A New and Efficient Route to Amino Derivatives of [1,6]- and [2,7]Naphthyridones

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Reaction of *N*-substituted amides of 2-chloro- or 4-chloronicotinic acid with CH-acidic nitriles in the presence of a base provides a convenient access to amino derivatives of 1,6-naphthyrid-5(6*H*)-one, compounds of type **4** and **5**, or 2,7-naphthyrid-1(2*H*)-one **7**.

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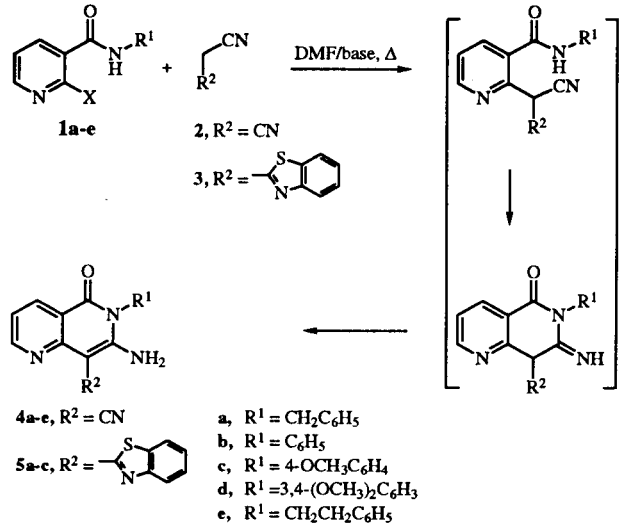
A few years ago, it has been shown that the reaction of secondary amides of *ortho*-halogenobenzoic acids with substituted acetonitriles like malononitrile, arylacetonitriles or hetarylacetontriles offers a simple and efficient route to a variety of 4-substituted 3-aminoquinolin-1(2*H*)-ones [1-3], as displayed in Scheme 1.

Scheme 1

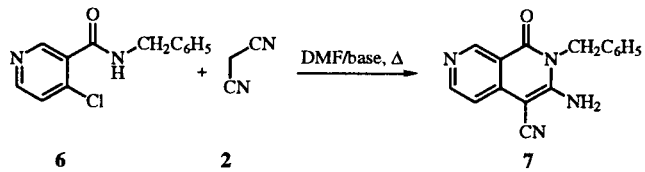
Our interest in developing synthetic approaches to polyfunctional derivatives of condensed *N*-heterocycles now led us to investigate the reaction behavior of such nitrile synthons towards secondary amides of *ortho*-chloronicotinic acids under alkaline conditions. Thus, treatment of various *N*-alkyl- and *N*-aryl-2-chloronicotinamides of type **1** with malononitrile (**2**) or 2-benzothiazolylacetonitrile (**3**), respectively, in the presence of a base (potassium carbonate, cesium carbonate, or 1,8-diazabicyclo[5.4.0]undec-7-ene) in dimethylformamide solution was found to give rise to the formation of a series of new 7-amino-1,6-napthyrid-5(6*H*)-ones, compounds **4a-e** and **5ac**, in reasonable to good yields. Obviously, in a first step the chloro function undergoes nucleophilic substitution by the carbanion generated from the RCH_2CN building block, then the ring is closed by addition of the amide NH function to the cyano group, followed by tautomerization (Scheme 2). This pathway also provides a convenient route to 3-amino-2,7-naphthyrid-1(2*H*)-one derivatives, as exemplified by the smooth conversion of *N*-benzyl-4-chloronicotinamide (**6**) into compound **7**, as displayed in Scheme 3.

Interestingly, when (1-methyl-2-benzimidazolyl)acetonitrile (**8**) is employed as the nitrile component, the reaction takes a different course: in all cases, starting from the amides **1a**, **1b** or **1c**, respectively, we isolated an identical product in 40-60% yield which was identified as the tetracyclic compound **9**; this benzimidazo[1,2-*g*][1,6]naphthyridine derivative had been prepared recently by us *via* a different route [4]. This finding may be interpreted in terms of preferential attack of the nucleophilic benzimidazole N-3 atom at the carboxamide function (with loss of RNH_2, *cf.* Scheme 4) rather than addition of the amide NH to the nitrile group as in the case of compounds **2** and **3**.

Scheme 2

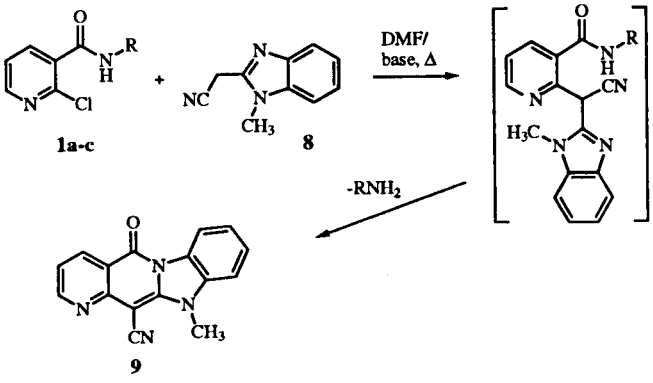


Scheme 3



As an extension of the 7-amino-1,6-naphthyridone syntheses described above, we investigated the possibility of combining the first cyclization step (which leads to the naphthyridine skeleton) with a subsequent ring annelation onto the [*g*] side of the system. This should be feasible if a sufficiently reactive leaving group is present in the *ortho* position at the *N*-phenyl moiety so that the 7-amino group can participate in an intramolecular nucleophilic substitution reaction. Analogous transformations, starting from appropriately substituted 2-chloro-5-nitrobenzoic acid

Scheme 4



anilides had been reported recently [3]. Indeed, when *N*-(2-chloro-5-trifluoromethylphenyl)-2-chloronicotinamide (**1f**) and the nitrile **3** were heated in dimethylformamide in the presence of potassium carbonate, the benzimidazo[1,2-*g*]-[1,6]naphthyridine derivative **10** could be isolated in 57% yield as the sole reaction product (Scheme 5).

In conclusion, the one-step reaction of secondary amides of *ortho*-chloronicotinic acids with CH-acidic nitriles under basic conditions provides an easy and convenient route to a variety of aminonaphthyridones, in certain cases the reaction leads to higher annelated systems. The structures of all new compounds are supported by their ir and nmr spectra as well as by their

Scheme 5

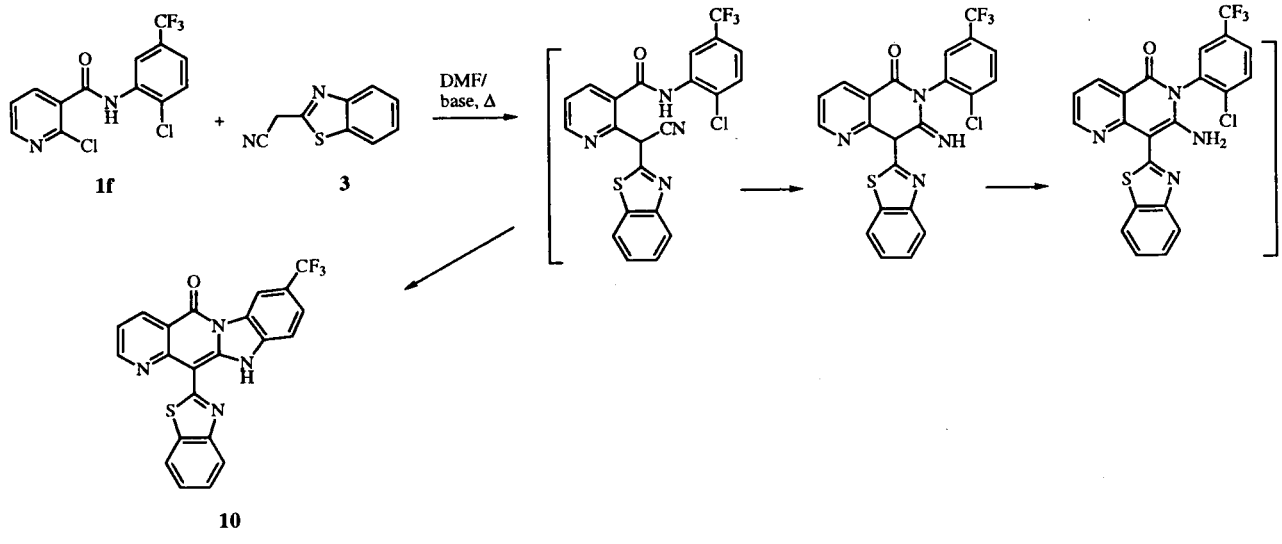


Table 1

Physical and Analytical Data for Compounds **4a-e**, **5a-c**, **7** and **10**

Compound No.	Method [a]	Reaction time (hours)	Yield (%)	Mp, °C Recrystallization solvent	Molecular Formula	Analysis, % Calcd./Found C	H	N
4a	A	6	73	228	$C_{16}H_{12}N_4O$	69.55	4.38	20.28
	B	8	65	2-propanol		69.62	4.26	20.31
4b	A	4	54	285	$C_{15}H_{10}N_4O$	68.69	3.84	21.36
				nitromethane		68.43	3.89	21.40
4c	A	5	52	265	$C_{16}H_{12}N_4O_2$	65.75	4.14	19.17
	C	7	34	nitromethane		65.48	3.94	19.03
4d	A	5	71	258	$C_{17}H_{14}N_4O_3$	63.35	4.38	17.38
				2-propanol		63.20	4.12	17.27
4e	A	5	58	244	$C_{17}H_{14}N_4O$	69.47	4.94	19.06
				DMF	x0.2 H_2O	69.51	4.60	18.97
5a	A	6	82	193	$C_{22}H_{16}N_4OS$	68.73	4.19	14.57
	B	7.5	75	nitromethane		68.44	4.41	14.59
5b	A	6	42	253	$C_{21}H_{14}N_4OS$	68.09	3.81	15.12
	B	7	56	nitromethane		67.80	3.90	15.17
5c	A	10	73	267	$C_{22}H_{16}N_4O_2S$	64.82	4.15	13.74
	C	12	61	1-propanol	x0.4 H_2O	64.74	3.87	13.67
7	A	4	75	247	$C_{16}H_{12}N_4O$	69.55	4.38	20.28
	B	5	62	acetonitrile		69.47	4.27	20.07
10	A	6	57	255	$C_{22}H_{11}F_3N_4OS$	60.55	2.54	12.84
				DMF		60.50	2.53	12.57

[a] See Experimental.

Table 2

IR and ^{1}H NMR Spectral Data for Compounds **4a-e**, **5a-c**, **7** and **10**

Compound No.	IR (cm^{-1})	^{1}H NMR (δ, ppm)
4a	3440, 3344, 3262, 3064, 2204, 1682, 1646, 1582, 1550, 1490, 1404, 1296, 1074, 780, 750, 692	8.75 (dd, J = 4.5 Hz and 1.8 Hz, 1H, 2-H), 8.29 (dd, J = 8.1 Hz and 1.8 Hz, 1H, 4-H), 7.61 (broad *s*, 2H, NH_2), 7.36-7.13 (m, 6H, 3-H, phenyl-H), 5.40 (*s*, 2H, CH_2)
4b	3448, 3330, 3226, 3010, 2204, 1678, 1630, 1594, 1578, 1548, 1490, 1414, 1290, 782, 716	8.77 (dd, J = 4.5 Hz and 1.8 Hz, 1H, 2-H), 8.24 (dd, J = 7.8 Hz and 1.8 Hz, 1H, 4-H), 7.62-7.50 (m, 3H, phenyl 3-H, 4-H, 5-H), 7.42-7.36 (m, 2H, phenyl 2-H, 6-H), 7.20 (dd, J = 7.8 Hz and 4.8 Hz, 1H, 3-H), 6.85 (broad *s*, 2H, NH_2)
4c	3448, 3326, 3220, 2204, 1686, 1624, 1582, 1548, 1510, 1488, 1414, 1288, 1248, 1170, 1026, 784	8.75 (dd, J = 4.8 Hz and 1.8 Hz, 1H, 2-H), 8.23 (dd, J = 7.8 Hz and 1.8 Hz, 1H, 4-H), 7.32-7.25 (BB' part of an AA'BB' system, 2H, phenyl 2-H, 6-H), 7.19 (dd, J = 7.8 Hz and 4.8 Hz, 1H, 3-H), 7.14-7.06 (AA' part of an AA'BB' system, 2H, phenyl 3-H, 5-H), 6.86 (broad *s*, 2H, NH_2), 3.82 (*s*, 3H, OCH_3)
4d	3414, 3322, 3204, 2938, 2204, 1682, 1620, 1582, 1552, 1516, 1478, 1404, 1260, 1240, 1128, 1026, 784	8.75 (dd, J = 4.8 Hz and 1.8 Hz, 1H, 2-H), 8.23 (dd, J = 8.1 Hz and 1.8 Hz, 1H, 4-H), 7.19 (dd, J = 8.1 Hz and 4.8 Hz, 1H, 3-H), 7.10 (d, J = 8.7 Hz, 1H, phenyl 5-H), 7.02 (d, J = 2.1 Hz, 1H, phenyl 2-H), 6.93-6.85 (m, 3H, NH_2, phenyl 6-H), 3.82 (*s*, 3H, 4-OCH_3), 3.73 (*s*, 3H, 3-OCH_3)
4e	3382, 3346, 3228, 2206, 1670, 1656, 1594, 1582, 1548, 1500, 1418, 1132, 784	8.71 (dd, J = 4.8 Hz and 1.8 Hz, 1H, 2-H), 8.24 (dd, J = 8.1 Hz and 1.8 Hz, 1H, 4-H), 7.70 (broad *s*, 2H, NH_2), 7.33-7.19 (m, 5H, phenyl-H), 7.16 (dd, J = 8.1 Hz and 4.8 Hz, 1H, 3-H), 4.35-4.26 (m, 2H, NCH_2CH_2C), 2.90-2.81 (m, 2H, NCH_2CH_2C)
5a	3466, 3050, 1668, 1592, 1566, 1492, 1452, 1422, 1290, 1278, 960, 788, 760, 692	8.96 (dd, J = 4.8 Hz and 1.8 Hz, 1H, 2-H), 8.49 (dd, J = 7.8 Hz and 1.8 Hz, 1H, 4-H), 8.02 (d, J = 7.8 Hz, 1H, benzothiazole 4-H), 7.85 (d, J = 7.8 Hz, 1H, benzothiazole 7-H), 7.46-7.22 (m, 8H, 3-H, benzothiazole 5-H, 6-H, phenyl-H), 5.55 (*s*, 2H, CH_2)
5b	3464, 3050, 1668, 1592, 1566, 1492, 1452, 1422, 1290, 960, 788, 760, 692	8.97 (dd, J = 4.8 Hz and 1.8 Hz, 1H, 2-H), 8.42 (dd, J = 8.1 Hz and 1.8 Hz, 1H, 4-H), 8.03 (d, J = 7.8 Hz, 1H, benzothiazole 4-H), 7.78 (d, J = 7.8 Hz, 1H, benzothiazole 7-H), 7.69-7.56 (m, 3H, phenyl 3-H, 4-H, 5-H), 7.51-7.46 (m, 2H, phenyl 2-H, 6-H), 7.45-7.38 (m, 1H, benzothiazole 6-H), 7.33-7.27 (m, 2H, 3-H, benzothiazole 5-H)
5c	3450, 3052, 1676, 1602, 1570, 1494, 1452, 1424, 1290, 1250, 1032, 788, 758	8.94 (dd, J = 4.5 Hz and 1.8 Hz, 1H, 2-H), 8.40 (dd, J = 7.8 Hz and 1.8 Hz, 1H, 4-H), 8.02 (d, J = 7.8 Hz, 1H, benzothiazole 4-H), 7.77 (d, J = 7.8 Hz, 1H, benzothiazole 7-H), 7.46-7.34 (m, 3H, benzothiazole 6-H, phenyl 2-H, 6-H), 7.32-7.23 (m, 2H, 3-H, benzothiazole 5-H), 7.20-7.14 (AA' part of an AA'BB' system, 2H, phenyl 3-H, 5-H), 3.86 (*s*, 3H, OCH_3)
7	3414, 3198, 3062, 2200, 1685, 1654, 1602, 1576, 1532, 1496, 1192, 976, 730	9.03 (*s*, 1H, 8-H), 8.53 (d, J = 5.7 Hz, 1H, 6-H), 7.91 (broad *s*, 2H, NH_2), 7.36-7.14 (m, 6H, 5-H, phenyl-H), 5.38 (*s*, 2H, CH_2)
10	3066, 1678, 1616, 1560, 1534, 1458, 1306, 1274, 1236, 1110, 1048, 976, 780, 672	13.62 (broad *s*, 1H, NH), 9.03 (dd, J = 4.8 Hz and 1.8 Hz, 1H, 2-H), 8.84 (*s*, 1H, 7-H), 8.71 (dd, J = 7.8 Hz and 1.8 Hz, 1H, 4-H), 8.12-7.98 (m, 3H, 9-H, benzothiazole 4-H, 7-H), 7.54-7.48 (m, 1H, benzothiazole 5-H or 6-H), 7.43 (dd, J = 7.8 Hz and 4.8 Hz, 1H, 3-H), 7.37-7.31 (m, 1H, benzothiazole 6-H or 5-H)

microanalyses; details are given in the Experimental and in Tables 1 and 2.

EXPERIMENTAL

Melting points were determined in a capillary tube and are uncorrected. The ir spectra were recorded for potassium bromide pellets on a Perkin-Elmer 1605 FT-IR spectrophotometer. The ^{1}H nmr spectra were obtained on a Varian Unity*plus* 300 (300 MHz) spectrometer, using deuteriodimethyl sulfoxide as the solvent. For tlc, Merck aluminium sheets pre-coated with Kieselgel 60 F_{254} were used (eluent: chloroform/methanol, 9:1). Elemental analyses were performed at the Microanalytical Laboratory, Institute of Physical Chemistry, University of Vienna.

Potassium carbonate and cesium carbonate were freshly dried over an open flame and ground before use. Hetarylacetonitriles were prepared according to literature procedures: (1-methyl-2-benzimidazolyl)acetonitrile (**8**) [6,7] and 2-benzothiazolylacetonitrile (**3**) [8]. The 2-chloronicotinamides **1a-f** and 4-chloronicotinamide **6** were prepared according to known procedures [9,11].

General Procedure for the Preparation of the Aminonaphthyridones **4a-e**, **5a-c**, **7** and the Condensed Naphthyridones **9** and **10**.

Method A.

A mixture of the nitrile **2**, **3**, or **8** (10 mmoles), a suitable 2- or 4-chloronicotinamide, **1a-f** or **6**, respectively, (15 mmoles) and 2.07 g (15 mmoles) of potassium carbonate in 40 ml of dimethylformamide was stirred at reflux temperature for 4 to 12 hours. After cooling, the solvent was removed under reduced pressure. Water (25 ml) was added, and the reaction mixture was neutralized (*p*H 6-7) by addition of acetic acid. The precipitate was collected by filtration, washed with cold water, dried and recrystallized from a suitable solvent. For reaction times and yields, physical, analytical, and spectral data see Tables 1 and 2.

Method B.

The same reaction conditions were applied except that 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (2.28 g, 15 mmoles) was used as a base.

Method C.

The same reaction conditions were applied except that cesium carbonate (4.89 g, 15 mmoles) was used as a base.

7-Amino-6-benzyl-8-cyano-1,6-naphthyrid-5(6*H*)-one (**4a**).

This compound was obtained from *N*-benzyl-2-chloronicotinamide (**1a**) and malononitrile (**2**) as colorless crystals.

7-Amino-8-cyano-6-phenyl-1,6-naphthyrid-5(6*H*)-one (**4b**).

This compound was obtained from *N*-phenyl-2-chloronicotinamide (**1b**) and malononitrile (**2**) as colorless crystals.

7-Amino-8-cyano-6-(4-methoxyphenyl)-1,6-naphthyrid-5(6*H*)-one (**4c**).

This compound was obtained from *N*-(4-methoxyphenyl)-2-chloronicotinamide (**1c**) and malononitrile (**2**) as colorless crystals.

7-Amino-8-cyano-6-(3,4-dimethoxyphenyl)-1,6-naphthyrid-5(6*H*)-one (**4d**).

This compound was obtained from *N*-(3,4-dimethoxyphenyl)-2-chloronicotinamide (**1d**) and malononitrile (**2**) as colorless crystals.

7-Amino-8-cyano-6-(2-phenylethyl)-1,6-naphthyrid-5(6*H*)-one (**4e**).

This compound was obtained from *N*-(2-phenylethyl)-2-chloronicotinamide (**1e**) and malononitrile (**2**) as almost colorless crystals.

7-Amino-8-(2-benzothiazolyl)-6-benzyl-1,6-naphthyrid-5(6*H*)-one (**5a**).

This compound was obtained from *N*-benzyl-2-chloronicotinamide (**1a**) and 2-benzothiazolylacetonitrile (**3**) as yellow crystals.

7-Amino-8-(2-benzothiazolyl)-6-phenyl-1,6-naphthyrid-5(6*H*)-one (**5b**).

This compound was obtained from *N*-phenyl-2-chloronicotinamide (**1b**) and 2-benzothiazolylacetonitrile (**3**) as yellow crystals.

7-Amino-8-(2-benzothiazolyl)-6-(4-methoxyphenyl)-1,6-naphthyrid-5(6*H*)-one (**5c**).

This compound was obtained from *N*-(4-methoxyphenyl)-2-chloronicotinamide (**1c**) and 2-benzothiazolylacetonitrile (**3**) as yellow crystals.

3-Amino-2-benzyl-4-cyano-2,7-naphthyrid-1(2*H*)-one (**7**).

This compound was obtained from *N*-benzyl-4-chloronicotinamide (**6**) and malononitrile (**2**) as colorless crystals.

12-Cyano-5,11-dihydro-11-methylbenzimidazo[1,2-*g*]1,6-naphthyrid-5-one (**9**) [4].

This compound was obtained in yields of 58% (method A) or 42% (method B), respectively, from *N*-benzyl-2-chloronicotinamide (**1a**) and (1-methyl-2-benzimidazolyl)acetonitrile (**8**) as pale yellow crystals, mp 292-293° (lit [4] 292-293°). The same product **9** was obtained in comparable yields when the 2-chloronicotinamides **1b** or **1c** were used as the starting material.

12-(2-Benzothiazolyl)-5,11-dihydro-8-trifluoromethylbenzimidazo[1,2-*g*][1,6]naphthyrid-5-one (**10**).

This compound was obtained from *N*-(2-chloro-5-trifluoromethylphenyl)-2-chloronicotinamide (**1f**) and 2-benzothiazolylacetonitrile (**3**) as yellow crystals.

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