Synthesis of 6-Aminoindolo[2,1-*a*]isoquinoline-5-carbonitriles by the Cu-Catalyzed Reaction of 2-(2-Bromophenyl)-1*H*-indoles with $CH_2(CN)_2$

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A series of 6-aminoindolo[2,1-*a*]isoquinoline-5-carbonitriles **4** have been prepared by treatment of 2-(2-bromophenyl)-1*H*-indoles **1**, available from 1-(2-bromophenyl)ethanones or 1-(2-bromophenyl)-propan-1-ones by using *Fischer* indole synthesis, with propanedinitrile in the presence of a catalytic amount of CuBr and an excess of K_2CO_3 in DMSO at 100°.

Introduction. – Compounds with the indolo[2,1-*a*]isoquinoline skeleton have received much attention, because some of them have been reported to exhibit a variety of biological activities [1]. Recently, several methods for the preparation of indolo[2,1-*a*]isoquinoline derivatives have been reported [1][2]. On the other hand, we recently reported that the reaction of 2-(2-bromophenyl)-1,4,5,6-tetrahydropyrimidines with propanedinitrile was catalyzed by CuI to afford 6-amino-3,4-dihydro-2*H*-pyrimido[2,1-*a*]isoquinoline-7-carbonitriles [3]. As an application of this method, we have now found that indolo[2,1-*a*]isoquinolines **4** with an NH_2 group at C(6) and a CN group at C(5) can be efficiently prepared by the CuBr-catalyzed reaction of 2-(2-bromophenyl)-1*H*-indoles **1** with propanedinitrile ($CH_2(CN)_2$). Herein, we present the results of our study, which offer a convenient and general synthetic route to this new type of indolo[2,1-*a*]isoquinoline derivatives. It should be noted that, during our work, we became aware of a report on the elaboration of these 1*H*-indole derivatives to the synthesis of indolo[2,1-*c*]quinazolines by *Zhang* and co-workers. [4].

Results and Discussion. – The transformation of **1**, which could be easily prepared from appropriate 2-bromophenyl ketones by *Fischer* indole synthesis, to 6-amino-indolo[2,1-*a*]isoquinoline-5-carbonitriles **4** was accomplished by treatment with $CH_2(CN)_2$ in the presence of CuBr (0.1 equiv.) and K_2CO_3 (2 equiv.) in DMSO at 100°, as outlined in the *Scheme*. Probably, cyclization by the attack of the indole N-atom on one of the two CN functions of the intermediates **2**, arising from Cu-catalyzed coupling of **1** with $CH_2(CN)_2$, took place to result in the formation of the corresponding imino nitrile derivatives **3** as the initial products, which underwent tautomerization to afford the desired products **4**. These compounds were isolated by aqueous workup and the subsequent purification by column chromatography on SiO_2 as described in the *Exper. Part*. The yields compiled in the *Table* are, in general, relatively good, though those of the products carrying MeO substituent(s) at C(2) and/or C(3) are only moderate (*Entries 3* and *4*). In these cases, considerable amounts of the starting

Scheme

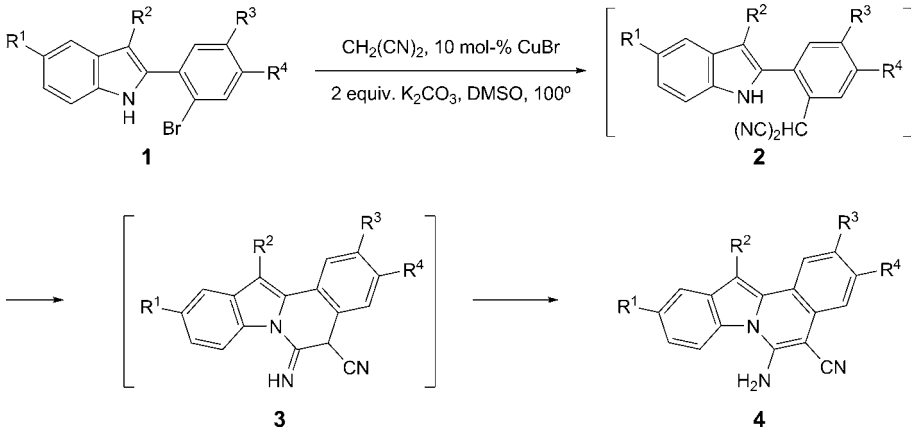

Table. *Preparation of 6-Aminoindolo[2,1-*a*]isoquinoline-5-carbonitriles* **4**

Entry	R^1	R^2	R^3	R^4	**4**	Yield[a]) [%]
1	H	H	H	H	**4a**	75
2	H	H	Cl	H	**4b**	75
3	H	H	MeO	H	**4c**	48
4	H	H	MeO	MeO	**4d**	47
5	H	Me	H	H	**4e**	77
6	Me	H	H	H	**4f**	70
7	Cl	H	H	H	**4g**	69
8	Cl	Me	H	H	**4h**	87

[a]) Yields of isolated products.

materials remained unchanged. The extended reaction time did not improve the yields. Unfortunately, however, the reasons for these results are uncertain.

Initially, CuI was used as a catalyst. Although the reactions proceeded at 60°, rather complicated mixtures of product were obtained, from which only low yields (*ca.* 30%) of the desired products were isolated. When CuBr was used, the reaction proceeded much more cleanly to give the desired products in rather better yields, though a higher reaction temperature was required. The use of less than 0.1 equiv. of the catalyst led to significantly reduced yields, and the use of 0.2 equiv. of the catalyst did not affect the yields.

In conclusion, the procedure reported here provides a convenient method for the preparation of 6-aminoindolo[2,1-*a*]isoquinoline-5-carbonitriles from 2-(2-bromophenyl)-1*H*-indoles, which are easily accessible by *Fischer* indole synthesis. This is the first example of the preparation of this type of indolo[2,1-*a*]isoquinoline derivatives. The present method may find some applications in organic synthesis, not only due to the simplicity of the procedures and the ready availability of the starting materials, but also due to the potential use of these products for further synthetic elaborations.

Experimental Part

General. All org. solvents used in this study were dried over appropriate drying agents and distilled prior to use. TLC: *Merck* silica gel *60 PF_{254}*. Column chromatography (CC): *Wako Gel C-200E*. M.p.: *Laboratory Devices MEL-TEMP II* melting-point apparatus; uncorrected. IR Spectra: *Perkin Elmer Spectrum65* FT-IR spectrophotometer; $\tilde{\nu}$ in cm^{-1}. ^{1}H-NMR Spectra: *Bruker Biospin AVANCE II 600* FT, *JEOL ECP500* FT, or *JEOL LA400* FT NMR spectrometers (at 600, 500, or 400 MHz, resp.), δ in ppm rel. to Me_4Si as internal standard, J in Hz. ^{13}C-NMR Spectra: *Bruker Biospin AVANCE II 600* FT or *JEOL ECP500* FT-NMR spectrometers (at 150 or 125 MHz, resp.), δ in ppm rel. to Me_4Si as internal standard. HR-MS (DART, pos. or ESI neg.): *Thermo Scientific Exactive* spectrometer; in *m*/*z*.

1-(2-Bromo-5-chlorophenyl)ethanone [5], *2-(2-bromophenyl)-1*H-*indole* (**1a**) [6], *2-(2-bromophenyl)-3-methyl-1*H-*indole* (**1e**) [7], *2-(2-bromophenyl)-5-methyl-1*H-*indole* (**1f**) [4], and *2-(2-bromophenyl)-5-chloro-1*H-*indole* (**1g**) [4] were prepared according to reported procedures. All other chemicals used in this study were commercially available.

*2-(2-Bromophenyl)-1*H-*indoles* **1b**–**1d** *and* **1h** were prepared from the appropriate 2-bromophenyl ketones and phenylhydrazine as described in [6] for the preparation of **1a**.

*2-(2-Bromo-5-chlorophenyl)-1*H-*indole* (**1b**). Yield: 62%. White solid. M.p. 100–101° (hexane/Et_2O). IR (KBr): 3455. ^{1}H-NMR (500 MHz, $CDCl_3$): 6.86 (*d*, *J* = 2.3, 1 H); 7.16 (*t*, *J* = 6.9, 1 H); 7.18 (*dd*, *J* = 8.4, 2.3, 1 H); 7.26 (*ddd*, *J* = 8.4, 6.9, 1.5, 1 H); 7.44 (*d*, *J* = 8.4, 1 H); 7.60–7.62 (*m*, 2 H); 7.67 (*d*, *J* = 8.4, 1 H); 8.64 (br. *s*, 1 H). Anal. calc. for $C_{14}H_9BrClN$ (306.59): C 54.85, H 2.96, N 4.57; found: C 54.83, H 3.13, N 4.58.

*2-(2-Bromo-5-methoxyphenyl)-1*H-*indole* (**1c**). Yield: 54%. Pale-yellow solid. M.p. 99–100° (hexane/Et_2O). IR (KBr): 3390. ^{1}H-NMR (500 MHz, $CDCl_3$): 3.84 (*s*, 3 H); 6.79 (*dd*, *J* = 9.2, 3.1, 1 H); 6.82 (*d*, *J* = 3.1, 1 H); 7.14 (*s*, 1 H); 7.15 (*t*, *J* = 7.6, 1 H); 7.23 (*t*, *J* = 7.6, 1 H); 7.43 (*d*, *J* = 7.6, 1 H); 7.56 (*d*, *J* = 9.2, 1 H); 7.67 (*d*, *J* = 7.6, 1 H); 8.65 (br. *s*, 1 H). Anal. calc. for $C_{15}H_{12}BrNO$ (302.17): C 59.62, H, 4.00, N 4.64; found: C 59.61, H 4.01, N 4.61.

*2-(2-Bromo-4,5-dimethoxyphenyl)-1*H-*indole* (**1d**). Yield: 51%. Pale-yellow solid. M.p. 151–153° (hexane/Et_2O). IR (KBr): 3358. ^{1}H-NMR (500 MHz, $CDCl_3$): 3.91 (*s*, 3 H); 3.93 (*s*, 3 H); 6.73 (*s*, 1 H); 7.09 (*s*, 1 H); 7.13 (*s*, 1 H); 7.14 (*t*, *J* = 7.6, 1 H); 7.22 (*dd*, *J* = 8.4, 7.6, 1 H); 7.43 (*d*, *J* = 7.6, 1 H); 7.65 (*d*, *J* = 8.4, 1 H); 8.61 (br. *s*, 1 H). Anal. calc. for $C_{16}H_{14}BrNO_2$ (332.20): C 57.85, H, 4.25, N 4.22; found: C 57.75, H 4.21, N 4.16.

*2-(2-Bromophenyl)-5-chloro-3-methyl-1*H-*indole* (**1h**). Yield: 65%. Colorless oil. R_f (CH_2Cl_2/hexane 1:5) 0.20. IR (neat): 3431. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.23 (*s*, 3 H); 7.17 (*dd*, *J* = 8.4, 1.5, 1 H); 7.28–7.31 (*m*, 2 H); 7.39–7.44 (*m*, 2 H); 7.58 (*s*, 1 H); 7.71 (*d*, *J* = 7.6, 1 H); 8.09 (*s*, 1 H). Anal. calc. for $C_{15}H_{11}BrClN$ (320.61): C 56.19, H, 3.46, N 4.37; found: C 56.10, H 3.69, N 4.33.

*Indolo[2,1-*a*]isoquinolines* **3**: *General Procedure.* A mixture of **1** (1.0 mmol) and $CH_2(CN)_2$ (66 mg, 1.0 mmol) in DMSO (5 ml), containing CuBr (14 mg, 0.10 mmol) and K_2CO_3 (0.28 g, 2.0 mmol), was heated under stirring at 100°. The progress of the reaction was monitored by TLC (SiO_2). After complete consumption or no more decrease of the starting material had been observed (*ca.* 2 h), the mixture was cooled to r.t., and 25% NH_4OH (10 ml), H_2O (10 ml), and AcOEt (20 ml) were successively added. The precipitate was removed by filtration through a *Celite* pad under reduced pressure, and the filtrate was separated. The aq. layer was extracted with AcOEt (2 × 10 ml). The combined org. layers were washed with H_2O (2 × 10 ml) and brine (10 ml), dried (Na_2SO_4), and concentrated by evaporation. The residue was purified by CC ($CHCl_3$) to give the desired products **4**.

*6-Aminoindolo[2,1-*a*]isoquinoline-5-carbonitrile* (**4a**). Yellow solid. M.p. 253–254° (THF). IR (KBr): 3449, 3324, 2209, 1651. ^{1}H-NMR (500 MHz, $CDCl_3$): 5.54 (br. *s*, 2 H); 7.32 (*s*, 1 H); 7.37–7.41 (*m*, 2 H); 7.46 (*dd*, *J* = 7.6, 6.9, 1 H); 7.51 (*dd*, *J* = 8.4, 6.9, 1 H); 7.69 (*d*, *J* = 8.4, 1 H); 7.85 (*d*, *J* = 7.6, 1 H); 8.06 (*d*, *J* = 7.6, 1 H); 8.12 (*d*, *J* = 8.4, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 61.8; 97.9; 113.7; 115.6; 120.5 (two overlapped Cs); 121.2; 121.9; 123.6; 123.7; 124.4; 128.9; 130.2; 131.7; 134.0; 135.3; 150.9. HR-DART-MS (pos.): 258.1019 ($[M+H]^+$, $C_{17}H_{12}N_3^+$; calc. 258.1031). Anal. calc. for $C_{17}H_{11}N_3$ (257.30): C 79.36, H 4.31, N 16.33; found: C 79.10, H 4.58, N 16.16.

*6-Amino-2-chloroindolo[2,1-*a*]isoquinoline-5-carbonitrile* (**4b**). Beige solid. M.p. 230–233° (THF). IR (KBr): 3443, 3327, 2209, 1648. ^{1}H-NMR (500 MHz, $CDCl_3$): 5.58 (br. *s*, 2 H); 7.31 (*s*, 1 H); 7.43–7.48

(*m*, 3 H); 7.62 (*d*, *J* = 7.6, 1 H); 7.87 (*d*, *J* = 8.4, 1 H); 8.02 (*s*, 1 H); 8.11 (*d*, *J* = 7.6, 1 H). ^{13}C-NMR (125 MHz, (D_6)DMSO): 68.5; 99.2; 115.6; 117.8; 120.7; 120.8; 122.3; 122.9; 123.1; 123.7; 126.5; 128.5; 128.7; 130.0; 131.8; 134.0; 151.0. HR-ESI-MS (neg.): 290.0493 ($[M-H]^-$, $C_{17}H_9ClN_3^-$; calc. 290.0485). Anal. calc. for $C_{17}H_{10}ClN_3$ (291.74): C 69.99, H 3.46, N 14.40; found: C 69.96, H 3.52, N 14.35.

6-Amino-2-methoxyindolo[2,1-a]isoquinoline-5-carbonitrile (**4c**). Beige solid. M.p. 208 – 209° (THF). IR (KBr): 3443, 3339, 2194, 1646. ^{1}H-NMR (500 MHz, $CDCl_3$): 3.93 (*s*, 3 H); 5.34 (br. *s*, 2 H); 7.11 (*dd*, *J* = 8.4, 2.3, 1 H); 7.24 (*s*, 1 H); 7.38 (*dd*, *J* = 8.4, 6.9, 1 H); 7.44 (*dd*, *J* = 7.6, 6.9, 1 H); 7.47 (*d*, *J* = 2.3, 1 H); 7.60 (*d*, *J* = 8.4, 1 H); 7.83 (*d*, *J* = 7.6, 1 H); 8.13 (*d*, *J* = 8.4, 1 H). ^{13}C-NMR (125 MHz, (D_6)DMSO): 55.6; 69.4; 98.2; 106.4; 115.7; 117.5; 118.2; 120.4; 120.6; 120.8; 121.8; 122.9; 123.4; 130.1; 131.9; 135.0; 149.7; 156.7. HR-DART-MS (pos.): 288.1131 ($[M+H]^+$, $C_{18}H_{14}N_3O^+$; calc. 288.1137). Anal. calc. for $C_{18}H_{13}N_3O$ (287.32): C 75.25, H 4.56, N 14.63; found: C 75.20, H 4.83, N 14.49.

6-Amino-2,3-dimethoxyindolo[2,1-a]isoquinoline-5-carbonitrile (**4d**). Beige solid. M.p. 206 – 208° (THF). IR (KBr): 3400, 3325, 2197, 1640, 1615. ^{1}H-NMR (500 MHz, (D_6)DMSO): 3.88 (*s*, 3 H); 3.90 (*s*, 3 H); 6.93 (*s*, 1 H); 7.13 (br. *s*, 2 H); 7.29 (*t*, *J* = 7.6, 1 H); 7.37 (*dd*, *J* = 9.1, 7.6, 1 H); 7.47 (*s*, 1 H); 7.69 (*s*, 1 H); 7.75 (*d*, *J* = 7.6, 1 H); 8.37 (*d*, *J* = 9.2, 1 H). ^{13}C-NMR (125 MHz, (D_6)-DMSO): 55.5; 56.0; 69.8; 96.0; 103.2; 111.9; 115.6; 118.3; 120.0; 121.0; 121.5; 123.5; 130.5; 130.7; 131.5; 135.4; 143.1; 149.9; 151.1. HR-DART-MS (pos.): 317.1241 ($[M+H]^+$, $C_{19}H_{18}N_3O_2^+$; calc. 317.1242). Anal. calc. for $C_{19}H_{15}N_3O_2$ (317.35): C 71.91, H 4.76, N 13.24; found: C 71.70, H 4.90, N 13.15.

6-Amino-12-methylindolo[2,1-a]isoquinoline-5-carbonitrile (**4e**). Beige solid. M.p. 214 – 216° (THF). IR (KBr): 3373, 3335, 2196, 2165. ^{1}H-NMR (500 MHz, (D_6)DMSO): 2.71 (*s*, 3 H); 7.23 (br. *s*, 2 H); 7.32 – 7.38 (*m*, 2 H); 7.43 (*t*, *J* = 7.6, 1 H); 7.46 – 7.50 (*m*, 2 H); 7.85 (*d*, *J* = 7.6, 1 H); 8.21 (*d*, *J* = 8.4, 1 H); 8.36 (*d*, *J* = 8.4, 1 H). ^{13}C-NMR (125 MHz, (D_6)DMSO): 11.3; 69.0; 108.2; 115.4; 118.2; 118.4; 121.0; 121.1; 122.3; 123.1; 124.0; 124.3; 127.9; 128.2; 129.8; 130.4; 131.2; 150.9. HR-DART-MS (pos.): 272.1185 ($[M+H]^+$, $C_{18}H_{14}N_3^+$; calc. 272.1187). Anal. calc. for $C_{18}H_{13}N_3$ (271.32): C 79.68, H 4.83, N 15.49; found: C 79.50, H 4.84, N 15.45.

6-Amino-10-methylindolo[2,1-a]isoquinoline-5-carbonitrile (**4f**). Beige solid. M.p. 262 – 263° (THF). IR (KBr): 3448, 3327, 2198, 1652. ^{1}H-NMR (600 MHz, $CDCl_3$): 2.55 (*s*, 3 H); 5.52 (br. *s*, 2 H); 7.21 (*dd*, *J* = 8.7, 1.3, 1 H); 7.24 (*s*, 1 H); 7.37 (*td*, *J* = 8.0, 1.0, 1 H); 7.50 (*ddd*, *J* = 8.0, 7.3, 1.0, 1 H); 7.63 (br. *s*, 1 H); 7.69 (*d*, *J* = 8.0, 1 H); 7.97 (*d*, *J* = 8.7, 1 H); 8.05 (*d*, *J* = 8.0, 1 H). ^{13}C-NMR (150 MHz, (D_6)DMSO): 21.0; 68.7; 97.4; 115.1; 118.0; 119.3; 119.9; 121.1; 123.3; 123.5; 124.2; 127.6; 128.7; 130.0; 130.4; 132.6; 135.2; 150.6. HR-DART-MS (pos.): 272.1177 ($[M+H]^+$, $C_{18}H_{14}N_3^+$; calc. 272.1187). Anal. calc. for $C_{18}H_{13}N_3$ (271.32): C 79.68, H 4.83, N 15.49; found: C 79.67, H 5.05, N 15.42.

6-Amino-10-chloroindolo[2,1-a]isoquinoline-5-carbonitrile (**4g**). Beige solid. M.p. 280 – 283° (THF). IR (KBr): 3426, 3326, 2208, 1653, 1600. ^{1}H-NMR (400 MHz, (D_6)DMSO): 7.32 – 7.39 (*m*, 2 H); 7.44 (br. *s*, 2 H); 7.52 – 7.57 (*m*, 3 H); 7.85 (*d*, *J* = 2.0, 1 H); 8.22 (*d*, *J* = 7.8, 1 H); 8.42 (*d*, *J* = 8.4, 1 H). ^{13}C-NMR (125 MHz, (D_6)DMSO): 66.6; 107.0; 117.2; 117.7; 119.0; 119.3; 121.3; 121.4; 123.9; 124.6; 127.8; 128.03; 129.3; 130.2; 131.5; 136.7; 150.6. HR-DART-MS (pos.): 292.0628 ($[M+H]^+$, $C_{17}H_{11}ClN_3^+$; calc. 292.0641). Anal. calc. for $C_{17}H_{10}ClN_3$ (291.74): C 69.99, H 3.46, N 14.40; found: C 69.85, H 3.57, N 14.30.

6-Amino-10-chloro-12-methylindolo[2,1-a]isoquinoline-5-carbonitrile (**4h**). Beige solid. M.p. 267 – 268° (THF). IR (KBr): 3425, 3327, 2206, 1647, 1607. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.73 (*s*, 3 H); 5.35 (br. *s*, 2 H); 7.34 (*dd*, *J* = 9.2, 1.5, 1 H); 7.41 (*t*, *J* = 7.6, 1 H); 7.51 (*t*, *J* = 7.6, 1 H); 7.71 (*d*, *J* = 7.6, 1 H); 7.78 (*br s*, 1 H); 8.05 (*d*, *J* = 9.2, 1 H); 8.24 (*d*, *J* = 7.6, 1 H). ^{13}C-NMR (125 MHz, (D_6)DMSO): 11.3; 69.9; 107.7; 117.0; 117.6; 117.9; 120.7; 121.1; 121.7; 124.2; 124.5; 126.2; 127.8; 128.3; 128.3; 131.2; 132.5; 150.5. HR-DART-MS (pos.): 306.0787 ($[M+H]^+$, $C_{18}H_{13}ClN_3^+$; calc. 306.0798). Anal. calc. for $C_{18}H_{12}ClN_3$ (305.77): C 70.71, H 3.96, N 13.74; found: C 70.43, H 4.08, N 13.47.

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