Pergamon

Tetrahedron Vol. 51, No. 45, pp. 12439-12444, 1995

0040-4020/95 $9.50+0.00

0040-4020(95)00799-7

A General Approach to 3-Aminoisoquinoline, Its N-Mono- and N,N-Disubstituted Derivatives

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Abstract: Condensation of 2-cyanomethyl benzaldehydes **1** with **2** (ammonia, primary or secondary amines) carried out in the presence of a catalytic amount of trifluoroacetic acid, afforded 3-aminoisoquinolines **3**. In the case of primary amines azomethines **4** were formed at first; they dissociated and subsequently yielded **3** in a rather slow process.

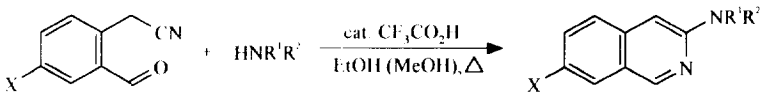
Currently available methods for the preparation of 3-aminoisoquinolines can be chosen from an array of alternative synthetic procedures collected in the recent paper by Suzuki and Abe.[1] Their facile route to 3-aminoisoquinolines substituted at C-4 with an electron-withdrawing groups still does not terminate the list of possible direct ways to this class of compounds, some of which are of pharmacological interest.[1-3]

The earlier work by Takeda *et al.*[4] indicates that the reaction of 2-cyanomethyl- and 2-(1-cyanoalkyl)-3-formylindoles with ammonia afforded 3-amino-5H-pyrido[4,3-b]indole or its 4-alkyl substituted derivatives, respectively. This attractive approach to other condensed aminopyridines could not be hitherto realized because 1-cyanomethyl-2-formylbenzenes were unavailable. However, our recent investigations on sigmatropic rearrangements of ylides generated from suitably substituted benzylammonium salts have led to the preparation of 2-cyanomethylbenzaldehydes.[5-7] According to our expectations these aldehydes proved indeed convenient starting materials for the synthesis of 3-aminoisoquinolines.

We have found that the simple heating of aldehydes **1** with ammonia, primary or secondary amines **2**, in the lower alcohol, at ambient temperature, in the presence of catalytic amount of trifluoroacetic acid, led to the formation of 3-aminoisoquinolines **3**[8,9] (Scheme 1, Table 1).

The yields of **3** depended on the kind of nitrogen derivative **2** used. Thus, ammonia (**2a**) and primary amines **2b,d-g** afforded isoquinolines **3** with good yields after heating for *ca* 10 - 20 h, except for t-butylamine (**2c**) which, possibly for steric reasons, reacted with **1a** much slower. On the other hand, secondary amines **2h,i** entered rather a slow reaction, giving the products **3ah** and **3ai** with low yields. Evidently, due to the low rate of the key reaction, secondary amines catalyzed undesired side process of **1** leading to the formation of tarry materials.

Following the reaction progress of **1** with primary amines by means of gas chromatography we found that the corresponding azomethines **4** were formed at first with high yields, even in the absence of the acidic catalyst (Scheme 2).



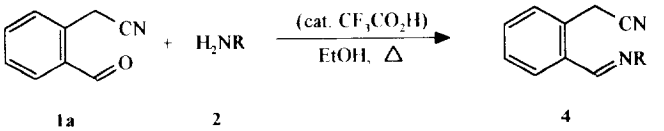
1 2 3

	X		R^1	R^2	Product		X		R^1	R^2	Product
1a	H	**2a**	H	H	**3aa**	**1a**	H	**2f**	H	Ph	**3af**
		2b	H	Me	**3ab**			**2g**	H	$PhCH_2$	**3ag**
		2c	H	t-Bu	**3ac**			**2h**	Me	Me	**3ah**
		2d	H	c-C_6H_{11}	**3ad**			**2i**	$(CH_2)_2O(CH_2)_2$		**3ai**
		2e	H	$(CH_2)_2OH$	**3ae**	**1b**	Cl	**2f**	H	Ph	**3bf**

Scheme 1

Table 1. Reaction Times, Yields and Characterization Data of **3**

Entry	Product	Reaction time (h)	Yield (%)	M.p. (°C) or b.p. (°C/Torr)	M.F. M.W.	Analysis (%); Calcd/Found C	H	N
1	**3aa**	4	69	177-178 benzene	$C_9H_8N_2$ 144.18	Lit.[10] m.p. 178°C.		
2	**3ab**	20	79	87-89 benzene-hexane	$C_{10}H_{10}N_2$ 158.20	75.92 75.90	6.37 6.36	17.71 18.00
3	**3ac**	240	50	95/0.01	$C_{13}H_{16}N_2$ 200.28	77.96 78.01	8.05 8.05	13.99 13.83
4	**3ad**	14	66	89-91 hexane	$C_{15}H_{18}N_2$ 226.32	79.61 79.55	8.02 8.05	12.38 12.49
5	**3ae**	14	53	105-107 benzene	$C_{11}H_{12}N_2O$ 188.23	70.19 70.04	6.43 6.35	14.88 15.00
6	**3af**	20	89	103-105 ethanol	$C_{15}H_{12}N_2$ 220.27	81.79 81.85	5.49 5.56	12.72 12.78
7	**3ag**	14	85	175-177 ethanol	$C_{16}H_{14}N_2$ 234.30	82.02 81.87	6.02 6.10	11.96 11.96
8	**3ah**	336	28	35-36	$C_{11}H_{12}N_2$ 172.23	76.71 76.55	7.02 7.15	16.27 16.23
9	**3ai**	240	20	126-127.5 ethanol	$C_{13}H_{14}N_2O$ 214.17	72.87 72.99	6.59 6.51	13.07 13.12
10	**3bf**	14	77	132-134 methanol	$C_{15}H_{11}ClN_2$ 254.72	70.73 70.66	4.35 4.39	11.00 11.12

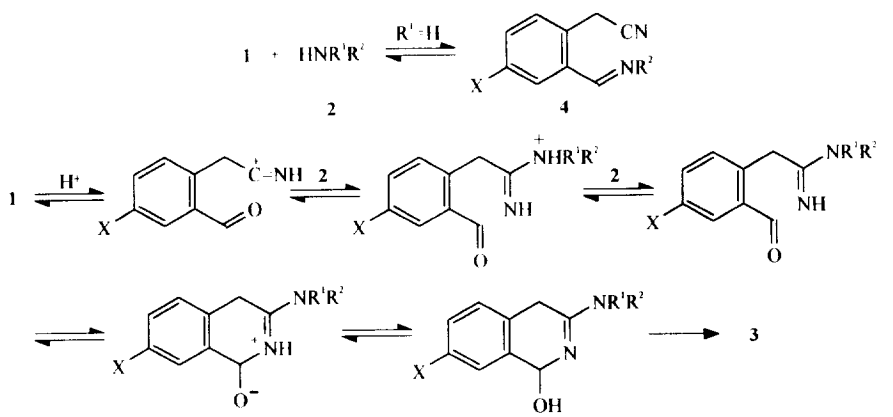


1a 2 4

R	2	4
Me	b	ab
t-Bu	c	ac
Ph	f	af

Scheme 2

Azomethine **4ac** was isolated while the products **4ab** and **4af** could not withstand vacuum distillation and were fully characterized by spectral means. Due to the reversibility of azomethine formation, amines **2** can add to cyano group in **1** affording isoquinolines **3**. The possible routes which accounted for the formation of **3** are visualized on Scheme 3.



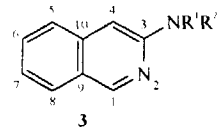
Scheme 3

The catalysis by trifluoroacetic acid may be manifested on either step of this reaction (protonation of cyano group in **1**, shifting of equilibrium **4**⇌**1**+**2** to the right, cyclization, elimination of water, *etc*).

Spectral investigations of the isoquinolines **3** prepared allowed us to ascribe unequivocally their structures[11] (Table 2 and 3). Therefore, the method described above constitutes a simple and general approach to 3-aminoisoquinolines **3**.

EXPERIMENTAL

Melting points (determined with a capillary melting point apparatus) and boiling points are uncorrected. ^1H and ^{13}C NMR spectra were measured on a Varian Gemini 200 spectrometer at 200 MHz and 50 MHz, respectively, as solutions in $CDCl_3$. Gas chromatography (GC) analyses were performed on a Hewlett-Packard 5890 Series II chromatograph, equipped with HP50 capillary column (30 m). Column chromatography was carried out on Macherey Nagel MN-Silica Gel 60 (100-200 mesh) using hexane-ethyl acetate mixture (gradient) as eluent. Aldehydes **1a,b** were prepared according to literature procedures,[6,7] other reagents and solvents were commercial grade.



3

Table 2. ^{1}H NMR spectra of 3-aminoisoquinolines **3**, δ ($CDCl_3$, 200 MHz), *J* (Hz)

Product	R^1	R^2	H-1	H-4	H-5 + H-6	H-7	H-8
3aa	4.32 (br. 2H)		8.86 (s, 1H)	6.73 (s, 1H)	7.43-7.55 (m, 2H)	7.19-7.28 (m, 1H)	7.77 (dd, ^3J=8.2, ^4J=0.82, 1H)
3ab	5.1 (brs, 1H)	2.93 (d, 3H, *J*=4.2)	8.84 (s, 1H)	6.46 (s, 1H)	7.40-7.57 (m, 2H)	7.13-7.22 (m, 1H)	7.73 (dm, ^3J=8.2, 1H)
3ac	4.72 (brs, 1H)	1.47 (s, 9H)	8.83 (s, 1H)	6.66 (s, 1H)	7.40-7.55 (m, 2H)	7.13-7.22 (m, 1H)	7.71 (dd, ^3J=8.2, ^4J=0.82, 1H)
3ad	4.85 (brs, 1H)	1.20-1.80 (m, 8H) 2.05-2.15 (m, 2H) 3.40-3.50 (m, 1H)	8.79 (s, 1H)	6.50 (s, 1H)	7.40-7.55 (m, 2H)	7.12-7.21 (m, 1H)	7.71 (dd, *J*=8.4, *J*=0.92, 1H)
3ae	3.48-3.53 (m, 2H) 3.89-3.94 (m, 2H)		8.76 (s, 1H)	6.67 (s, 1H)	7.45-7.55 (m, 2H)	7.16-7.24 (m, 1H)	7.70 (d, *J*=8.5, 1H)
3af	7.04-7.46 (m, 8H)		8.98 (s, 1H)	together with R	7.47-7.60 (m, 2H)	together with R	7.81 (dd, ^3J=8.2, ^4J=0.76, 1H)
3ag	5.53 (brs, 1H)	4.53 (s, 2H) 7.15-7.50 (m, 8H)	8.80 (s, 1H)	6.53 (s, 1H)	together with R^2	together with R^2	7.75 (d, *J*=8.16, 1H)
3ah	3.16 (s, 6H)		8.92 (s, 1H)	6.61 (s, 1H)	7.40-7.57 (m, 2H)	7.14-7.22 (m, 1H)	7.74 (d, ^3J=8.2, 1H)
3ai	3.52-3.57 (m, 4H) 3.88-3.93 (m, 4H)		8.96 (s, 1H)	6.77 (s, 1H)	7.46-7.62 (m, 2H)	7.20-7.33 (m, 1H)	7.80 (d, ^3J=8.2, 1H)
3bf	7.05-7.5 (m, 9H)		8.86 (s, 1H)	together with R	together with R	-	7.76 (m, 1H)

Table 3. ^{13}C NMR spectra of 3-aminoisoquinolines **3**, δ ($CDCl_3$, 50 MHz)

Product	R	C-1	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
3aa	-	151.26	156.35	97.05	124.07	129.93	121.57	127.50	122.44	138.42
3ab	29.65	151.59	156.47	94.68	124.61	130.17	122.10	127.67	123.25	138.93
3ac	29.35; 50.44	151.57	154.39	98.18	124.72	130.09	122.22	127.59	123.07	138.64
3ad	24.83; 25.81 32.96; 50.85	151.83	154.66	95.63	124.56	130.22	122.04	127.74	123.22	139.03
3ae	45.46; 61.51	151.32	155.32	96.92	124.68	130.52	122.63	127.80	123.40	138.96
3af	119.94; 123.48 129.35; 141.01	151.90	152.00	98.88	125.11	130.50	122.50	127.65	124.39	138.52
3ag	47.10; 127.21 127.94; 128.68 139.31	150.36	154.53	96.73	124.91	130.98	122.93	127.31	123.22	138.40
3ah	38.54	150.95	156.62	96.68	124.83	130.02	122.13	127.62	122.42	138.90
3ai	46.66; 66.83	151.22	156.77	99.02	125.30	130.34	123.54	127.60	123.90	138.61
3bf	120.27; 122.93 129.44; 140.59	150.90	152.41	98.52	126.24	131.46	128.62	126.77	124.56	136.82

3-Aminoisoquinoline (3aa). - To methanol (10 ml) which has been saturated at 0°C with ammonia, aldehyde **1a** (0.30 g, 2 mmol) then trifluoroacetic acid (3-5 drops) were added, and the mixture was refluxed for 4h while a slow stream of ammonia was passed. Next, methanol was evaporated, the residue was dissolved in benzene (5 ml), washed with water, dried (Na_2SO_4), concentrated, and crystallized to give **3aa** (Table 1, Entry 1).

3-Aminoisoquinolines 3ab, 3ad-ag and 3bf. - To the solution of aldehyde **1a** (0.30 g, 2mmol) or **1b** (0.36 g, 2 mmol) in ethanol (5 ml) the corresponding amine (2.5 mmol, Table 1) followed by trifluoroacetic acid (3-5 drops) were added, and the mixture was refluxed for the time indicated in Table 1 (in the case of the reaction with **2b**, 5 ml of its 33% solution in ethanol was used, and the mixture was kept at 40°C). The mixture was cooled to room temperature, the solid product was filtered off and crystallized (Table 1, Entries 6, 7) or ethanol was removed under reduced pressure and the residue was crystallized (Table 1, Entries 2, 4, 5, 10).

3-Aminoisoquinolines 3ac, 3ah and 3ai. - The solution of aldehyde **1a** (0.30 g, 2mmol) in ethanol (5 ml), trifluoroacetic acid (5 drops) and amine (1 ml of **2c,i** or 2 ml of **2h** which was cooled to ca 0°C) was refluxed or kept at 40°C in the case of the reaction with **2h** for the time indicated in the Table 1. The solvent was evaporated, the residue was dissolved in benzene (10 ml) and extracted with 10% hydrochloric acid (3×10ml). Combined aqueous acidic phases were extracted with benzene (10 ml), alkalized with solid sodium hydrogen carbonate, extracted with hexane (3×10ml), the organic extracts were dried (Na_2SO_4), and the solvent was evaporated. The products were isolated by distillation (**3ac**) or by column chromatography (**3ah**, **3ai**) and crystallized (**3ai**) (Table 1, Entries 3, 8, 9).

Azomethines 4ab and 4af. - Aldehyde **1a** (0.30 g, 2 mmol) was dissolved in 33% ethanolic solution of **2b** (5 ml) or in solution of **2f** (0.11 g, 2.1 mmol) in ethanol (5 ml). The mixture was stirred at room temperature for 4 h, the solvent was evaporated, the residue was dissolved in benzene (10 ml), washed with water and dried (Na_2SO_4). The solvent was evaporated to give crude azomethine. Attempted vacuum distillation of these azomethines resulted in their decomposition.

2-Cyanomethylbenzylidenemethylamine (**4ab**): oil, 0.32 g, purity (GC) 89%, sample contains 9% of **2ab**; ^{1}H NMR, δ 3.49 (d, *J*=1.6 Hz, 3H), 4.20 (2H, s), 7.3 - 7.5 (4H, m). 8.34 (q, *J*=1.6 Hz, 1H).

2-Cyanomethylbenzylideneaniline (**4af**): oil, 0.44 g, purity (GC) 96%, sample contains 2% of **1a**; ^{1}H NMR, δ 4.40 (s, 2H), 7.2 - 7.75 (m, 9H), 8.57 (s, 1H).

2-Cyanomethylbenzylidene-t-butylamine (4ac). - Aldehyde **1a** (0.30 g, 2 mmol), t-butylamine (0.70 g, *ca* 1 ml, 9.5 mmol) and trifluoroacetic acid (1 drop) were dissolved in ethanol (5 ml), the mixture was kept at room temperature for 24 h and worked up as described above. Pure azomethine was obtained by vacuum distillation, b.p. 100°C / 0.01 Torr, 0.36 g (90%), purity (GC) 99%; ^{1}H NMR, δ 1.31 (s, 9H), 4.32 (s, 2H), 7.3 - 7.55 (m, 4H), 8.37 (s, 1H). Anal. Calcd. for $C_{13}H_{16}N_2$ (200.28): C, 77.96; H, 8.05; N, 13.99; found: C, 77.93; H, 8.08; N, 14.09%.

ACKNOWLEDGMENT

Financial support by the State Committee for Scientific Research, Warsaw, Poland (Grant No. 2 2616 92 03) is gratefully acknowledged.

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(*Received in UK* 20 *July* 1995; *revised* 19 *September* 1995; *accepted* 21 *September* 1995)