Use of the *N*-Formyliminium Ion Cyclization for the Synthesis of 3-Aryl-1,2,3,4-tetrahydroisoquinolines

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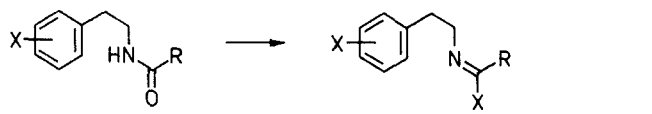
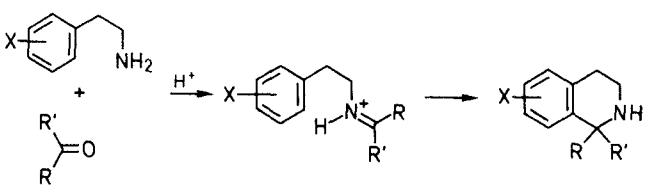
Received 6 April 1992; revised 3 June 1992

Classical cyclization procedures for the synthesis of 3-arylisoquinolines are fraught with complications. Here, we present the application of an *N*-acyliminium cyclization to such target molecules. *N*-(1,2-diarylethyl)formamides **1**, **4a–4d**, and **4f** were cyclized to the respective tetrahydroisoquinolines by using paraformaldehyde under mildly acidic conditions. Yields ranged from good to excellent. Cyclization of **4e** was unsuccessful possibly because the presence of the 4-methoxyphenyl group leads to ionization of the formamido group.

Over the years, the Bischler–Napieralski (B–N) and Pictet–Spengler (P–S) reactions have been extensively employed for the synthesis of myriad isoquinoline derivatives.[1–3] Both procedures involve cyclization of a 2-arylethylamine unit by installation of C-1 of the ultimate isoquinoline nucleus (Schemes 1 and 2). The P–S process (Scheme 2) uses an iminium species as an electrophilic intermediate to furnish a 1,2,3,4-tetrahydroisoquinoline, and is limited to ring closures of relatively nucleophilic arenes, such as methoxyphenyl; while the B–N process (Scheme 1) uses an "activated" amide to furnish a 3,4-dihydroisoquinoline, and works for less nucleophilic arenes, such as phenyl.

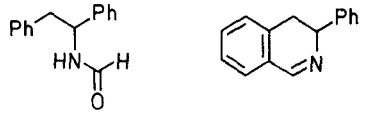


Scheme 1



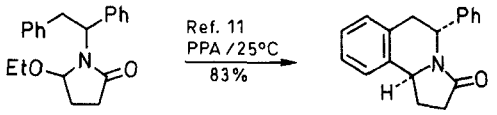
Scheme 2

In the case of electron-rich arene nucleophiles, these synthetic methods can be very successful under relatively mild acidic conditions. However, more rigorous conditions, such as powerful acids and temperatures in the range of 80–120 °C, are often required to effect cyclization with less reactive arene groups. In the B–N reaction, for example, the severe conditions make it difficult to synthesize 3-arylisoquinoline systems because of competing elimination reactions, which result in the formation of stilbene derivatives.[4,5] The failure of 1,2-diarylethylamides to cyclize cleanly to 3-aryl-3,4-dihydroisoquinolines has been rationalized in terms of a retro-Ritter reaction in an intermediate nitrilium species.[6] In fact, we confirmed this unfelicitous situation in our own failed attempts to convert formamide **1** to dihydroisoquinoline **2** according to conventional protocols; (*E*)-stilbene was the only isolable organic product.



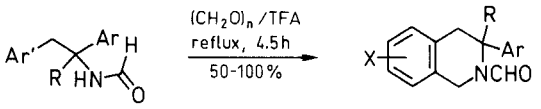
1 **2**

To solve this problem in a general way, we envisioned exploitation of the widely applicable *N*-acyliminium ion cyclization.[7–10] Encouragement came from the fact that, in one instance, we had already used *N*-acyliminium chemistry to perform a sensitive cyclization of this type in high yield, as depicted in Scheme 3.[11] Examination of the literature turned up a promising operational procedure. Lukanov et al.[12] reported a convenient cyclization of *N*-formyliminium ions for conversion of 2-arylethylamines to tetrahydroisoquinolines; however, they did not investigate the procedure with 1,2-diarylethylamines. We now describe the successful application of their paraformaldehyde/trifluoroacetic acid (TFA) cyclization method to the synthesis of 3-aryl-1,2,3,4-tetrahydroisoquinolines.



Scheme 3

We first tested the *N*-formyliminium procedure of Lukanov et al.[12a] in the cyclization of formamide **1**. Reaction of **1** with paraformaldehyde in TFA gave desired product **3** in 71 % purified yield (Table; Scheme 4). Besides being high-yielding, this procedure is extremely convenient to perform and to work up. Product **3** served well as a conduit to useful isoquinoline compounds. The formamide group was readily hydrolyzed with ethanolic potassium hydroxide to give 3-phenyl-1,2,3,4-tetrahydroisoquinoline, which could then be oxidized regiospecifically with manganese(IV) oxide to give imine **2**.[13,14] This cyclization procedure was also applied to the conversion of (*R*)-**1** to (*R*)-**3**, in which the enantiomeric integrity was maintained.



1, 4 a-f 3, 5 a-d, f

4,5	Ar	Ar'	R	4,5	Ar	Ar'	R
a	Ph	Ph	Me	d	4-BrC_6H_4	Ph	H
b	4-FC_6H_4	3-FC_6H_4	H	e	4-$MeOC_6H_4$	Ph	H
c	3-$F_3CC_6H_4$	Ph	H	f	3-O_2N-4-$MeOC_6H_3$	Ph	H

3, 5a, c–f: X = H, **5b:** X = 6-F, **5b′:** X = 8-F

Scheme 4

Table. Synthesis of 3-Aryl-2-formyl-1,2,3,4-tetrahydroisoquinolines

Starting Material	Product	Acid Used[a]	Yield (%)
1	**3**	TFA	71[b]
4a	**5a**	TFA/AcOH (1:4)	50[b]
4b	**5b/5b′**[c]	TFA	100
4c	**5c**	TFA	98
4d	**5d**	TFA	70
4e	**5e**	TFA or TFA/AcOH (1:4)	0
4f	**5f**	TFA	70

[a] TFA = trifluoroacetic acid. [b] Analytically pure product. [c] Isomer ratio: **5b/5b′** = 96:4.

Given this successful chemistry, we investigated the *N*-formyliminium cyclization for some other 3-arylisoquinoline derivatives, **5a–5f**, the results for which are shown in the Table. Cyclization of **4a** failed in TFA, as elimination became a problem; however, this was rectified by use of the weaker acid medium of TFA/acetic acid (AcOH) (1:4). The cyclization of **4e** did not work in TFA, as decomposition occurred; the reaction was also unsuccessful in TFA/AcOH (1:4) or AcOH. This problem may derive from the now-competitive E1 process because of the electron-rich *p*-anisyl ring. Indeed, cyclization of **4f**, which has a deactivated *p*-anisyl ring, did work quite well.

The *N*-formyliminium cyclization procedure provides a simple, convenient, high-yield synthesis for 3-arylisoquinoline derivatives. Our method can be viewed as being complementary to the one recently described by Larsen et al.[5]

TFA (99%) and 1,2-diphenylethylamine were obtained from Aldrich Chemical Co. Unless otherwise noted, 1,2-diarylethylamines were prepared by the method of Hart et al.[15] All melting points are corrected by calibration to a set of reference standards and were determined on a Thomas-Hoover apparatus. ^1H NMR spectra were obtained on a Bruker AFC 300 WB (300 MHz) spectrometer with TMS as an internal reference. Chemical-ionization mass spectra (CI-MS) were recorded on a Finnigan 3300 system with methane as reagent gas. Fast-atom-bombardment mass spectra (FAB-MS) were recorded on a VG 7070E high resolution mass spectrometer by using an Ar beam at 7 kV and 2 mA of current in a thioglycerol matrix. Where necessary, analytical samples were obtained by preparative TLC on tapered silica gel plates (300–1700 μm).

***N*-(1,2-Diphenylethyl)formamide (1);[4a,16] Typical Formylation:**
This is the general method used to prepare the various formamides employed as starting materials. 1,2-Diphenylethylamine (10.15 g, 0.05 mol) and ethyl formate (40 mL) were heated at reflux with stirring for 24 h, then allowed to cool to r.t. Hexanes (10 mL) were added to the solid mass, which was further cooled to 0°C. The solids were filtered, rinsed with dry Et_2O and dried in air to give 10.6 g (94%) of bright, colorless, fine needles, mp 125–128°C (Lit.[16] mp 123–124°C).

CI-MS (CH_4): m/z = 226 MH^+.

^1H NMR ($CDCl_3$): (3.7:1 mixture of rotamers): δ = 2.96–3.21 (m, 2H), 4.69–4.76 (m, 0.27H), 5.33, 5.38 (dd, J = 7.4 Hz, 0.73H), 5.84 (br s, 0.73H), 5.99 (br s, 0.27H), 7.05–7.39 (m, 10H), 7.85 (d, J = 11.8 Hz, 0.27H), 8.14 (s, 0.73H).

N-(1-Methyl-1,2-diphenylethyl)formamide **(4a)**:[17]
mp 106–107°C (Lit.[17] mp 108.5–110.5°C).

CI-MS (CH_4): m/z = 240 MH^+.

^1H NMR ($CDCl_3$) (1.25:1 mixture of rotamers): δ = 1.73 (s, 3H), 1.75 (s, 2.4H), 3.10, 3.16 (dd, J = 13.3 Hz, 0.8H), 3.18, 3.45 (dd, J = 13.1 Hz, 1H), 5.65 (br s, 0.8H), 6.01 (br d, 1H), 6.86–6.92 (m, 2H), 7.20–7.39 (m, 8H), 8.08 (d, J = 12.2 Hz, 1H), 8.18 (d, J = 1.8 Hz, 0.8H).

N-[1-(4-Fluorophenyl)-2-(3-fluorophenyl)ethyl]formamide **(4b)**:
mp 101–102°C.

$C_{15}H_{13}F_2NO$	calc.	C 68.96	H 5.01	N 5.36
(261.3)	found	68.79	5.00	5.28

CI-MS (CH_4): m/z = 262 MH^+.

^1H NMR ($CDCl_3$) (5.3:1 mixture of rotamers): δ = 2.97–3.17 (m, 2H), 4.68, 4.73 (dd, J = 8.4 Hz, 0.19H), 5.28, 5.33 (dd, J = 7.5 Hz, 0.81H), 5.86 (br s, 0.81H), 6.19 (br s, 0.19H), 6.74–7.28 (m, 8H), 7.89 (d, J = 11.8 Hz, 0.19H), 8.15 (s, 0.81H).

N-[2-Phenyl-1-(3-trifluoromethylphenyl)ethyl] formamide **(4c)**:
mp 100–101°C.

$C_{16}H_{14}F_3NO$	calc.	C 65.52	H 4.81	N 4.77
(293.3)	found	65.60	4.65	4.61

CI-MS (CH_4) m/z 294 MH^+.

^1H NMR ($CDCl_3$) (6.25:1 mixture of rotamers): δ = 2.99–3.21 (m, 2H), 4.81–4.83 (m, 0.16H), 5.37, 5.42 (dd, J = 7.5 Hz, 0.84H), 5.88 (very br s, 1H), 7.03–7.60 (m, 9H), 7.90 (d, J = 11.8 Hz, 0.16H), 8.16 (s, 0.84H).

N-[1-(4-Bromophenyl)-2-phenylethyl]formamide **(4d)**:
mp 169–170°C.

CI-MS (CH_4): m/z = 304 MH^+.

$C_{15}H_{14}BrNO$	calc.	C 59.23	H 4.65	N 4.60
(304.2)	found	59.23	4.69	4.55

^1H NMR ($CDCl_3$ plus one drop of DMSO-d_6) (6.5:1 mixture of rotamers): δ = 2.97–3.13 (m, 2H), 4.59–4.64 (m, 0.15H), 5.22, 5.28 (dd, J = 7.5 Hz, 0.85H), 7.07–7.48 (m, 9H), 7.85 (d, J = 11.6 Hz, 0.15H), 8.10 (s, 0.85H).

N-[1-(4-Methoxyphenyl)-2-phenylethyl] formamide **(4e)**:
mp 156–157.5°C.

$C_{16}H_{17}NO_2$	calc.	C 75.27	H 6.71	N 5.49
(255.2)	found	75.47	6.66	5.14

CI-MS (CH_4): m/z = 256 MH^+.

^1H NMR ($CDCl_3$) (3.4:1 mixture of rotamers): δ = 3.11 (d, J = 7.1 Hz, 2H), 3.78 (s, 2.13H), 3.81 (s, 0.87H), 4.65, 4.68 (dd, J = 8.5 Hz, 0.29H), 5.27, 5.32 (dd, J = 7.4 Hz, 0.71H), 5.79 (very br s, 1H), 6.82–7.25 (m, 9H), 7.84 (d, J = 11.9 Hz, 0.29H), 8.13 (s, 0.71H).

N-[1-(4-Methoxy-3-nitrophenyl)-2-phenyl]formamide **(4f)**:
mp 125.5–126.5°C.

$C_{16}H_{16}N_2O_4$	calc.	C 63.99	H 5.37	N 9.33
(300.3)	found	63.92	5.05	9.40

CI-MS (CH_4): m/z = 301 MH^+.

^{1}H NMR ($CDCl_3$) (8.8:1 mixture of rotamers): δ = 3.10 (d, J = 6.6 Hz, 2 H), 3.94 (s, 2.7 H), 3.97 (s, 0.33 H), 4.78 (m, 0.11 H), 5.29, 5.34 (dd, J = 7.4 Hz, 0.89 H), 5.93 (br d, J = 7.3 Hz, 1 H), 6.99–7.30 (m, 6 H), 7.37, 7.40 (dd, J = 2.3 Hz, 1 H), 7.75 (d, J = 2.3 Hz, 1 H), 7.90 (d, J = 11.7 Hz, 0.11 H), 8.15 (s, 0.89 H).

2-Formyl-1,2,3,4-tetrahydro-3-phenylisoquinoline (3); Typical *N*-Formyliminium Cyclization:

This is representative of the TFA procedure.[18] Formamide **1**[4a,16] (49.4 g, 0.219 mol) and $(CH_2O)_n$ (7.95 g) were added sequentially to TFA (219 mL), under Ar. The reaction was heated at reflux with stirring for 4.5 h, and allowed to cool. The solution was poured onto ice (800 g) and then diluted with H_2O (500 mL). The aqueous mixture was extracted with CH_2Cl_2 (2 × 200 mL) and the organic extracts were neutralized with sat. aq $NaHCO_3$. The organic layer was washed sequentially with 10% aq Na_2CO_3 and H_2O, dried ($MgSO_4$), and concentrated to give, after air-drying, 49.9 g (96%) of the title compound as a pale yellow solid. An analytical sample was prepared by recrystallization from EtOH to afford a colorless granular solid, mp 120–121 °C.

$C_{16}H_{15}NO$	calc.	C 80.98	H 6.37	N 5.90
(237.3)	found	81.26	6.44	5.92

FAB-MS (thioglycerol): m/z = 238 MH^+.

^{1}H NMR ($CDCl_3$) (1.5:1 mixture of amide rotamers): δ = 3.22–3.38 (m, 2 H), 4.16 (d, J = 17.2 Hz, 0.6 H), 4.22 (d, J = 16.1 Hz, 0.4 H), 4.46 (d, J = 16.2 Hz, 0.4 H), 5.05–5.11 (overlapping d and m, J of d = 16.8 Hz, 1.2 H), 5.90–5.93 (m, 0.4 H, CH), 7.02–7.31 (m, 9 H), 8.35 (s, 0.4 H, CHO), 8.37 (s, 0.6 H, CHO).

2-Formyl-1,2,3,4-tetrahydro-3-methyl-3-phenylisoquinoline (**5a**):

$C_{17}H_{17}NO \cdot 0.125\,H_2O$	calc.	C 80.52	H 6.85	N 5.52	H_2O	0.88
(251.3/253.5)	found	80.47	6.99	5.96		0.88

CI-MS (methane): m/z = 252 MH^+.

^{1}H NMR ($CDCl_3$): δ = 1.77 (s, 3 H, CH_3), 3.08 (d, J = 15.7 Hz, 1 H), 3.37 (d, J = 15.7 Hz, 1 H), 4.28 (d, J = 16.8 Hz, 1 H), 5.08 (d, J = 16.7 Hz, 1 H), 7.09–7.32 (m, 9 H), 8.4 (s, 1 H, CHO).

6-Fluoro[8-Fluoro]-2-formyl-3-(4-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline (**5b[5b']**):

$C_{16}H_{13}F_2NO \cdot 0.25\,H_2O$	calc.	C 69.18	H 4.90	N 5.04	H_2O	1.62
(273.3/277.8)	found	69.34	4.91	5.00		1.21

FAB-MS (thioglycerol): m/z = 274 MH^+.

^{1}H NMR ($CDCl_3$) (1.4:1 mixture of amide rotamers): δ = 3.16–3.36 (m, 2 H), 4.07 (d, J = 17.0 Hz, 0.58 H), 4.15 (d, J = 16.0 Hz, 0.46 H), 4.44 (d, J = 16.1 Hz, 0.42 H), 5.01–5.06 (d and m, J of d = 17.5 Hz, 1.16 H), 5.89 (m, 0.38 H, CH), 7.02–7.19 (m, 7 H), 8.32 (s, 0.42 H, CHO), 8.37 (s, 0.58 H, CHO).

2-Formyl-1,2,3,4-tetrahydro-3-(3-trifluoromethylphenyl)isoquinoline (**5c**):

$C_{17}H_{14}F_3NO$	calc.	C 66.88	H 4.62	N 4.59
(305.3)	found	66.84	4.74	4.48

FAB-MS (thioglycerol): m/z = 306 MH^+.

^{1}H NMR ($CDCl_3$): (1:1 mixture of amide rotamers): δ = 3.17–3.48 (m, 2 H), 4.19 (d, J = 17.2 Hz, 0.5 H), 4.27 (d, J = 15.9 Hz, 0.5 H), 4.53 (d, J = 15.9 Hz, 0.5 H), 5.09 (d, J = 17.3 Hz, 0.5 H), 5.16–5.17 (m, 0.5 H, CH), 5.83–5.86 (m, 0.5 H, CH), 7.07–7.51 (m, 7 H_{arom}), 8.37 (s, 0.5 H,CHO), 8.38 (s, 0.5 H, CHO).

3-(4-Bromophenyl)-2-formyl-1,2,3,4-tetrahydroisoquinoline (**5d**):

$C_{16}H_{14}BrNO \cdot 0.1\,H_2O$	calc.	C 60.43	H 4.50	N 4.40	H_2O	0.57
(315.3/317.3)	found	60.25	4.71	4.60		0.64

CI-MS (methane): m/z = 316 MH^+.

^{1}H NMR ($CDCl_3$) (1.2:1 mixture of amide rotamers): δ = 3.15–3.43 (m, 2 H), 4.13 (d, J = 15.5 Hz, 0.50 H), 4.22 (d, J = 16.0 Hz, 0.50 H), 4.48 (d, J = 16.1 Hz, 0.45 H), 5.01–5.03 (d and m, J of d = 17.2 Hz, 1.12 H), 5.82–5.83 (m, 0.42 H, CH), 7.02–7.40 (m, 8 H), 8.34 (s, 0.46 H, CHO), 8.36 (s, 0.54 H, CHO).

2-Formyl-1,2,3,4-tetrahydro-3-(4-methoxy-3-nitrophenyl)isoquinoline (**5f**):

$C_{17}H_{16}N_2O_4$	calc.	C 65.38	H 5.16	N 8.97
(313.3)	found	65.05	5.16	8.87

FAB-MS (thioglycerol): m/z = 313 MH^+.

^{1}H NMR ($CDCl_3$) (1:1.1 mixture of amide rotamers): δ = 3.14–3.45 (m, 2 H), 3.90 (s, 3 H, OMe), 4.15 (d, J = 17.3 Hz, 0.50 H), 4.28 (d, J = 16.0 Hz, 0.54 H), 4.53 (d, J = 15.9 Hz, 0.58 H), 5.05–5.11 (d and m, J of d = 17.6 Hz, 1.0 H), 5.79 (m, 0.54 H, CH), 6.97 (d, J = 8.8 Hz, ortho to OMe), 7.10–7.41 (m, 5 H), 7.65–7.66 (m, 1 H, para to NO_2), 8.36 (s, 0.52 H, CHO), 8.39 (s, 0.48 H, CHO).

1,2,3,4-Tetrahydro-3-(3-trifluoromethylphenyl)isoquinoline; Example of Formamide Hydrolysis:[19]

Formamide **5c** (21.7 g, 0.071 mol) in 95% EtOH (150 mL) was treated with KOH pellets (18.8 g, 85% assay) and the mixture was stirred and heated at reflux for 2.3 h. It was cooled, concentrated in vacuo, and extracted twice with Et_2O. The combined extracts were stirred with 10% HCl whence the product crystallized. The white solid was rinsed with Et_2O and dried to afford 20.24 g of title compound as the HCl salt (90%). A small sample was recrystallized from *i*-PrOH to give an analytical sample, mp 246–247 °C.

$C_{16}H_{14}F_3N \cdot HCl$	calc.	C 61.25	H 4.82	N 4.46
(277.3/313.8)	found	61.29	4.85	4.35

FAB-MS (thioglycerol): m/z = 278 MH^+.

^{1}H NMR (DMSO-d_6): δ = 3.18–3.42 (m, 2 H, CH_2), 4.42 (d, J = 16.1 Hz, 1 H, NCH_2), 4.46 (d, J = 16.2 Hz, 1 H, NCH_2), 4.81–4.84 (m, 1 H, CH), 7.25–7.31 (m, 4 H), 7.72–7.77 (m, 1 H, meta to CF_3), 7.83 (d, J = 7.9 Hz, 1 H, para to CF_3), 8.00 (d, J = 7.7 Hz, 1 H, ortho to CF_3), 8.09 (s, 1 H, ortho to CF_3).

(*R*)-1,2,3,4-Tetrahydro-3-phenylisoquinoline; Cyclization and Hydrolysis Involving Enantiomerically Enriched Compounds:

1,2-Diphenylethylamine (4.0 g, 20 mmol, 97% assay) was added to a solution of (+)-tartaric acid (3.0 g, 20 mmol) in deionized H_2O (100 mL), with stirring.[20] Within 2 min, white crystals began to separate; after 18 h, the mixture was filtered. The solid was rinsed with dry Et_2O and air-dried to yield 1.12 g of product, mp (160–200 °C) 208–213 °C (dec). A sample was converted to free base and assayed for enantiomeric purity by ^{1}H NMR employing (*R*)-(−)-1-(9-anthryl)-2,2,2-trifluoroethanol[21] had an ee of at least 98%. Formamide (*R*)-**1** was prepared and cyclized to (*R*)-**3**, which was hydrolyzed to the title compound and isolated as a HCl salt in 38% yield with an ee of 98%, mp (271) 277–279 °C (dec); $[\alpha]_D^{24}$ = + 22.3° (*c* = 0.82, MeOH).

^{1}H NMR (free base; $CDCl_3$): δ = 1.87 (br s, 1 H, NH), 2.98 (d, J = 7.1 Hz, 2 H), 4.02 (overlapping dd, J = 7.0 Hz, 1 H), 4.23 (AB quartet, J = 15.6 Hz, 2 H), 7.07–7.44 (m, 9 H).

We thank Dr. Gregory Leo, Dr. G. Caldwell, Diane Gauther, John Masucci, and William Jones for analytical and spectroscopic data.

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