 1077 (1977).