Convenient Synthesis of *N*-Substituted 1-Alkyl and 1-Aryl-3-Aminoisoquinolines

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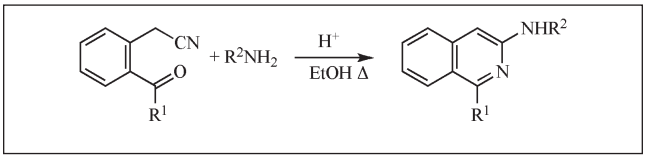

Cyclocondensation of 2-acylphenylacetonitriles **1** with amines affords 1-substituted 3-aminoisoquinolines **2** in good yields.

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For many years 3-aminoisoquinolines have been an interesting structural class of compounds, which have found many uses in the fields of medicinal and synthetic chemistry.

Aminoisoquinoline units have formed an integral part of many biologically active compounds. For example, 3-amino-4-arylisoquinolines, 3-amino-4-(*p*-aminophenyl)-isoquinoline and 3-amino-4-(*p*-acetamidophenyl)isoquinoline present central nervous system activity, characterized by general CNS depression and anticonvulsant activity [1,2].

Moreover, 3-amino, 5-amino and 8-aminoisoquinolines also have been studied as antimalarials in the last years [3-4]. Recently 2-aminoisoquinolines were investigated as benzamidine isoster in the design and synthesis of orally active thrombin inhibitors [5-6].

There are a variety of methodologies available that may be used to give access to a series of differentially substituted aminoisoquinolines. Numerous preparations are summarized in the paper by Suzuki and Abe [7]. Nevertheless, many of these methods suffer from difficult access to starting material, laborious multi step procedure and drastic reaction conditions. In particular, the reported methods for the preparations of 1-substituted-3-aminoisoquinolines also have limitations [8].

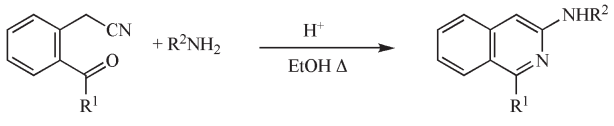
Preparation of 1-halo 3-aminoisoquinolines and their 4-alkylated derivatives were reported in recent years *via* the Johnson and Nasutavicus procedure from 2-cyanobenzylcyanide and hydrogen halides [9-10]. More recently, the reaction of dinitrile with a variety of lithium amides, alkyllithiums and phenyllithium afford the corresponding 1-substituted amino, 1-alkyl and 1-phenyl derivatives of 3-aminoisoquinolines [11]. This methodology was applied for the synthesis of 1,4-disubstituted-3-aminoisoquinolines using α-substituted derivatives in good yields [12].

In a previous work the condensation of 2-cyanomethylbenzaldehydes with ammonia, primary or secondary amines in the presence of a catalytic amount of trifluoroacetic acid to afford 3-aminoisoquinolines in good yields was described [13].

Bearing in mind these results, we have studied the analogous cyclocondensation of 2-acylphenylacetonitriles (**1**) with amines to give 1-substituted 3-aminoisoquinolines (**2**) (Scheme1).

The starting 2-acylphenylacetonitriles (**1**) are versatile intermediates in organic synthesis. We have developed an efficient route *via* reaction of 2-cyanomethylbenzoylchloride with Grignard reagents in the presence of cuprous iodide at –5 ºC [14]. Recently we have used **1** in the preparations of 2*H*-isoquinolin-3-ones through intramolecular cyclization under strongly acidic conditions with excellent yields [15].

Scheme 1



1 **2**

R^1= CH_2CH_3; *i*-$CH(CH_3)_2$; $CH_2C_6H_5$; C_6H_5; *4*-ClC_6H_4; *4*-$CH_3C_6H_4$
R^2= CH_3; C_6H_5

The reaction was performed by heating an ethanolic solution of **1** (1 mmol) and the amine (2.0-2.5 mmol) with catalytic amount of trifluoroacetic acid. Reaction was carried out for several days (up to 5 days). Different reaction temperatures were necessary depending on the amine employed. Other acid catalysts examined were Amberlyst 15 resins and methanesulfonic acid.

The products of these reactions were isolated by evaporation of the solvent and purified by column chromatrography on silica gel (70-230 mesh) using hexane/ethyl acetate and cristallized from hexane or ethanol. The yields and reaction conditions using methylamine and aniline are shown in Table 1, and The products are identified by ^1H and ^{13}C NMR and elemental analysis.

Table 1
3-Aminoisoquinolines (**2**)

Compound	R^1	R^2	Temp (ºC)	Time (h)	Yield (%)
2a	CH_2CH_3	CH_3	45	96	92
2b	CH_2CH_3	Ph	80	72	86
2c	i-$CH(CH_3)$	CH_3	45	120	48
2d	i-$CH(CH_3)$	Ph	80	96	52
2e	$CH_2C_6H_5$	CH_3	45	48	67
2f	$CH_2C_6H_5$	Ph	80	24	71
2g	C_6H_5	CH_3	45	72	70
2h	C_6H_5	Ph	80	72	76
2i	4-ClC_6H_4	CH_3	45	72	70
2j	4-ClC_6H_4	Ph	80	48	71
2k	4-$CH_3C_6H_4$	CH_3	45	96	68
2l	4-$CH_3C_6H_4$	Ph	80	72	65

Good yields were obtained with trifluoroacetic acid. When Amberlyst 15 resins or methanesulfonic acid was added in place of trifluoroacetic acid product **2** was not formed. In these cases, the 2*H*-isoquinolin-3-one was formed with traces of the isoquinoline product.

In conclusion, we have developed a new, simple and effective methodology for the conversion of 2-acylphenylacetonitriles (**1**) to N-substituted 1-alkyl and 1-aryl-3-aminoisoquinolines (**2**) in a single reaction step, with good yields.

EXPERIMENTAL

Thin layer chromatography was performed on Merck precoated silica gel 60 F_{254} plates and column chromatography was carried out using silica gel (Merck 60, 230-400 mesh). All reagents were of commercial quality or were purified before use. Melting points were determined with a Büchi apparatus. NMR spectra were recorded on a Brucker AC 250 spectrometer and were reported in ppm downfield from TMS employed as an internal standard (δ). Elemental analysis was carried out at the Institut für Organische Chemie of the Stuttgart University.

The 2-acylphenylacetonitriles (**1a-f**) were prepared applying a known method from 2-cyanomethylbenzoylchloride by reaction with Grignard reagents in the presence of cuprous iodide at –5 ºC [14].

Cyclocondensation of 2-**A**cylphenylacetonitriles (1) with **M**ethylamine**.**

General Procedure.

To a 33% solution of methylamine in ethanol (3 mL, 2.5 mmol), 2-acylphenylacetonitrile (**1**) (1 mmol) and trifluoroacetic acid was added (1-2 drops). The mixture was stirred at 45 ºC for the time indicated in Table 1. The progress of the reaction was monitored by thin layer chromatography. When the reaction was complete, the mixture was concentrated *in vacuo*, and the crude product was isolated by column chromatography using a mixture of hexane/ethyl acetate (9:1) as the eluent and crystallized.

Cyclocondensation of 2-Acylphenylacetonitriles (1) with Aniline**.**

General Procedure**.**

To a solution of aniline (0.186 g, 2 mmol, 0.18 mL) and 2-acylphenylacetonitrile (**1**) (1 mmol) in ethanol (3 mL) trifluoroacetic acid was added (1-2 drops). The mixture was stirred for time and at the temperature indicated in Table 1. The progress of the reaction was monitored by thin layer chromatography. When the reaction was complete, the solvent was concentrated *in vacuo*, and the crude product was isolated by column chromatography using a mixture of hexane/ethyl acetate (9:1) as the eluent and crystallized.

1-Ethyl-3-methylaminoisoquinoline (**2a**).

This compound was obtained as yellow prisms (ethanol), mp 97-98 ºC; ^{1}H nmr: δ 1.48(t, 3H, J= 7.6 , CH_2CH_3); 3.28 (q, 2H, J= 7.6, CH_2-CH_3); 6.32 (s, 1H, H-4); 7.21 (ddd, 1H, J_{7-6}= 7.1, J_{7-8}= 7.9, J_{7-5}= 1.0, H-7); 7.41 (ddd, 1H, J_{6-5}= 8.0, J_{6-7}= 7.1, J_{6-8}= 0.9 , H-6); 7.65 (d, 1H, J_{5-6}= 8.0, H-5), 8.01 (d, 1H, J_{7-8}= 7.9, H-8); ^{13}C nmr (62.9 MHz): δ 13.5(CH_2-CH_3); 28.2 (-CH_2-CH_3); 98.6 (C-4); 122.7 (C-8a); 123.1 (C-7); 124.1 (C-5); 126.2 (C-8); 130.3 (C-6); 143.0 (C-4a); 155.8 (C-1); 164.7 (C-3).

Anal. Calcd. for $C_{12}H_{14}N_2$ (186.12): C, 77.38; H, 7.58; N, 15.04. Found: C, 77.01; H, 7.71; N, 15.28.

1-Ethyl-3-phenylaminoisoquinoline (**2b**).

This compound was obtained as yellow prisms (ethanol), mp: 77-78 ºC; ^{1}H nmr: δ 1.45(t, 3H, J= 7.5 , CH_2CH_3); 3.25 (q, 2H, J= 7.5, CH_2-CH_3); 6.58 (H-4); 6.98-7.08 (m, 2H, NH, H-7); 7.23-7.38 (m, 5H, Ph); 7.40- 7.58 (m, 2H, H-5, H-6), 7.99 (dd, J_{7-8}= 8.6, J_{8-6}= 1.5, H-8); ^{13}C nmr (62.9 MHz): δ 13.3(CH_2-CH_3); 28.1 (-CH_2-CH_3); 97.3 (C-4); 119.6 (C-2', C-6'); 122.1 (C-8a); 122.4 (C-7); 123.2 (C-5); 125.2 (C-8); 126.0 (C-4'), 129.2 (C-3', C-5'); 129.9 (C-6); 139.0 (C-1'); 141.2 (C-4a); 152.3 (C-1); 163.5 (C-3).

Anal. Calcd. for $C_{17}H_{16}N_2$ (248.13): C, 82.22; H, 6.49; N, 11.28. Found: C, 82.18; H, 6.39; N, 11.42.

1-(*i*-Propyl)-3-methylaminoisoquinoline (**2c**).

This compound was obtained as yellow prisms (ethanol) mp: 63-64 ºC; ^{1}H nmr: δ 1.36 (d, 6H J= 6.8 , CH-(CH_3)$_2$); 2.94 (s, 3H, N-CH_3); 3.81 (sept., 1 H J= 6.8 , CH-(CH_3)$_2$); 4.60 (brs, 1H, NH); 6.33 (s, 1H, H-4); 7.17 (ddd, 1 H, J_{7-6}= 7.0, J_{7-8}= 8.0, J_{7-5}= 0.9, H-7); 7.43(td, 1H, J_{6-7}= 7.0, J_{6-8}= 0.9, H-6), 7.55(d, 1H, J_{5-6}= 8.0, H-5); 7.99 (d, 1H, J_{8-7} = 8.0, H-8); ^{13}C nmr (62.9 MHz) δ 22.0 ((CH_3)$_2$-CH); 29.7 (N-CH_3); 30.5 (-CH-(CH_3)$_2$);

93.0 (C-4); 120.9 (C-8a); 121.8 (C-7); 124.9 (C-5); 125.7 (C-8); 129.4 (C-6); 139.7 (C-4a); 155.4 (C-1); 165.8 (C-3).

Anal. Calcd. for $C_{13}H_{16}N_2$ (200.27): C, 77.96; H, 8.05; N, 13.99. Found: C, 77.79; H, 8.16; N, 14.05.

1-(*i*-Propyl)-3-phenylaminoisoquinoline (**2d**).

This compound was obtained as yellow prisms (hexane) mp: 81-82 ºC ; ^{1}H nmr: δ 1.41 (d, 6H J= 6.8 , CH-(C*H*$_3$)$_2$); 3.85 (sept., 1 H J= 6.8 , C*H*-(CH$_3$)$_2$); 6.57 (s, 1H, H-4); 6.69-7.05 (m, 2 H, NH and H-7); 7.24-7.44 (m, 2H, H-2', H-6'); 7.47-7.49 (m, 4H, H-6, H-3', H-4', H-5'); 7.54 (t, 1H, J_{5-6}= 8.0, H-5); 8.05 (d, 1H, J_{8-7} = 8.5, H-8); ^{13}C nmr (62.9 MHz) δ 22.1 ((*C*H$_3$)$_2$-CH); 30.7 (-*C*H-(CH$_3$)$_2$); 97.4 (C-4); 119.3 (C-2', C-6') 121.9 (C-8a); 123.1 (C-7); 124.8 (C-5); 126.2 (C-8); 129.2 (C-3', C-4', C-5'); 129.6 (C-6); 139.2 (C-4a); 141.2 (C-1'); 150.4 (C-1); 166.2 (C-3).

Anal. Calcd. for $C_{18}H_{18}N_2$ (262.14): C, 82.41; H, 6.92; N, 10.68. Found: C, 82.38; H, 6.76; N, 10.86.

1-Benzyl-3-methylaminoisoquinoline (**2e**).

This compound was obtained as yellow needles (ethanol), mp: 115-117 ºC; ^{1}H nmr: δ 2.92 (d, 3H, J= 5.3, NH-CH$_3$); 4.49 (s, 2H, C*H*$_2$Ph); 4.73 (brs, 1H, NH); 6.38 (s, 1H, H-4); 7.06-7.39 (m, 6H , H-7, CH$_2$Ph); 7.40-7.43 (m, 1H, H-6); 7.54 (d, 1H, J_{7-8}= 8.5, H-5); 7.90 (dd, 1H, J $_{7-8}$= 8.5, J $_{6-8}$= 0.7, H-8) ^{13}C nmr (62.9 MHz) δ 29.74 (NH-CH$_3$); 41.51 (-*C*H$_2$-Ph); 93.95 (C-4); 121.85 (C-8a); 122.2 (C-7); 125.6 (C-5); 126.0 (C-8); 128.3 (C-2', C-6'); 128.5 (C-3', C-4', C-5'); 129.7 (C-6) ; 139.4 (C-1'); 139.9 (C-4a); 155.5 (C-1); 159.4 (C-3).

Anal. Calcd. for $C_{17}H_{16}N_2$ (248.32): C, 82.23; H, 6.49; N, 11.28. Found: C, 82.20; H, 6.51; N, 11.30.

1-Benzyl-3-phenylaminoisoquinoline (**2f**).

This compound was obtained as yellow needles (ethanol), mp: 97-98 ºC; ^{1}H nmr: δ 4.55 (s, 2H, C*H*$_2$Ph); 6.63 (s, 1H, H-4); 7.00-7.04 (m, 1H , H-7); 7.15-7.34 (m, 11 H, NH, 2 Ph); 7.44 (dd, 1H, J_{6-5}= 8.2 , J_{7-5} = 0.8, H-6); 7.52 (d, 1H, J_{6-5}= 8.2 , H-5) ; 7.97 (d, 1H, J $_{7-8}$= 8.5, H-8) ^{13}C nmr (62.9 MHz) δ 41.5 (-*C*H$_2$-Ph); 98.2 (C-4); 119.5 (C-2", C-6", NH-Ph); 122.2 (C-7); 122.9 (C-8a); 123.5 (C-5); 125.8 (C-4'); 126.0 (C-8); 126.2 (C-4", NH-Ph); 128.4 (C-2', C-6'); 128.7 (C-3', C-5'); 129.3 (C-3", C-5", NH-Ph); 130.0 (C-6) ; 139.3 (C-1'); 139.4 (C-1"); 141.1 (C-4a); 150.6 (C-1); 159.9 (C-3).

Anal. Calcd. for $C_{22}H_{18}N_2$ (310.39): C, 85.13; H, 5.85; N, 9.03. Found: C, 84.94; H, 6.08; N, 8.99.

1-Phenyl-3-methylaminoisoquinoline (**2g**).

This compound was obtained as yellow prisms (ethanol), mp 142-144 ºC; ^{1}H nmr: δ 2.88 (d, 3H, J= 5.1, NH-CH$_3$); 5.01 (brs, 1H, NH) ; 6.48 (s, 1H, H-4); 7.10 (ddd, 1H, J $_{7-8}$= 8.3, J_{7-6}= 7.08, J_{7-5}= 0.98, H-7); 7.41-7.53 (m, 4H, H-6, H-2', H-4', H-6'); 7.59-7.66 (m, 3H, H-5, H-3', H-5'); 7.81 (dd, 1H, J_{8-7}= 8.3, J_{8-6}= 0.7, H-8); ^{13}C nmr (62.9 MHz) δ 29.8 (NH-CH$_3$); 94.5 (C-4); 121.5 (C-8a); 122.2 (C-7); 125.3 (C-5); 127.8 (C-8); 128.2 (C-2', C-6'); 128.4 (C-4'); 129.7 (C-3', C-5'); 129.9 (C-6); 139.6 (C-1'); 140.2 (C-4a); 155.6 (C-1) ; 160.1 (C-3).

Anal. Calcd. for $C_{16}H_{14}N_2$ (234.29): C, 82.02; H, 6.02; N, 11.96. Found: C, 81.94; H, 6.28; N, 11.78.

1-Phenyl-3-phenylaminoisoquinoline (**2h**).

This compound was obtained as yellow prisms (ethanol), mp: 89-90 ºC; ^{1}H nmr: δ 6.70 (s, 1H, H-4); 6.09-7.44 (m, 12 H , H-7, NH, 2 Ph); 7.49 (d, 1H, J_{6-5}= 8.1, H-6); 7.59 (d, 1H, J_{6-5}= 8.1 , H-5) ; 7.78 (dd, 1H, J_{8-7}= 8.5, J_{8-6}= 0.7, H-8); ^{13}C nmr (62.9 MHz) δ 98.3 (C-4); 119.7 (C-2", C-6"); 122.3 (C-8a); 123.3 (C-7); 125.5 (C-5); 127.6 (C-4"); 128.2 (C-2', C-6'); 128.5 (C-8); 129.3 (C-3", C-5"); 129.7(C-4'); 130.1 (C-3', C-5'); 130.0 (C-6); 139.2 (C-1"); 139.6 (C-1'); 140.9 (C-4a); 150-8 (C-1) ; 160.3 (C-3).

Anal. Calcd. for $C_{21}H_{16}N_2$ (296.13): C, 85.11; H, 5.44; N, 9.45. Found: C, 85.31; H, 5.55; N, 9.14.

1-(*p*-Chlorophenyl)-3-methylaminoisoquinoline (**2i**).

This compound was obtained as yellow prisms (ethanol), mp: 152-154 ºC; ^{1}H nmr: δ 2.97 (s, 3H, NH-CH$_3$); 4.83 (brs, 1H, NH); 6.54 (s, 1H, H-4); 7.15 (ddd, 1H, J $_{7-8}$= 8.5, J_{7-6}= 6.8, J_{7-5}= 1.2, H-7); 7.44-7.53 (m, 3H, H-6, H-2', H-6'); 7.57-7.70 (m, 3H, H-5, H-3', H-5'); 7.80 (dd, 1H, J_{8-7}= 8.5, J_{8-6}= 0.9, H-8); ^{13}C nmr (62.9 MHz) δ 29.7 (NH-CH$_3$); 94.8 (C-4); 121.2 (C-8a); 122.4 (C-7); 125.3 (C-5); 127.2 (C-8); 128.3 (C-2', C-6'); 131.0 (C-3', C-5'); 131.1 (C-6); 134.4 (C-4'); 137.9 (C-1'); 140.2 (C-4a); 155.4 (C-1); 158.6 (C-3).

Anal. Calcd. for $C_{16}H_{13}ClN_2$ (268.74): C, 71.51; H, 4.88; Cl, 13.19 N, 10.42. Found: C, 71.56; H, 4.91; Cl, 13.29; N, 10.24.

1-(*p*-Chlorophenyl)-3-phenylaminoisoquinoline (**2j**).

This compound was obtained as yellow prisms (hexane), mp: 51-52 ºC; ^{1}H nmr: δ 6.70 (s, 1H, H-4); 7.07 (ddd, 1H, J_{6-7} = 7.6, J_{7-8} = 8.5, J_{7-5}= 0.9, H-7); 7.21-7.29 (m, 2H, NH, H-4", NHPh); 7.33-7.40 (m, 4H, H-2', H-6', H-2", H-6"); 7.50-7.56 (m, 3H, H-6, H-3", H-5"); 7.61-7.68 (m, 3H, H-5, H-3', H-5'); 7.85 (d, 1H, J_{8-7}= 8.5, H-8); ^{13}C nmr (62.9 MHz) δ 98.8 (C-4); 119.9 (C-2", C-6", NHPh); 122.5 (C-8a); 122.4 (C-7); 123.8 (C-5); 125.8 (C-8); 127.2 (C-4"); 128.6 (C-2', C-6'); 129.4 (C-3", C-5"); 130.3 (C-6); 131.1 (C-3', C-5'); 134.4 (C-4'); 137.9 (C-1'); 138.2 (C-1"); 140.0 (C-4a); 154.7 (C-1); 158.9 (C-3).

Anal. Calcd. for $C_{21}H_{15}ClN_2$ (330.81): C, 76.24; H, 4.57; Cl, 10.72 N, 8.47. Found: C, 76.04; H, 4.60; Cl, 10.97; N, 8.39.

1-(*p*-Methylphenyl)-3-methylaminoisoquinoline (**2k**).

This compound was obtained as yellow prisms (ethanol), mp: 140.5-141 ºC; ^{1}H nmr: δ 2.42 (s, 3H, Ph-C*H*$_3$); 2.94 (s, 3H, NH-CH$_3$); 4.83 (brs, 1H, NH); 6.48 (s, 1H, H-4); 7.09 (ddd, 1H, J $_{7-8}$= 8.1, J_{7-6}= 6.7, J_{7-5}= 1.2, H-7); 7.23-7.64 (m, 5H, H-6, H-2', H-3', H-5', H-6'); 7.68 (d, 1H, J = 6.9, H-5); 7.85 (dd, 1 H, J_{7-8}= 8.1, J_{6-8}= 0.9, H-8); ^{13}C nmr (62.9 MHz) δ 21.6 (CH$_3$); 29.3 (NH-CH$_3$); 94.4 (C-4); 121.4 (C-8a); 122.0 (C-7); 125.1 (C-5) ; 127.6 (C-8); 129.8 (C-2', C-6'); 130.4 (C-3', C-5'); 131.4 (C-4'); 136.2 (C-6); 138.1 (C-1'); 141.0 (C-4a); 155.5 (C-1); 160.0 (C-3).

Anal. Calcd. for $C_{17}H_{16}N_2$ (248.13): C, 82.22; H, 6.49; N, 11.28. Found: C, 82.20; H, 6.51; N, 11.30.

1-(*p*-Methylphenyl)-3-phenylaminoisoquinoline (**2l**).

This compound was obtained as yellow prisms (hexane), mp: 52-54 ºC; ^{1}H nmr: δ 2.44 (s, 3H, Ph-C*H*$_3$); 6.84 (s, 1H, H-4); 7.05 (ddd, 1H, J_{7-8}= 8.5, J_{7-6} = 6.7, J_{7-5}= 1.1, H-7); 7.14-7.24 (m, 2H, NH, H-4", NHPh); 7.26-7.40 (m, 4H, H-2', H-6', H-2", H-6"); 7.48 (ddd, 1H, J_{6-7} = 6.7, J_{6-5} = 7.9, J_{6-8}= 1.0 H-6); 7.60 (d, 1H, J_{5-6}= 7.9, H-5); 7.92 (d, 1H, J_{8-7}= 8.5, H-8); ^{13}C nmr (62.9 MHz) δ 21.0 (CH$_3$); 98.2 (C-4); 119.6 (C-2", C-6", NHPh); 122.2 (C-8a); 122.4 (C-7); 123.3 (C-5); 125.6 (C-4"); 127.6 (C-8); 128.3 (C-2', C-6'); 129.3 (C-3", C-5"); 129.7 (C-3', C-5'); 130.1 (C-4'); 136.3 (C-6); 138.4 (C-1'); 139.6 (C-1"); 141.0 (C-4a); 150.7 (C-1); 160.4 (C-3).

Anal. Calcd. for $C_{22}H_{18}N_2$ (310.14): C, 85.13; H, 5.85; N, 9.03. Found: C, 84.94; H, 6.00; N, 9.06.

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