A Facile Synthesis of 1,2,3,4-Tetrahydroisoquinolines Through Cyclization of *O,N*-Acetals

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A mild and efficient method for the synthesis of 1,2,3,4-tetrahydroisoquinolines by a modified Pictet-Spengler reaction involving Lewis acid-mediated cyclization of *O,N*-acetals is described.

The majority of isoquinoline syntheses involve acid-catalysed ring closure to a benzene ring and benefit considerably from the presence of an electron-donating substituent.[1] Although the

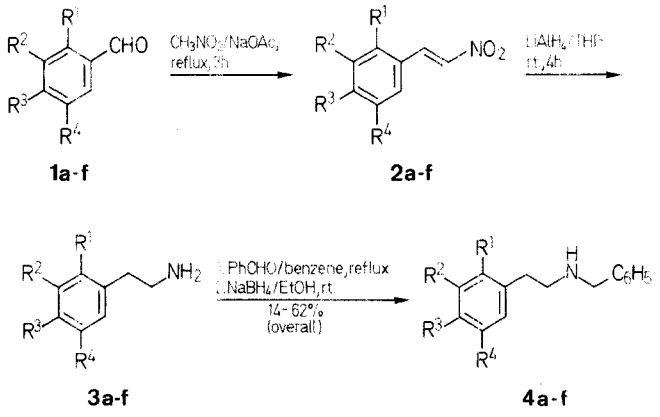
Pictet-Spengler reaction has proven to be an excellent method for the preparation of 1,2,3,4-tetrahydroisoquinolines,[2,3] the ring-closure reaction is sensitive to substituent effects. If an alkoxy or hydroxy group *meta* to the side chain of an imine is absent, cyclization fails to occur. During our synthetic studies in the field of isoquinolinequinone antibiotics such as mimocin[4] and saframycin B,[5] we intended the cyclization of 2-(3-methylphenyl)ethanamines having a highly oxygenated benzene ring to 1,2,3,4-tetrahydroisoquinoline derivatives. As a more electrophilic iminium salt equivalent we considered an *O,N*-acetal to be appropriate because it is a potential and masked iminium salt, and is readily prepared by conventional methods.[6,7] The use of such *O,N*-acetals in the preparation of 1,2,3,4-tetrahydroisoquinolines has hitherto not been reported.

We report here a mild and efficient method for the synthesis of 1,2,3,4-tetrahydroisoquinolines through cyclization of *O,N*-acetals. The starting *N*-benzyl-2-(2,4,5-trimethoxy-3-methylphenyl)ethylamine (**4a**) was prepared by a slightly modified reported procedure.[8] 2,4,5-Trimethoxy-3-methylbenzaldehyde (**1a**) was condensed with nitromethane to afford the β-nitrostyrene **2a** which was reduced with lithium aluminum hydride to yield the amine **3a**.[9] Condensation of **3a** with benzaldehyde gave a Schiff base which was reduced with sodium borohydride to afford amine **4a** (Table 1).

The reaction of **4a** with paraformaldehyde in the presence of potassium carbonate in ethanol quantitatively afforded an *O,N*-acetal **5a** (Table 2) which was treated with trifluoroacetic acid for 1 h to give the 1,2,3,4-tetrahydroisoquinoline **6a** in 80% overall yield (Table 3).

Table 2. ^{1}H-NMR-Spectral Data of *O,N*-Acetals Prepared

O,N-Acetal	(CCl_4/TMS_{int}) δ, *J*(Hz)
5a	1.13 (t, 3H, *J* = 7); 2.10 (s, 3H); 2.75 (br. s, 4H); 3.30 (q, 2H, *J* = 7); 3.50 (s, 3H); 3.62 (s, 3H); 3.68 (s, 3H); 3.78 (s, 2H); 4.08 (s, 2H); 6.38 (s, 1H); 7.15 (s, 5H)
5b	1.13 (t, 3H, *J* = 7); 2.80 (br. s, 4H); 3.34 (q, 2H, *J* = 7); 3.58 (s, 3H); 3.62 (s, 3H); 3.78 (s, 2H); 4.08 (s, 2H); 6.55 (m, 3H); 7.12 (s, 5H)
5c	1.13 (t, 3H, *J* = 7); 2.68 (m, 4H); 3.30 (q, 2H, *J* = 7); 3.67 (s, 6H); 3.76 (s, 2H); 4.08 (s, 2H); 6.40 (br. s, 3H); 7.12 (s, 5H)
5d	1.13 (t, 3H, *J* = 7); 2.81 (br. s, 4H); 3.35 (q, 2H, *J* = 7); 3.62 (s, 3H); 3.75 (s, 2H); 4.09 (s, 2H); 4.90 (s, 2H); 6.68 (br. s, 2H); 7.15–7.30 (m, 11H)
5e	1.11 (t, 3H, *J* = 7); 2.03 (s, 3H); 2.70 (br. s, 4H); 3.27 (q, 2H, *J* = 7); 3.53 (s, 3H); 3.70 (s, 3H); 3.75 (s, 2H); 4.02 (s, 2H); 6.23 (d, 1H, *J* = 8); 6.68 (d, 1H, *J* = 8); 7.07 (s, 5H)
5f	1.12 (t, 3H, *J* = 7); 2.74 (br. s, 4H); 3.30 (q, 2H, *J* = 7); 3.70 (s, 3H); 3.75 (s, 5H); 4.08 (s, 2H); 6.70 (m, 3H); 7.15 (m, 5H)



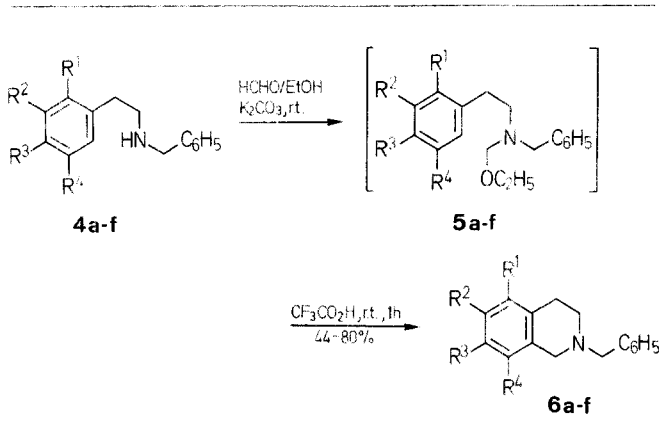


Table 1. *N*-Benzyl-2-phenylethylamines **4a–f** Prepared

Product	R^1	R^2	R^3	R^4	Yield[a] (%)	b.p. (°C)/Torr	Molecular Formula[b] or Lit. b.p. (°C)/Torr	^{1}H-NMR ($CDCl_3$/TMS) δ, *J*(Hz)
4a	OCH_3	CH_3	OCH_3	OCH_3	34	195–197/2	$C_{19}H_{25}NO_3$ (315.4)	1.28 (s, 1H); 2.12 (s, 3H); 2.70 (br. s, 4H); 3.58 (s, 3H); 3.70 (s, 8H); 6.44 (s, 1H); 7.15 (m, 5H)
4b	OCH_3	H	H	OCH_3	47	155/1	$C_{17}H_{21}NO_2$ (271.4)	1.80 (s, 1H); 2.75 (br. s, 4H); 3.55 (s, 3H); 3.57 (s, 3H); 3.65 (s, 2H); 6.51 (m, 3H); 7.10 (m, 5H)
4c	H	OCH_3	OCH_3	H	62	180/2	178/0.5[12]	1.35 (s, 1H); 2.67 (m, 4H); 3.67 (s, 8H); 6.40 (s, 3H); 7.13 (s, 5H)
4d	$OCH_2C_6H_5$	H	H	OCH_3	14	160/2	$C_{23}H_{25}NO_2$ (347.4)	2.30 (br. s, 1H); 2.80 (s, 4H); 3.62 (s, 3H); 3.64 (s, 2H); 4.90 (s, 2H); 6.67 (m, 2H); 7.17–7.25 (m, 11H)
4e	OCH_3	CH_3	OCH_3	H	27	190/2	$C_{18}H_{23}NO_2$ (285.4)	1.47 (s, 1H); 2.08 (s, 3H); 2.75 (s, 4H); 3.62 (s, 3H); 3.73 (s, 5H); 6.41 (d, 1H, *J* = 9); 6.86 (d, 1H, *J* = 9); 7.13 (m, 5H)
4f	OCH_3	OCH_3	H	H	17	195/2 m.p. 119–120°[c]	m.p. 120–121°[c,13]	2.20 (br. s, 1H); 2.76 (s, 4H); 3.70 (s, 5H); 3.74 (s, 3H); 6.60–6.80 (m, 3H); 7.13 (m, 5H)

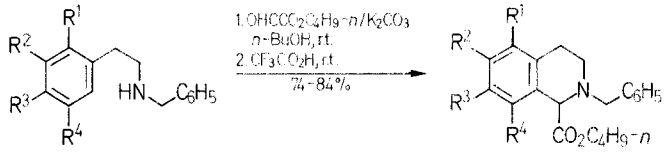
[a] Yields based on **1**.
[b] Satisfactory microanalyses obtained: C ±0.30, H +0.15, N +0.12.
[c] Amine hydrochloride.

Table 3. 2-Benzyl-1,2,3,4-tetrahydroisoquinolines **6a–f** and **7a, b** Prepared

Product	Yield[a] (%)	m.p. (°C) (solvent) or b.p. (°C)/Torr	Molecular Formula[b]	IR ($CHCl_3$) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS_{int}) δ, J(Hz)
6a	80	b.p. 128–132/1	$C_{20}H_{25}NO_3$ (327.4)		2.12 (s, 3H); 2.65 (m, 4H); 3.50 (s, 2H); 3.59 (s, 5H); 3.68 (s, 3H); 3.72 (s, 3H); 7.23 (m, 5H)
6b	69	m.p. 77–78.5 (ether)	$C_{18}H_{21}NO_2$ (283.4)		2.66 (t, 2H, J = 5.7); 2.75 (t, 2H, J = 5.7); 3.60 (s, 2H); 3.69 (s, 3H); 3.70 (s, 2H); 3.73 (s, 3H); 6.57 (d, 1H, J = 9); 6.60 (d, 1H, J = 9); 7.30 (m, 2H); 7.50 (m, 3H)
6c	62	m.p. 86–88[d] (ether)	$C_{18}H_{21}NO_2$ (283.4)		2.73 (m, 4H); 3.50 (br. s, 2H); 3.63 (s, 2H); 3.78 (s, 3H); 3.82 (s, 3H); 6.40 (s, 1H); 6.50 (s, 1H); 7.03–7.50 (m, 5H)
6d	44	m.p. 68–70	$C_{24}H_{25}NO_2$		2.73 (m, 4H); 3.53 (br. s, 2H); 3.63 (s, 5H); 4.90 (s, 2H); 6.40 (d, 1H, J = 7); 6.58 (d, 1H, J = 7); 7.03–7.53 (m, 10H)
6e	57[c]		$C_{19}H_{23}NO_2$ (297.4)		2.08 (s, 3H); 2.72 (m, 4H); 3.50 (s, 2H); 3.61 (s, 2H); 3.65 (s, 3H); 3.73 (s, 3H); 6.17 (s, 1H); 7.27 (m, 5H)
6f	60[c]		$C_{18}H_{21}NO_2$ (283.4)		2.65 (m, 4H); 3.42 (s, 2H); 3.53 (s, 2H); 3.66 (s, 3H); 3.71 (s, 3H); 6.50 (s, 2H); 7.20 (m, 5H)
7a	74[c]		$C_{25}H_{33}NO_5$ (427.5)	1725 (C=O)	0.90 (t, 3H, J = 7); 1.17–1.83 (m, 4H); 2.17 (s, 3H); 2.43–3.17 (m, 4H); 3.60 (d, 1H, J = 16); 3.70 (s, 3H); 3.73 (s, 3H); 3.80 (s, 3H); 3.92 (d, 1H, J = 16); 4.07 (t, 2H, J = 7); 4.48 (s, 1H); 7.00–7.50 (m, 5H)
7b	84[c]		$C_{23}H_{29}NO_4$ (383.5)	1725 (C=O)	0.90 (t, 3H, J = 7); 1.05–1.80 (m, 4H); 2.40–3.10 (m, 4H); 3.48 (d, 1H, J = 16); 3.58 (s, 3H); 3.62 (s, 3H); 3.88 (d, 1H, J = 16); 4.02 (t, 2H, J = 7); 4.48 (s, 1H); 6.45 (s, 2H); 6.98–7.40 (m, 5H)

[a] Yields based on **4**.
[b] Satisfactory microanalyses obtained: C ±0.10, H ±0.14, N ±0.05. Mass and UV spectra in accord with structures.
[c] Purified by column chromatography on silica gel, eluent: hexane.
[d] Lit.[14] m.p. 88–90°C.

In order to examine the scope of this procedure, the *N*-benzyl-2-phenylethylamines **4b–f** (Table 1) were prepared and converted into the corresponding 2-benzyl-1,2,3,4-tetrahydroisoquinolines **6b–f** (Table 3).

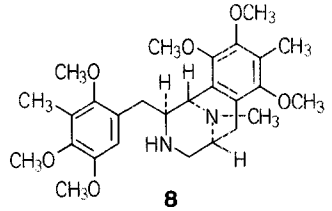


4a,b **7a,b**

When butyl glyoxylate[10] was used in the reaction with **4a** and **4b**, 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid esters **7a** and **7b**, respectively, were obtained (Table 3).

Compound **7a** is a versatile starting material for the synthesis of the isoquinolinequinone antibiotics renierone and *N*-formyl-1,2-dihydrorenierone.[11]

The usefulness of our procedure was further demonstrated by the cyclization of compound **8**[15] to the pentacyclic compound **9** in 81% yield.



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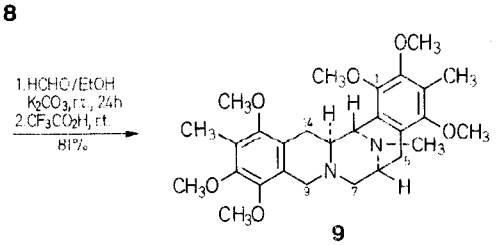

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These results show that the present method offers a facile entry to highly functionalized 1,2,3,4-tetrahydroisoquinolines. The application of the method to a synthesis of the dimeric isoquinolinequinone antibiotic saframycin B is under investigation.

N-Benzyl-2-(2,4,5-trimethoxy-3-methylphenyl)ethylamine (4a); Typical Procedure:

2,4,5-Trimethoxy-3-methyl-β-nitrostyrene (**2a**): Ammonium acetate (850 mg, 11 mmol) is added to a stirred solution of 2,4,5-trimethoxy-3-methylbenzaldehyde (**1a**; 10.5 g, 50 mmol) in nitromethane (100 mL) at room temperature. The mixture is heated at reflux for 3 h, then poured into H_2O (200 mL) and extracted with benzene (3 × 200 mL). The combined extracts are dried (Na_2SO_4) and evaporated under reduced pressure and the remaining yellow solid is recrystallized from MeOH to afford prisms of product **2a**; yield: 8.61 g (68%); m.p. 121–123°C (Lit.[9] m.p. 121–123°C).

2-(2,4,5-Trimethoxy-3-methylphenyl)ethylamine (**3a**): Lithium aluminum hydride (3.0 g, 79 mmol) is added to a stirred solution of compound **2a** (7.59 g, 30 mmol) in dry THF (150 mL). The mixture is stirred at room temperature for 4 h, excess reagent is decomposed with H_2O, and the mixture is filtered. The filtrate is evaporated under reduced pressure to give a pale yellow oil which is distilled *in vacuo* to give product **3a**; yield: 4.40 g (65%); b.p. 142–144°C/2 Torr.

N-Benzyl-2-(2,4,5-trimethoxy-3-methylphenyl)ethylamine (**4a**): Benzaldehyde (0.82 mL, 8.07 mmol) is added to a solution of amine **3a** (1.8 g, 8 mmol) in benzene (50 mL). The mixture is heated at reflux under a Dean-Stark separator. The organic layer is dried (Na_2SO_4) and the solvent is removed *in vacuo* to give the intermediate Schiff base as a colorless oil. This is dissolved in EtOH (50 mL) and $NaBH_4$ (300 mg, 7.9 mmol) is added in one portion with stirring. The mixture is stirred for 30 min, then diluted with H_2O (100 mL), and extracted with $CHCl_3$ (3 × 100 mL). The combined extracts are dried (Na_2SO_4) and evaporated *in vacuo* to give a pale yellow oil which is purified by distillation to afford amine **4a**; yield: 1.91 g (76%); b.p. 195–197°C/2 Torr (Table 1).

2-Benzyl-1,2,3,4-tetrahydroisoquinolines (6a–f); General Procedure:

A solution of the *N*-benzyl-2-phenylethylamine **4** (1.5 mmol) and anhydrous K_2CO_3 (828 mg, 6 mmol) in EtOH (0.26 mL) is stirred for 10 min at room temperature. Paraformaldehyde (60 mg, 2 mmol) is then added in one portion, the mixture is stirred overnight at room temperature, then filtered. The filtrate is evaporated under reduced pressure to give

the *O,N*-acetal **5** (Table 2) which is used without purification. To the *O,N*-acetal **5** is added trifluoroacetic acid (3 mL); this mixture is stirred at room temperature for 1 h, then concentrated. The remaining mixture is washed with saturated $NaHCO_3$ solution (50 mL), and extracted with $CHCl_3$ (3×50 mL). The combined extracts are dried (Na_2SO_4) and evaporated to dryness. The residue is chromatographed on silica gel and the product **6** is purified by recrystallization or distillation. (Table 3).

Butyl 2-Benzyl-5,7,8-trimethoxy-6-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (7a); Typical Procedure:

A solution of *N*-benzyl-2-phenylethylamine **4a** (315 mg, 1 mmol) in butanol (5 mL) is stirred with butyl glyoxalate[10] (650 mg, 5 mmol) and anhydrous K_2CO_3 (690 mg, 5 mmol) for 30 min. Then, trifluoroacetic acid (2 mL) is added and stirring is continued for 60 min. The resultant yellow oil is chromatographed on silica gel using hexane/EtOAc (10:1) as eluent to afford **7a** as a colorless oil; yield: 315 mg (74%). (Table 3).

1,2,4,10,11,13-Hexamethoxy-3,12,16-trimethyl-(6α,14aα,15α)-6,7,9,14,14a,15-hexahydro-6,15-imino-5*H*-isoquino[3,2-*b*][3]benzazocine (9):

A mixture of 2-[(2,4,5-trimethoxy-3-methylphenyl)methyl]-7,9,10-trimethoxy-8,11-dimethyl-(1α,2α,5α)-1,2,3,4,5,6-hexahydro-1,5-imino-3-benzazocine (**8**[15]; 48.6 mg, 0.1 mmol) in EtOH (0.58 mL) and anhydrous K_2CO_3 (221 mg, 1.6 mmol) is stirred for 10 min at room temperature. Paraformaldehyde (24 mg, 0.8 mmol) is then added in one portion and the mixture is stirred for 24 h, then filtered, and the filtrate evaporated *in vacuo*. The residue (72.4 mg) is stirred with trifluoroacetic acid (2 mL) for 1 h at room temperature. The mixture is diluted with H_2O (20 mL) and extracted with $CHCl_3$ (3×20 mL). The combined extracts are washed with 5% $NaHCO_3$ solution (40 mL), dried (Na_2SO_4), and evaporated. Recrystallization of the residue from EtOAc/ether gives product **9** as colorless prisms; yield: 40.2 mg (81%); m.p. 158.5–160°C.

$C_{28}H_{38}N_2O_6$	calc.	C 67.44	H 7.68	N 5.62
(498.6)	found	67.14	7.86	5.54

MS: m/e = 498 (M^+, 18%); 248 (100); 234 (10); 218 (11).

IR (KBr): ν = 2930; 1465; 1405; 1115; 1070 cm^{-1}.

UV (MeOH): λ_{max} = 224 (log ε = 4.33); 272 (2.83); 278 (2.90) nm.

^{1}H-NMR ($CDCl_3$/TMS): δ = 2.12 (s, 3H, Ar–CH_3); 2.16 (s, 3H, Ar–CH_3); 2.24 (dd, 1H, J = 12.2 Hz, 11.5 Hz, 14β-H); 2.32 (s, 3H, N–CH_3); 2.61 (d, 1H, J = 18.3 Hz, 5β-H); 2.72 (ddd, 1H, J = 12.2 Hz, 3.4 Hz, 2.0 Hz, 14a-H); 3.01 (dd, 1H, J = 12.2 Hz, 3.4 Hz, 14α-H); 3.05 (d, 2H, J = 2.0 Hz, 7,7-H_2); 3.06 (dd, 1H, J = 18.3 Hz, 7.9 Hz, 5α-H); 3.12 (d, 1H, J = 15.6 Hz, 9α-H); 3.25 (m, 1H, 6-H); 3.58 (s, 3H, OCH_3); 3.70 (s, 3H, OCH_3); 3.73 (s, 3H, OCH_3); 3.76 (s, 3H, OCH_3); 3.77 (s, 3H, OCH_3); 3.85 (s, 3H, OCH_3); 3.95 (d, 1H, J = 15.6 Hz, 9β-H); 4.08 (dd, 1H, J = 2.2 Hz, 0.5 Hz, 15-H).

^{13}C-NMR ($CDCl_3$/TMS): δ = 9.1 (q, Ar–CH_3); 9.3 (q, Ar–CH_3); 22.5 (t, C-5); 26.8 (t, C-14); 41.3 (q, N–CH_3); 52.5 (d, C-6); 53.3 (t, C-9); 57.0 (d, C-15); 59.4 (q, OCH_3); 59.4 (q, OCH_3); 59.5 (q, OCH_3); 59.8 (q, OCH_3); 60.0 (q, OCH_3); 60.1 (q, OCH_3); 60.6 (d, C-14a); 63.4 (t, C-7); 122.6 (s); 123.4 (s); 123.5 (s); 124.3 (s); 124.4 (s); 125.5 (s); 145.1 (s); 147.9 (s); 149.1 (s); 149.1 (s); 151.5 (s); 152.0 (s).

Received: 29 December 1986; revised: 18 March 1987

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