Chemistry of Heterocyclic Compounds, Vol. 45, No. 12, 2009

SYNTHESIS OF 7-(4-PIPERIDYL)-[1,6]NAPHTHYRIDIN-5-ONE AND 3-(4-PIPERIDYL)ISOQUNOLIN-1-ONE

D. A. Kovalskiy[1]* and V. P. Perevalov[2]

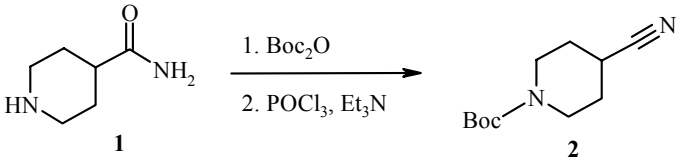
7-(4-Piperidyl)[1,6]napththiridin-5-one was synthesized on the basis of 2-methylnicotinic acid. 3-(4-Piperidyl)isoquinolin-1-one was synthesized from the diethylamide of o-toluic acid and Weinreb's amide of N-Boc-isonipecotic acid.

Keywords: Weinreb's amide, isocoumarin, isoquinoline, 1,6-naphthyridine, 3-(4-piperidyl)isoquinolin-1-one, 7-(4-piperidyl)[1,6]naphthyridin-5-one, metallation.

Previously we synthesized 2-piperidylisoquinolines and 7-piperidyl[1,6]naphthyridines [1,2] from which we synthesized tertiary amines, amides, and sulfamides. In the search for biologically active compounds it is important to vary the substituents on the molecule studied. This is achieved, firstly by using starting materials with different substituents and, secondly, by introducing additional functional groups at later stages.

In the publications quoted the results of work on the introduction of hydroxyl groups in positions 1 and 5 in 2-piperidylisoquinoline and 7-piperidyl[1,6]naphthyridine respectively. Derivatives of the $-OSO_2R$ type (e.g., OTf) are excellent leaving groups in reactions with O-, N-, and C-nucleophiles, which opens the way to further modification of the heterocyclic nucleus. Direct introduction of hydroxyl groups into isoquinoline and naphthyridine is practically impossible, therefore we sought alternative routes based on the formation of the required group during the course of the synthesis.

There are data in the literature on the interaction of dilithium derivatives of 2-methylnicotinic acid and aromatic nitriles with the formation of 7-aryl[1,6]naphthyridin-5-ones [3]. To carry out this scheme we first synthesized N-Boc-4-cyanopiperidine by introducing Boc groups into 4-piperidinecarboxamide with subsequent dehydration with phosphorus oxychloride in the presence of a base.



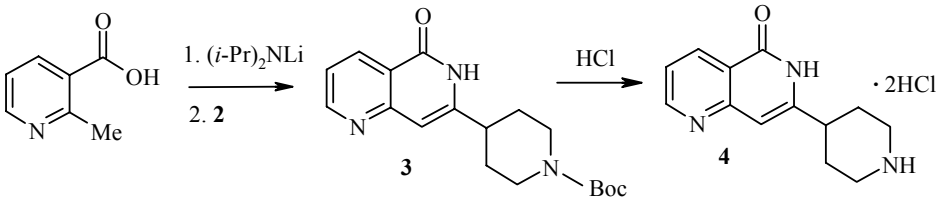
1 **2**

* To whom correspondence should be addressed, e-mail: DKovalskiy@asinex.com.

[1]ASINEX, Moscow 125480, Russia.
[2]D. I. Mendeleev University of Chemical Technology of Russia, Moscow 125047, Russia; e-mail: pvp@muctr.edu.ru.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, 1864-1869, December, 2009. Original article submitted April 17, 2009.

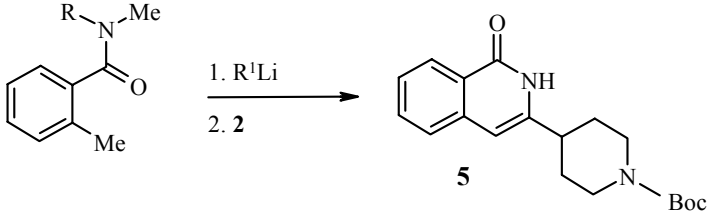
The nitrile **2** obtained was used, as described in paper [3], as an electrophile in the reaction with the dianion obtained *in situ* by treatment of 2-methylnicotinic acid with 2 equivalents of lithium diisopropylamide. Acid hydrolysis then removed the Boc groups.



The yield of N-Boc-7-(4-piperidyl)[1,6]naphthyridin-5-one (**3**) appeared to be considerably lower than for the case with aromatic nitriles. It is probable that this is caused by a side reaction associated with the possibility of deprotonation of nitrile **3** at the methylene-active unit.

An attempt to synthesize the corresponding isoquinolone by the same scheme starting from *o*-toluic acid was unsuccessful and the required product was not detected by chromato-mass spectrometric analysis. However, on metallation of the acid an intense coloration of the reaction mixture was observed, characteristic of the formation of the tolyl anion.

There are several methods reported in the literature for the synthesis of 3-substituted isoquinolinones, two of which are based on the metallation of monomethyl- and dimethylamides of *o*-toluic acid [4,5]. When both schemes were carried out with nitrile **2** it was shown that, in the first case a mixture of compounds was produced which did not include the desired product, while in the second case N-Boc-3-(4-piperidyl)isoquinolin-1-one (**5**) in a yield of 16%.



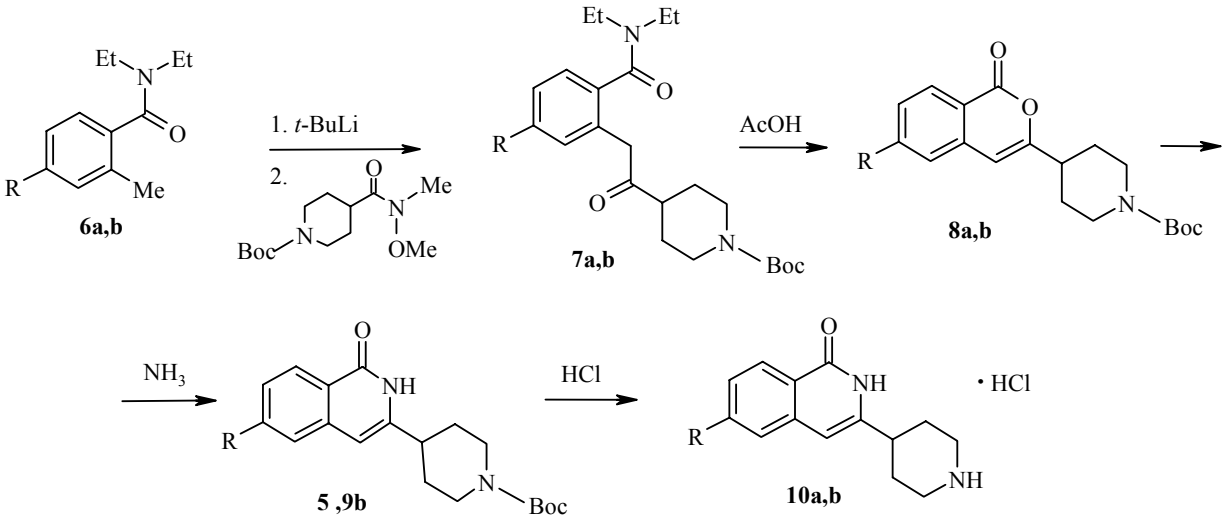
R = H, R^1= Bu; R = Me, R^1 = $(i\text{-Pr})_2N$

Table 1. Characteristics of Compounds **3-5**, **9b**, **10a,b**

Compound	Empirical formula	Found, % / Calculated, %				$[M+H]^+$, *m/z*	mp, °C	Yield, %
		C	H	Cl	N			
3	$C_{18}H_{23}N_3O_3$	65.82 / 65.63	7.10 / 7.04		12.68 / 12.76	330	189-193	51
4	$C_{13}H_{17}Cl_2N_3O$	51.55 / 51.67	5.80 / 5.67	23.54 / 23.46	13.97 / 13.90	230, 224	>250	89
5	$C_{19}H_{24}N_2O_3$	69.40 / 69.49	7.44 / 7.37		8.59 / 8.53	329	210-212	96*
9b	$C_{20}H_{26}N_2O_4$	67.08 / 67.02	7.33 / 7.31		10.55 / 10.58	359	237-241	75
10a	$C_{14}H_{17}ClN_2O$	63.58 / 63.51	6.49 / 6.47	13.31 / 13.39	10.51 / 10.58	229, 223	>250	99
10b	$C_{15}H_{19}ClN_2O_2$	61.15 / 61.12	6.53 / 6.50	12.08 / 12.03	9.47 / 9.50	259, 253	>250	97

* Yield starting from isocoumarin **8a**.

The continuing low yield forced us to tackle the problem from the other side. It is known that isocoumarin reacts with N-nucleophiles to form pyridones. A scheme for the preparation of 3-substituted isocoumarins, described in [6], was a ready base for the synthesis 3-piperidylisoquinolones. Thus, the ketones **7a,b** were obtained by treating the diethylamides of *o*-toluic acid **6a,b** with *tert*-butyl lithium followed by acylation with Weinreb's amide [1]. The ketones cyclized to 3-piperidylisocoumarins **8a,b** on treatment with acetic acid, and these were converted into N-Boc-3-(4-piperidyl)isoquinolin-1-ones **5,9b** by treatment with ammonia on heating under pressure.



6 8, **10 a** R = H, **6 10 b** R = OMe

Comparison of the results of experiments carried out under the two schemes described above showed that the yields of isoquinolinones **5** and **9b** obtained by the second variant, i.e., starting from diethylamides **6a** and **6b,** were considerably higher, 30 and 40% respectively.

Thus the preparation of 7-(4-piperidyl)-1,6-naphthyridin-5-one and 3-(4-piperidyl)isoquinolin-1-one differs from the route which we described previously [1,2] for derivatives of isoquinoline and 1,6-naphthyridine. The presence of two reaction centers – the OH and NH groups – opens the route to the synthesis of new compounds possessing potential biological activity.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Mercury 400 (400 MHz) machine in DMSO-d_6 or $CDCl_3$ solution with TMS as internal standard. Melting points were measured on a Gallenkamp machine. Progress of reactions was monitored by TLC of Silica gel/TLC cards (Fluka) with various eluants. Chromato-mass spectra were recorded with a Surveyor MSQ apparatus (Thermo Finnigan) with chemical ionization in solution (15 eV) with a YMC (Hydrosphere C18, 12 nm, S -3μm, 33.3 mm i.d.) in an eluant gradient (acetonitrile – 0.1% aqueous solution of formic acid with a rate of flow of the eluant of 1.3 ml/min). A mixture of hexane and ethyl acetate was used as the eluant for chromatography, with "DuraSil H" (60-100 μm) as the carrier.

N-Boc-4-Cyanopiperidine (2). Di-*tert*-butyl pyrocarbonate (187 g, 0.86 mol) in acetonitrile (200 ml) was added dropwise to a suspension of isonipecotamide **1** (100 g, 0.78 mol) in acetonitrile (400 ml) and stirred for 4 h. At the end of the reaction the precipitate was filtered off and washed with cold acetonitrile. The mother

Table 2. ^{1}H NMR Spectra of Compounds **2-5**, **6b**, **8a,b**, **9b**, **10a,b**

Compound	Chemical shifts, δ, ppm, *J* (Hz)*
2	1.49 (9H, s, *t*-Bu); 1.71 (4H, m, C$\underline{H}_2$CHC$\underline{H}_2$); 2.80–2.85 (3H, m, CH_2N+CH), 4.19 (2H, m, CH_2N)
3	1.41 (9H, s, *t*-Bu); 1.52–1.64 (2H, m, C$\underline{H}_2$CH); 1.87 (2H, m, C$\underline{H}_2$CH); 2.64 (1H, m, $CH_2C\underline{H}CH_2$); 2.76 (2H, m, CH_2N); 4.08 (2H, m, CH_2N); 6.41 (1H, s, H-8); 7.38 (1H, dd, *J* = 7.3 and *J* = 4.6, H-3); 8.41 (1H, d, *J* = 8.2, H-4); 8.81 (1H, d, *J* = 3.2, H-2); 11.39 (1H, br. s, OH)
4	1.90 and 2.11 (4H, both m, C$\underline{H}_2$CHC$\underline{H}_2$); 2.81-3.00 (3H, m, CH_2N + $CH_2C\underline{H}CH_2$); 3.39 (2H, m, CH_2N); 6.59 (1H, s, H-8); 7.62 (1H, dd, *J* = 7.3 and *J* = 5.5, H-3); 8.79 (1H, d, *J* = 7.8, H-4); 8.98 (1H, d, *J* = 8.9, H-2); 9.09 (1H, br. s, NH); 9.30 (1H, br. s, HCl); 11.81 (1H, br. s, OH)
5	1.40 (9H, s, *t*-Bu); 1.55 (2H, m, C$\underline{H}_2$CH), 1.89 (2H, m, C$\underline{H}_2$CH); 2.60 (1H, m, $CH_2C\underline{H}CH_2$); 2.75 (2H, m, CH_2N); 4.06 (2H, m, CH_2N); 6.31 (1H, s, H-4); 7.39 (1H, t, *J* = 7.3, H-6); 7.55 (1H, d, *J* = 7.8, H-5); 7.62 (1H, t, *J* = 7.3, H-7); 8.10 (1H, d, *J* = 7.8, H-8); 11.09 (1H, br. s, OH)
6b	0.92 (3H, t, *J* = 7.1, C$\underline{H}_3CH_2$); 1.14 (3H, t, *J* = 7.1, C$\underline{H}_3CH_2$); 2.11 (3H, s, CH_3); 3.02 (2H, q, *J* = 7.0, $CH_3C\underline{H}_2$); 3.46 (2H, q, *J* = 7.0, $CH_3C\underline{H}_2$); 3.79 (3H, s, OCH_3); 6.73–6.81 (2H, m, H-3,5); 7.02 (1H, d, *J* = 8.2, H-6)
8a	1.39 (9H, s, *t*-Bu); 1.47 (2H, m, C$\underline{H}_2$CH), 1.91 (2H, m, C$\underline{H}_2$CH); 2.66 (1H, m, $CH_2C\underline{H}CH_2$); 2.83 (2H, m, CH_2N); 4.04 (2H, m, CH_2N); 6.59 (1H, s, H-4); 7.55 (2H, m, H-5 + H-7); 7.80 (1H, t, *J* = 7.3, H-6); 8.10 (1H, d, *J* = 7.8, H-8)
8b	1.40 (9H, s, *t*-Bu); 1.48 (2H, m, C$\underline{H}_2$CH); 1.87 (2H, m, C$\underline{H}_2$CH); 2.72 (1H, m, $CH_2C\underline{H}_2CH_2$); 2.83 (2H, m, CH_2N); 3.87 (3H, s, OCH_3); 4.03 (2H, m, CH_2N); 6.50 (1H, s, H-4); 7.08 (2H, m, H-5, 7); 8.00 (1H, d, *J* = 8.7, H-8)
9b	1.40 (9H, s, *t*-Bu); 1.48 (2H, m, C$\underline{H}_2$CH); 1.87 (2H, m, C$\underline{H}_2$CH); 2.72 (1H, m, $CH_2C\underline{H}_2CH_2$); 2.83 (2H, m, CH_2N); 3.83 (3H, s, OCH_3); 3.89 (1H, m, CH_2N); 4.02 (1H, m, CH_2N); 6.31 (1H, s, H-4); 6.95 (2H, m, H-5,7); 8.01 (1H, d, *J* = 8.7, H-8); 10.95 (1H, br. s, OH)
10a	1.78-1.91 (2H, m, $CH_2CHC\underline{H}_2$); 2.11 (2H, m, C$\underline{H}_2$CHCH$_2$); 2.71 (1H, m, $CH_2C\underline{H}CH_2$); 2.92 (2H, m, CH_2N); 3.33 (2H, m, CH_2N); 6.30 (1H, s, H-4); 7.41 (1H, t, *J* = 7.8, H-6); 7.62 (2H, m, H-5, 7); 8.11 (1H, d, *J* = 7.8, H-8); 9.00 (2H, br. s, NH + HCl); 11.13 (1H, br. s, OH)
10b	1.85 (2H, m, $CH_2CHC\underline{H}_2$); 2.09 (2H, m, C$\underline{H}_2$CHCH$_2$); 2.71 (1H, m, $CH_2C\underline{H}CH_2$); 2.92 (2H, m, CH_2N); 3.05 (2H, m, CH_2N); 3.82 (3H, s, OCH_3); 6.25 (1H, s, H-4); 6.97 (1H, d, *J* = 8.7, H-7); 7.08 (1H, s, H-5); 8.02 (1H, d, *J* = 8.7, H-8); 9.05 (1H, br. s, NH); 9.14 (1H, br. s, HCl); 10.96 (1H, br. s, OH)

* Compound **2** was recorded in $CDCl_3$, compounds **3-6**, **8-10a,b** were recorded in DMSO-d_6.

liquor was evaporated to 2/3 of the original volume and the precipitate was filtered off. The combined solids were dried to give N-Boc-piperidine-4-carboxamide (167 g, 94%). Phosphorus oxychloride (93 g, 0.6 mol) was added dropwise to a solution of N-Boc-piperidine-4-carboxamide (115 g, 0.5 mol) in dichloromethane (400 ml) and triethylamine (100 g, 1 mol), at 0°C and stirred for 2 h. At the end of the reaction a saturated solution of potash was added dropwise. The organic layer was separated, dried over Na_2SO_4, and evaporated. Compound **2** (72.9 g, 69%) was obtained after purification by column chromatography.

N-Boc-7-(4-Piperidyl)[1,6]naphthyridin-5-one (3). BuLi (31 ml, 0.05 mol, 1.6 mol/l in hexane) was added to a solution of diisopropylamine (5.56g, 0.05 mol) in THF (100 ml) at -65°C in an atmosphere of argon.

The mixture was kept for 20 min, then 2-methylnicotinic acid (2.74 g, 0.02 mol) was added and stirred for 2 h. A solution of compound **2** (6.3 g, 0.03 mol) in THF (50 ml) was added dropwise to the intensely colored reaction mass, stirred for 4 h, and treated with saturated NH_4Cl solution (50 ml). The solvent was evaporated to ¾ of the original volume, the precipitate was filtered off and recrystallized from ethyl acetate to give naphthyridine **3** (3.34 g, 51%).

7-(4-Piperidyl)[1,6]naphthyridin-5-one Hydrochloride (4). Dioxane (20 ml), saturated with hydrogen chloride, was added to a boiling solution of compound **3** (3.34 g, 10 mmol) in 2-propanol (50 ml). The precipitate was filtered off, washed with 2-propanol, and dried to give compound **4** (2.7 g, 99%).

Diethylamide of *o*-toluic acid (6a). Diethylamine (58.4 g, 0.8 mol) in dichloromethane (200 ml) was added dropwise to a solution of *o*-toluoyl chloride (50 g, 0.32 mol) in dichloromethane (350 ml) and stirred for 1 h. At the end of the reaction diethylamine hydrochloride was filtered off and washed with a saturated solution of potash. The organic layer was separated, dried over Na_2SO_4, and evaporated. The diethylamide **6a** (56.2 g, 91%) was obtained after distillation (b.p. 108-112°C, m.p. 60-61°C).

Diethylamide 6b was obtained analogously from 2-methyl-5-methoxybenzoyl chloride (29.3 g, 0.16 mol) in a yield of 31.2 g (88%) as a viscous liquid.

N-Boc-3-(4-Piperidyl)isocoumarin (8b). *t*-Bu Li (80 ml, 0.14 mol, 1.7 mol/l in pentane) was added dropwise to a solution of amide **6b** (25 g, 0.11 mol) in THF (250 ml) at -75°C in an atmosphere of argon and stirred for 3 h. The methoxymethylamide of N-Boc-isonipecotic acid (30.7 g, 0.11 mol) was added dropwise, kept for 3 h, and treated with saturated NH_4Cl solution (100 ml). The solution was evaporated, extracted with ethyl acetate, the organic layer was separated, dried over Na_2SO_4, and purified by flash chromatography. The viscous oil, containing predominantly ketone **7b**, was boiled in a mixture of toluene (100 ml) and acetic acid (50 ml). At the end of the reaction the solution was evaporated, treated with a saturated solution of potash, and extracted with ethyl acetate. Compound **8b** (21.5 g, 53%) was obtained after purification by column chromatography.

N-Boc-6-methoxy-3-(4-piperidyl)isoquinolin-1-one (9b). A solution of compound **8b** (21.5 g, 0.06 mol) in methanol (200 ml) was saturated with ammonia, and heated to 100°C for 5 h in a high pressure reactor. At the end of the reaction the solvent was evaporated, the precipitate was filtered off, washed with hexane, and dried to give compound **9b** (16.2 g, 75%).

6-Methoxy-3-(4-piperidyl)isoquinolin-1-one Hydrochloride (10b). Dioxane (50 ml), saturated with hydrogen chloride, was added by portions to a boiling solution of substance **9b** (10 g, 28 mmol) in 2-propanol (150 ml). At the end of the reaction the precipitate was filtered off, washed with 2-propanol, and dried to give **10b** (8 g, 97%).

Compounds 8a, **5**, and **10a** (Tables 1 and 2) were made analogously.

REFERENCES

1. D. Kovalskiy and V. Perevalov, *Khim. Geterotsikl. Soed.,*1204 (2009). [*Chem. Heterocycl. Comp.,* **45**, 957 (2009)].
2. D. Kovalskiy and V. Perevalov, *Khim. Geterotsikl. Soed.,*1319 (2009). [*Chem. Heterocycl. Comp.,* **45**, 1053 (2009)].
3. C. Cywin and D. McNeil, *Bioorg, Med. Chem. Lett.,* **13**, 1415 (2003).
4. W. Cho and E. Kim, *Bioorg, Med. Chem. Lett.,* **10**, 2953 (2002).
5. W. Cho and E. Kim, *Bioorg, Med. Chem. Lett.,* **6**, 2449 (1998).
6. S. Ohta and Y. Kamata, *Chem. Pharm. Bull.,* **41**, 1188 (1993).