One-Pot Synthesis of Spiro Isochromane-3,3′-piperidines, -3,4′-piperidines and -3,3′-pyrrolidines

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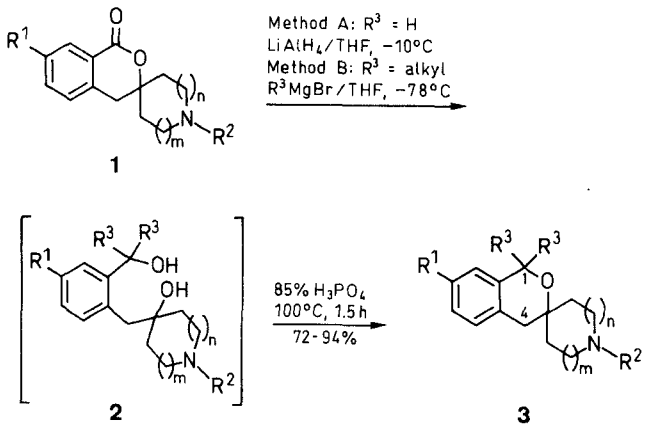
Spiro isochromane-1-ones **1** were treated with lithium aluminum hydride or Grignard reagents to afford diol intermediates **2**, which cyclize in 85% phosphoric acid at 100°C to spiro isochromanes **3** in 72–94% isolated yields.

As part of a program directed towards the design of novel Class III antiarrhythmic agents,[1] the spiro isochromanes **3** were required as synthetic intermediates. Interestingly, the preparation of this class of 3-spiro-fused heterocycles has not been documented. However, several general methods have been described for the preparation of the isochromane nucleus; these rely on acid-catalyzed cyclodehydration of homophthalyl alcohols,[2,3] Friedel–Crafts reaction of phenethyl alcohols with formaldehyde,[4] and intramolecular titanium tetrachloride-catalyzed cyclization of phenethyl alcohol acetals.[5] We report here a versatile, high yielding, one-pot preparation of the spiro-fused isochromanes **3**. This method is illustrated in the scheme outlined below.



Scheme

1	R^1	R^2	n	m
a	H	CH_2Ph	1	1
b	H	Me	1	1
c	$NHSO_2Me$	Me	1	1
d	$NHSO_2Me$	Et	0	2
e	H	CH_2Ph	0	1

3	R^1	R^2	R^3	n	m
a	H	CH_2Ph	H	1	1
b	H	CH_2Ph	Me	1	1
c	H	CH_2Ph	Et	1	1
d	H	Me	H	1	1
e	$NHSO_2Me$	Me	H	1	1
f	$NHSO_2Me$	Me	Me	1	1
g	$NHSO_2Me$	Et	H	0	2
h	H	CH_2Ph	H	0	1
i	H	CH_2Ph	Me	0	1

This approach from readily available lactones **1** accesses a variety of 3-spiro cycloaza alkyl analogs. The first step is reduction of lactone **1** (Method A) with lithium aluminum hydride in tetrahydrofuran at 0°C to form the diols **2** (R = H) in situ, which undergo an acid-catalyzed cyclization with hot (100°C) 85% phosphoric acid to provide the isochromane **3** (R = H). The C-1 substituents are incorporated in the first step (Method B) by reacting lactone **1** with the appropriate Grignard reagent in tetrahydrofuran at −78°C to give intermediate **2** which cyclizes to isochromane **3** (R = Me or Et) after treatment with 85% phosphoric acid. The cyclization step is not affected by the alkyl substituents introduced on the pyran ring despite the increased steric crowding. The entire process is expedited, and the yields of pure isochromanes **3** are dramatically improved, by avoiding isolation of the polar water-soluble intermediate **2**. Structural assignment of products **3a–i** are supported by the expected ^1H NMR resonances observed for C-1 methylenes (δ = 4.7–4.9) and C-4 methylenes (δ = 2.6–2.9) (Table).

The generality of this method is demonstrated by the variety of spiro isochromane-3,3′-piperidines, -3,4′-piperidines, and -3,3′-pyrrolidines prepared by this procedure (Table). The readily accessible starting materials, high overall yields, and ease of isolation of products make this sequence an attractive method for preparing the compounds described, as well as for other highly substituted isochromanes.

Melting points are uncorrected. ^1H NMR spectra were measured at 300 MHz with TMS as internal standard. Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. THF was distilled from sodium/benzophenone ketyl prior to use. Reactions were conducted under an Ar atmosphere. Microanalyses were obtained on a Control Equipment Co. Model 240XA instrument. Lactones **1a**, **1b**, and **1e** were obtained by modification (see below) of a procedure previously described[6] which resulted in significantly improved yields. Lactones **1c** and **1d** were prepared by standard procedures from the parent lactones via the following sequence: 1. regioselective nitration of the aromatic ring (1.5 equiv HNO_3, H_2SO_4, 0°C, 85%); 2. reduction to the aniline (Raney Nickel, H_2/50 p.s.i, EtOH, 100%); and 3. conversion to the methanesulfonamide (1.1 equiv MsCl, pyridine, 25°C, 90%).

1,4-Dihydro-1′-methylspiro(2-benzopyran-3,4′-piperidin-1-one) (1b): A solution of *N*-methyltoluamide (12.0 g, 80.5 mmol) in THF (350 mL) was stirred and maintained at 0°C while 1.6 M BuLi in hexane (103 mL, 165 mmol) was added dropwise. After an additional 1 h at 0°C, the mixture was cooled to −78°C and treated with 1-methyl-4-piperidone (15.1 g, 121.0 mmol). After an additional 0.5 h at −78°C, the mixture was allowed to warm to 0°C. The reaction was quenched with H_2O (250 mL), and the layers were separated. The aqueous layer was extracted with $CHCl_3$ (2 × 300 mL), and the combined organic layers were concentrated in vacuo to give an oil. The oil was dissolved in AcOH (30 mL)/H_2O (30 mL), cooled in an ice bath, and treated dropwise with conc. H_2SO_4 (20 mL). The mixture was refluxed (110°C) for 2 h, cooled and quenched with ice/H_2O (300 mL). The pH was adjusted to 9.0 with 40% aq NaOH and extracted with $CHCl_3$ (2 × 200 mL). The

Table. Spiro Isochromanes **3** Prepared

Starting Material	Method	Product[a]	Yield[b] (%)	mp (°C)[c]	Molecular Formula[d]	^{1}H NMR ($CDCl_3$/TMS) δ, J (Hz)
1a	A ($LiAlH_4$)	**3a**	82	235–236	$C_{20}H_{24}ClNO$ (329.9)	1.65 (m, 2H), 1.82 (br m, 2H), 2.43 (m, 2H), 2.60 (br m, 2H), 2.68 (s, 2H), 3.54 (s, 2H), 4.75 (s, 2H), 6.95–7.35 (m, 9H)
1a	B (MeMgBr)	**3b**	94	119–121	$C_{22}H_{28}ClNO$ (357.9)	1.50 (s, 6H), 1.65 (m, 4H), 2.50 (m, 4H), 2.71 (s, 2H), 3.52 (s, 2H), 7.05–7.38 (m, 9H)
1a	B (EtMgBr)	**3c**	82	201–203	$C_{24}H_{32}ClNO$ (386.0)	0.82 (t, 6H, J = 7), 1.65 (m, 6H), 1.85 (m, 2H), 2.50 (br m, 4H), 2.70 (s, 2H), 3.50 (s, 2H), 7.00–7.40 (m, 9H)
1b	A ($LiAlH_4$)	**3d**	87	224–225	$C_{14}H_{20}ClNO$ (253.8)	1.72 (m, 2H), 1.84 (br m, 2H), 2.35 (s, 3H), 2.43 (m, 2H), 2.62 (br m, 2H), 2.70 (s, 2H), 4.76 (s, 2H), 7.01 (m, 1H), 7.10 (m, 1H), 7.16 (m, 2H)
1c	A ($LiAlH_4$)	**3e**	91	266–267	$C_{15}H_{23}ClN_2O_3S$ (346.9)	1.65 (m, 2H), 1.82 (br m, 2H), 2.30 (s, 3H), 2.40 (m, 2H), 2.55 (m, 2H), 2.65 (s, 2H), 2.95 (s, 3H), 4.72 (s, 2H), 6.92 (s, 1H), 7.00 (d, 1H, J = 7), 7.08 (d, 1H, J = 7)
1c	B (MeMgBr)	**3f**	85	203–205	$C_{17}H_{27}ClN_2O_3S \cdot 0.25H_2O$ (374.9)	1.48 (s, 6H), 1.70 (m, 4H), 2.30 (s, 3H), 2.45 (br m, 4H), 2.69 (s, 2H), 2.98 (s, 3H), 7.05 (m, 3H)
1d	A ($LiAlH_4$)	**3g**	72	280–284 (dec)	$C_{16}H_{25}ClN_2O_3S$ (360.9)	1.05 (t, 3H, J = 7.2), 1.41 (m, 1H), 1.60 (m, 1H), 1.80 (m, 2H), 2.18 (m, 2H), 2.45 (m, 2H), 2.70 (m, 4H), 3.02 (s, 3H), 4.74 (s, 2H), 6.92 (s, 1H), 7.08 (m, 2H)
1e	A ($LiAlH_4$)	**3h**	89	158–159	$C_{19}H_{22}ClNO$ (315.9)	1.78 (m, 1H), 2.12 (m, 1H), 2.50 (d, 1H, J = 9.6), 2.65 (m, 1H), 2.80 (d, 1H, J = 9.6), 2.81 (m, 1H), 2.86 (d, 1H, J = 14), 2.91 (d, 1H, J = 14), 3.61 (d, 1H, J = 12.9), 3.69 (d, 1H, J = 12.9), 4.80 (d, 1H, J = 15), 4.87 (d, 1H, J = 15), 6.90–7.40 (m, 9H)
1e	B (MeMgBr)	**3i**	82	168–170	$C_{21}H_{26}ClNO$ (343.9)	1.50 (s, 3H), 1.55 (s, 3H), 1.81 (m, 1H), 2.00 (m, 1H), 2.51–2.70 (m, 4H), 2.80 (d, 2H, J = 5), 3.55 (d, 1H, J = 14), 3.65 (d, 1H, J = 14), 7.05–7.40 (m, 9H)

[a] Eluents for chromatography: 50% EtOAc in hexane for **3a–c, h, i**; 10% MeOH in CH_2Cl_2 for **3e–g**; 5% MeOH in CH_2Cl_2 for **3d**.
[b] Isolated yield of the pure hydrochloride salt.
[c] Melting point of the hydrochloride salts.
[d] Satisfactory microanalyses obtained for the hydrochloride salts: C ± 0.4, H ± 0.23, N ± 0.29.

combined extracts were dried (Na_2SO_4) and concentrated in vacuo to an oil. The oil was dissolved in EtOH (400 mL) and treated with 2.2 M HCl in *i*-PrOH (36 mL). The precipitate was collected and dried in vacuo to give **1b** as a white powder identical in all respects to that reported previously;[6] yield: 9.2 g (42%).

Spiro Isochromanes 3a,d,e,g,h; General Procedure:
Method A: A solution of the appropriate lactone **1a–e** or a suspension of its hydrochloride in THF (3.3 mmol in 10 mL) was cooled to −10 °C and treated dropwise with 1.0 M $LiAlH_4$ in THF (4.5 mL, 4.5 mmol). The reaction was maintained at 0 °C for 1 h and then quenched by careful addition of H_2O (1.0 mL). The mixture was concentrated on a rotary evaporator, redissolved in 85% H_3PO_4 (10 mL), and heated at 100 °C for 1.5 h. The mixture was poured into ice, and the pH adjusted to 8.5 with 40% aq NaOH. The product was extracted with CH_2Cl_2 (3 × 60 mL), dried (Na_2SO_4), concentrated and chromatographed on silica gel (Table). The hydrochloride salts were obtained as analytically pure samples from EtOAc/hexane by addition of 2.2 M HCl in *i*-PrOH to give, after drying in vacuo, the yields indicated in the Table.

Spiro Isochromanes 3b,c,f,i; General Procedure:
Method B: A solution of lactone **1a, 1c,** or **1e** (as free base)[7] in THF (3.3 mmol in 10 mL) was cooled to −78 °C and treated dropwise with the appropriate Grignard reagent in THF (10 mmol). The reaction was allowed to warm to 25 °C and quenched with H_2O (1 mL). The mixture was concentrated on a rotary evaporator, redissolved in 85% H_3PO_4 (10 mL) and heated at 100 °C for 1.5 h. The products were isolated as in method A above to give the yields indicated in the Table.

(1) Vaughan Williams, E.M. In *Symposium on Cardiac Arrhythmias*; Sandoe, E.; Flensted-Jansen, E.; Oleson, K.H., Eds., AB Astra: **1970**; pp 449–472.
(2) Siegal, S.; Coburn, S.K. *J. Am. Chem. Soc.* **1951**, *73*, 5494.
(3) Warner, J.L.; Shriner, R.L. *J. Am. Chem. Soc.* **1957**, *79*, 3165.
(4) Thibault, J. *Ann. Chim.* **1971**, *6*, 263.
(5) Mohler, D.L.; Thompson, D.W. *Tetrahedron Lett.* **1987**, *28*, 2567.
(6) Yamamoto, M.; Kuniko, H.; Ikeda, M.; Ohtake, H.; Tasaka, K. *J. Med. Chem.* **1981**, *24*, 194.
(7) The hydrochloride salts may be used but require longer reaction times (approximately 12 h).