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SYNTHESIS OF 7-(3-PIPERIDYL)-[1,6]NAPHTHYRIDINE AND 7-(4-PIPERIDYL)[1,6]NAPHTHYRIDINE

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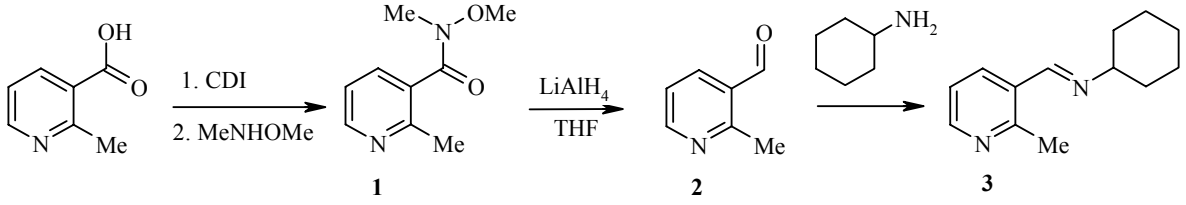
7-(3-Piperidyl)- and 7-(4-piperidyl)[1,6]naphthyridines have been synthesized from 2-methylpyridine-3-carbaldehyde cyclohexylimine and the methylmethoxycarboxamides (Weinreb amides) of N-Boc-substituted nipecotic and isonipecotic acids.

Keywords: Weinreb amide, isoquinoline, naphthyridine, piperidine.

We have previously synthesized 3-(3-piperidyl)isoquinoline and 3-(4-piperidyl)isoquinoline *via* acylation of the methyl group of *o*-tolylaldehyde cyclohexylimine by the methylmethoxycarboxamides of N-Boc nipecotic and isonipecotic acids (Weinreb amides) and subsequent cyclization [1]. Aza analogs of 3-substituted isoquinolines are the 7-substituted [1,6]-, [2,6]-, [3,6]- and [4,6]naphthyridines. There are virtually no literature reports of the preparation of such structures with the exception of a group of publications [2, 3] describing the cyclization of 2-imino- and 2-oximino-3-ethynylpyridines. The main attraction of this scheme is that both 7-substituted and 7,8-disubstituted [1,6]naphthyridines can be synthesized depending on the nature of the electrophile. However, the shortcomings of the method are the limited range of readily available acetylenes and the high cost of the palladium catalysts.

The method we have used previously in the synthesis of 3-substituted isoquinolines provides the basis for the preparation of the [1,6]naphthyridines containing a piperidine unit in the 7 position. When compared with the isoquinoline the naphthyridine fragment has an extra nitrogen atom which can behave as a proton acceptor and so increase the bonding with biological substrates.



1 **2** **3**

CDI – 1,1'-carbonyldiimidazole

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The 2-methylpyridine-3-carbaldehyde cyclohexylimine (**3**) was chosen as precursor of the [1,6]naphthyridine fragment and synthesized by a standard method.

The N-Boc-substituted methylmethoxycarboxamides of the 4- and 3-piperidinecarboxylic acids [1] (**4** and **5** respectively) served as the source of the piperidyl fragment. Metallation of imine **3** was carried out using diisopropylamide and lithium 2,2,6,6-tetramethylpiperidide. It was found that metallation with $(i\text{-Pr})_2NLi$ is more efficient and leads to a higher yield of the target compound while needing the use of two equivalents of the base.

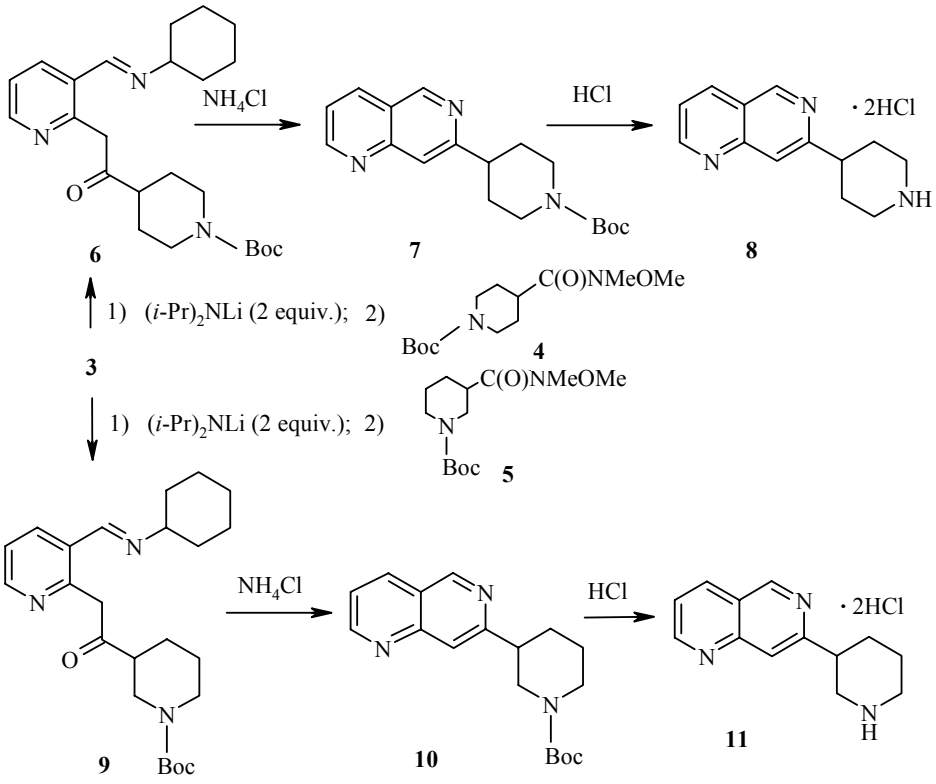


TABLE 1. Characteristics of Compounds **7, 9-12**

Compound	Empirical formula	Found, % / Calculated, %			$[M + H]^+$, *m/z*	mp, °C	Yield, %
		C	H	N			
7	$C_{18}H_{23}N_3O_2$	69.07 / 68.98	7.35 / 7.40	13.42 / 13.41	314	105-108	67
8*	$C_{13}H_{17}Cl_2N_3$	54.61 / 54.56	6.05 / 5.99	14.59 / 14.68	214, 208	240-245	96
10	$C_{18}H_{23}N_3O_2$	69.04 / 68.98	7.43 / 7.40	13.38 / 13.41	314	112-115	54
11*²	$C_{13}H_{17}Cl_2N_3$	54.67 / 54.56	6.03 / 5.99	14.72 / 14.68	214, 208	220-222	94
12	$C_{18}H_{22}BrN_3O_2$	55.67 / 55.11	5.91 / 5.65	10.44 / 10.71	286, 288, 292, 294	121-122	56

* Found, %: Cl 24.82; calculated, %: Cl 24.77.

*² Found, %: Cl 24.87; calculated, %: Cl 24.77.

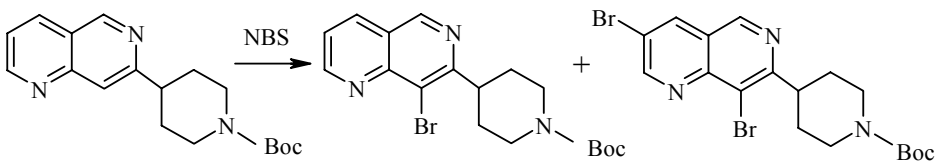
TABLE 2. ^{1}H NMR Spectra of Compounds **1-3, 7, 8, 10-13**

Compound	Chemical shifts, δ, ppm (*J*, Hz, DMSO-d_6)
1	2.47 (3H, s, CH_3); 3.22 (3H, s, OCH_3); 3.45 (3H, s, NCH_3); 7.25 (1H, dd, *J* = 6.9 and *J* = 5.0, H-5); 7.67 (1H, d, *J* = 7.3, H-4); 8.48 (1H, d, *J* = 3.7, H-6)
2	2.74 (3H, s, CH_3); 7.41 (1H, dd, *J* = 7.4 and *J* = 5.0, H-5); 8.13 (1H, d, *J* = 7.8, H-4); 8.63 (1H, d, *J* = 3.2, H-6); 10.22 (1H, s, CHO)
3	1.20-1.82 (10H, m, $(CH_2)_5$); 2.64 (3H, s, CH_3); 3.29 (1H, m, $CH_2C\underline{H}CH_2$); 7.26 (1H, dd, *J* = 7.3 and *J* = 5.0, H-5); 8.06 (1H, d, *J* = 7.8, H-4); 8.46 (1H, d, *J* = 3.2, H-6); 8.61 (1H, s, C<u>H</u>=N)
7	1.42 (9H, m, $C(CH_3)_3$); 1.79-1.92 (2H, m, $C\underline{H}_2CH$); 2.01-2.11 (2H, m, $C\underline{H}_2CH$); 2.92 (2H, m, CH_2N); 3.05 (1H, m, $CH_2C\underline{H}CH_2$); 4.28 (2H, m, CH_2N); 7.45 (1H, dd, *J* = 7.8 and *J* = 4.1, H-3); 7.73 (1H, s, H-8); 8.23 (1H, d, *J* = 7.8, H-4); 9.04 (1H, d, *J* = 2.7, H-2); 9.23 (1H, s, H-5)
8	2.03-2.20 (4H, m, $C\underline{H}_2CHC\underline{H}_2$); 3.00-3.11 (2H, m, CH_2N); 3.30 (1H, m, $CH_2C\underline{H}CH_2$); 3.39 (2H, m, CH_2N); 7.78 (1H, dd, *J* = 8.2 and *J* = 4.6, H-3); 7.90 (1H, s, H-8); 8.72 (1H, d, *J* = 8.2, H-4); 9.09 (1H, br. s, NH); 9.20 (1H, d, *J* = 3.2, H-2); 9.31 (1H, br. s, HCl); 9.53 (1H, s, H-5)
10	1.39 (9H, m, $C(CH_3)_3$); 1.45-2.10 (4H, m, $CHC\underline{H}_2C\underline{H}_2$); 2.82 (1H, m, CH_2N); 2.96 (1H, m, CH_2N); 3.10 (1H, m, $CH_2C\underline{H}CH_2$); 3.92 (1H, m, CH_2N); 4.15 (1H, m, CH_2N); 7.61 (1H, dd, *J* = 7.7 and *J* = 4.1, H-3); 7.78 (1H, s, H-8); 8.50 (1H, d, *J* = 7.8, H-4); 9.06 (1H, d, *J* = 2.7, H-2); 9.23 (1H, s, H-5)
11	1.81-2.12 (4H, m, $CHC\underline{H}_2C\underline{H}_2$); 2.96 (1H, m, $CH_2C\underline{H}CH_2$); 3.35 (2H, m, CH_2N); 3.56 (2H, m, CH_2N); 7.81 (1H, dd, *J* = 8.2 and *J* = 4.6, H-3); 8.06 (1H, s, H-8); 8.81 (1H, d, *J* = 8.2, H-4); 9.26 (1H, d, *J* = 3.2, H-2); 9.50 (1H, br. s, NH); 9.55 (2H, m, H-5 + HCl)
12	1.42 (9H, m, $C(CH_3)_3$); 1.75-1.89 (4H, br. s, $C\underline{H}_2CHC\underline{H}_2$); 2.91 (2H, br. s, CH_2N); 3.69 (1H, m, $CH_2C\underline{H}CH_2$); 4.12 (2H, m, CH_2N); 7.72 (1H, dd, *J* = 8.2 and *J* = 4.1, H-3); 8.58 (1H, d, *J* = 7.8, H-4); 9.19 (1H, d, *J* = 3.7, H-2); 9.31 (1H, s, H-5)
13	1.42 (9H, m, $C(CH_3)_3$); 1.79 (4H, br. s, $C\underline{H}_2CHC\underline{H}_2$); 2.90 (2H, br. s, CH_2N); 3.65 (1H, m, $CH_2C\underline{H}CH_2$); 4.12 (2H, m, CH_2N); 8.93 (1H, s, H-4); 9.24 (1H, s, H-2); 9.29 (1H, s, H-5)

The ^{1}H NMR spectra (Table 2) of the N-Boc-substituted 7-piperidyl[1,6]naphthyridines **7** and **10** show signals for the piperidyl fragment at 1.5-4.0 and a set of signals in the range 7.45-9.55 ppm for the aromatic fragment protons. The spectra of compounds **8** and **11** show general agreement with a low field shift for the aromatic proton signals of 0.16-0.49 ppm relative to those of compounds **7** and **10**. This points to the formation of a hydrochloride in the naphthyridine fragment in which the protons signals of the salt part are strongly broadened as a result of exchange with water present in the DMSO. The salt part of the piperidine fragment appears as broadened signals at 9.31 and 9.55 ppm for compounds **8** and **11** respectively. The nine protons of the *tert*-butoxycarbonyl group resonate as a sharp singlet at 1.4-1.5 ppm.

The presence of halogens (bromine or iodine) in the heterocyclic ring permit the introduction of O-, N-, and C-nucleophiles. The study [2] described the synthesis of 8-iodo[1,6]naphthyridines *via* the cyclization of 2-ethynyl-3-iminopyridines in the presence of iodine monochloride. The introduction of halogens into an already prepared [1,6]naphthyridine can theoretically occur at positions 3 and 8.

We have found that bromination of compound **7** using N-bromosuccinimide in acetic acid gives the 8-bromo-7-piperidyl[1,6]naphthyridine **12** despite the presence of a bulky substituent in an *ortho* position.



7 **12** **13**

Bromination does not proceed to completion but heating to 60ºC in the presence of excess N-bromosuccinimide accumulates the dibromo derivative **13**. The use of N-iodosuccinimide demands refluxing and leads to a complex mixture of compounds.

Hence we have prepared the novel naphthyridine derivatives 7-(3-piperidyl)- and 7-(4-piperidyl)-[1,6]naphthyridine. The route presented above has been used for the first time in the preparation of naphthyridines and permits the introduction of different substituents into position 7 of the heterocyclic system.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Mercury 400 (400 MHz) instrument using DMSO-d_6 with TMS internal standard. Melting points were measured on a Gallenkamp instrument. The course of a reaction was monitored using TLC on Silica gel/TLC-card (Fluka) plates in different eluents. Column chromatography was performed on Durasil H silica gel (60-100 μm) with a hexane–ethyl acetate gradient.

Chromato mass spectrometry was carried out on a Surveyor MSQ instrument (Thermo Finnigan) with chemical ionization in solution (15 eV) using a YMC column (Hydrosphere C18, 12 nm, S-3 μm, 33×3 mm i.d.) and with gradient elution (acetonitrile – 0.1% aqueous formic acid solution, eluent flow rate 1.3 ml/min).

2-Methylnicotinic Acid Methoxymethylamide (1). N,N-Carbonyldiimidazole (56 g, 0.35 mol) was added portionwise with stirring to a suspension of 2-methylnicotinic acid (47 g, 0.34 mol) in acetonitrile (300 ml). After 30 min N,O-dimethylhydroxylamine hydrochloride (39.8 g, 0.41 mol) was added followed by a solution of triethylamine (42 g, 0.41 mol) in acetonitrile (50 ml). The product was held for 5-7 h and triethylamine hydrochloride was filtered off and washed with cold ethyl acetate. The mother liquor was evaporated to two thirds of the original volume, diluted with ethyl acetate (150 ml), and washed with a 5% solution of sodium bicarbonate. The organic layer was separated, dried with Na_2SO_4, and evaporated. Distillation (bp 120-125ºC, 1 mm Hg) gave amide **1** (53.1 g, 86%).

2-Methylpyridine-3-carbaldehyde (2). A solution of amide **1** (11 g, 0.06 mol) in THF (100 ml) was added dropwise to a suspension of lithium aluminium hydride (2.2 g, 0.06 mol) in THF (100 ml) at -50ºC and held for 30 min. The product was treated dropwise with 50% aqueous THF solution (15-20 ml) and the inorganic residue was washed with ethyl acetate. The organic layer was dried with Na_2SO_4 and evaporated. Flash chromatographic purification gave the aldehyde **2** (6.7 g, 92%).

2-Methylpyridine-3-carbaldehyde Cyclohexylimine (3). A solution of carbaldehyde **2** (6.5 g, 0.05 mol), cyclohexylamine (5.2 g, 0.05 mol), and *p*-toluenesulfonic acid (0.01 g) in benzene (150 ml) was refluxed in a Dean-Stark apparatus. The solvent was evaporated and the oil obtained was mixed with ether (40 ml) and cooled. The precipitate was filtered off to give the imine **3** (6.5 g, 61%).

7-(N-Boc-4-piperidyl)[1,6]naphthyridine (7). BuLi (2.5 molar in hexane, 60 ml, 0.16 mol) was added to a solution of diisopropylamine (15.9 g, 0.16 mol) in THF (370 ml) at -60ºC. After 10 min at -60ºC a solution of imine **3** (15.15 g, 0.075 mol) in THF (50 ml) was added dropwise. The violet colored solution obtained was stirred under an argon stream at -60ºC for 20 min and then a solution of amide **4** (26.5 g, 0.1 mol) in THF was added in one portion. The product was stirred for 30 min and treated with a saturated solution of NH_4Cl (100 ml). Solvent was evaporated, the residue was extracted with ethyl acetate, and the extract was evaporated. The oily product obtained was treated with aqueous ammonia (150 ml), treated with several drops of acetic acid, and stirred at 80ºC for 2 h. It was then extracted with ethyl acetate and the organic layer was washed with water, dried over Na_2SO_4, and evaporated. Flash column chromatographic purification gave compound **7** (15.7 g, 67%).

Naphthyridine 10 (Tables 1 and 2) was prepared similarly.

7-(4-Piperidyl)[1,6]naphthyridine Dihydrochloride (8). Dioxane saturated with hydrogen chloride (15-20 ml) was added dropwise to a refluxing solution of compound **7** (15.7 g, 0.05 mol) in 2-propanol (50 ml). At the completion of the reaction the precipitate was filtered off, washed with 2-propanol, and dried to give compound **8** (15.5 g, 96%).

Dihydrochloride 11 was prepared similarly.

7-(N-Boc-4-piperidyl)-8-bromo[1,6]naphthyridine (12). A mixture of the naphthyridine **7** (0.4 g, 1.3 mmol) and N-bromosuccinimide (0.22 g, 1.3 mmol) in glacial acetic acid (8 ml) was stirred for 12 h. Solvent was evaporated and the residue was treated with a saturated solution of potassium carbonate (15 ml) and extracted with ethyl acetate. Column chromatographic purification gave the bromide **12** (0.28 g, 56%) and the dibromide **13** (0.026 g, 4%).

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