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Development of a Catalytic Tributyltin Hydride Cyclisation Process

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Abstract:

The development of a pilot plant process to prepare the spirocyclic piperidine (2) from the tetrahydropyridine (4) via a radical cyclisation reaction is described. The pilot plant process involves the use of a catalytic amount of tributyltin hydride (0.14 equiv) generated in situ by the reaction of tributyltin chloride with sodium borohydride (1.1 equiv) in 2-propanol/ethanol containing azo-bis(isobutyronitrile) (AIBN). Initial laboratory conditions are described as well as the changes made on transfer to the pilot plant. Measurement of the levels of residual amounts of tin in the batches of (2) produced are reported.

The spirocyclic indoline **2**[1] is a key intermediate in the preparation of SB-245570 **3**, a $5HT_{1B}$ autoreceptor antagonist, indicated for the treatment of depression. SB-245570 **3** was prepared by the carbonyl diimidazole coupling of the spirocycle **2** with the biphenylcarboxylic acid **1**[1] (Scheme 1).

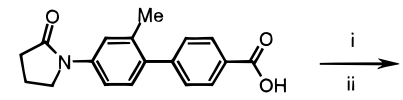
Our initial approaches to **2** are outlined in Scheme 2. The tetrahydropyridine **4**[1,2] was transformed to **2** in a two-step process using tributyltin hydride (1.4 equiv) in toluene at 80 °C in the presence of AIBN (0.23 equiv) to effect spirocyclisation, followed by acid hydrolysis of the *N*-acetyl group. Work-up and recrystallisation from cyclohexane, gave a 66% overall yield of **2**. The process to prepare **2** was carried out on a 0.2 molar scale, and the residual tin level was 200 ppm (ICP/AES)-Method A.

Whilst the above process was sufficient for the initial supplies of the indoline **2**, it was thought to be undesirable to scale up this process further for the following reasons.

1. The level of residual tin in the product **2** was higher than that desired.

2. The handling of multi-kilo quantities of highly toxic tributyltin hydride on the pilot plant was hazardous.

Scheme 1[a]



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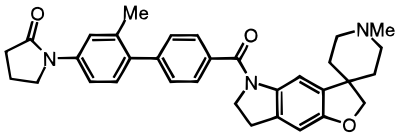

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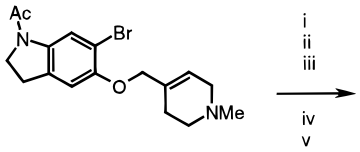
SB-245570

[a] Reagents and conditions: (i) *N*,*N*′-carbonyldiimidazole (1.05 equiv), THF, reflux; (ii) **2** (1.1 equiv), reflux, 80%.

Scheme 2[a]



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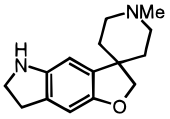

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[a] **Method A**: Reagents and conditions: (i) Bu_3SnH, 1.4 equiv, AIBN (0.23 equiv), PhMe, 80 °C; (ii) HCl (aqueous); (iii) wash:hexane; (iv) reflux 2 h, basify, NaOH/toluene; (v) evaporate, recrystallize: cyclohexane.

3. The cost of the tributyltin hydride required for the process was relatively high (£700/kg) and unacceptable.

Of the possibilities for solving the above problems, there was some precedent for the use of a catalytic amount of tributyltin chloride in the presence of a reducing agent to accomplish the desired transformation. Indeed, Corey[3] initially reported the reduction of the variety of alkyl and aryl bromides using tributyltin chloride (0.1 equiv)/sodium borohydride (3.5 equiv) in ethanol using UV initiation. Other catalytic systems have been used for radical cyclisation reactions. In particular, the use of tributyltin chloride (0.1 equiv) and sodium cyanoborohydride (2 equiv) in refluxing

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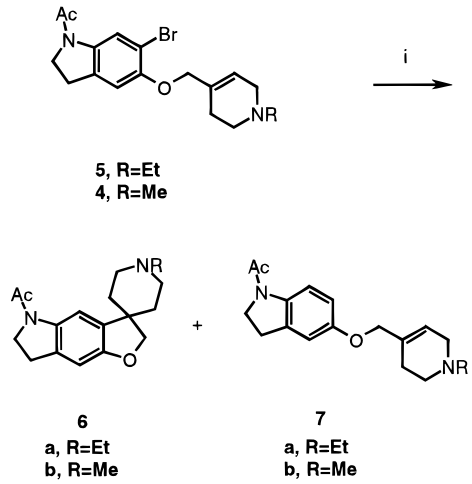
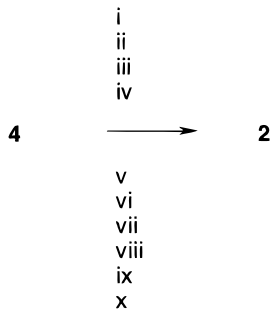
Scheme 3[a]



[a] Reagents and conditions: (i) reducing agent; solvent, reflux; AIBN, (0.23 equiv); Bu_3SnCl, (0.1 equiv), (for further conditions refer to Table 1).

Scheme 4[a]



[a] **Method B**: Reagents and conditions: (i) $NaBH_4$, (1.1 equiv); IPA; Bu_3SnCl, (0.1 equiv); AIBN, (0.23 equiv); reflux; (ii) evaporate; (iii) 5 M HCL; (iv) wash: toluene. petrol (60−80); (v) reflux; (vi) 40% NaOH, toluene; (vii) evaporate, recrystallise: cyclohexane. **Method C**: Reagents and conditions: (i) IPA, AIBN (0.23 equiv), Bu_3SnCl (0.14 equiv), heat to 80 °C; (ii) $NaBH_4$ (1.1 equiv), EtOH, 10% aqueous NaOH (0.05 equiv), add over 1 h; (iii) reflux 2 h; (iv) H_2O, concen. HCl (1.1 equiv); (v) distill out IPA, EtOH; (vi) concen. HCl (14 equiv); (vii) wash toluene/petrol 60−80; (viii) reflux 2 h; (ix) basify 40% NaOH, toluene; (x) concentrate, recrystallise:cyclohexane.

Table 1. **Initial catalytic tin experiments**

entry	solvent	time (h)	reducing agent (2 equiv)	yield (isolated) (%)	ratio (%PAR HPLC) 6a:7a:5
1	^{t}BuOH	16	$NaBH_3CN$	76	70:10:10
2	EtOH	9.5	$NaBH_4$ (2+1+1 equiv)	90	78:13:2
3	^{i}PrOH	5	$NaBH_4$	81	80:12:<1
4	^{i}PrOH	5	$NaBH_4$ (1.1 equiv)	82	85:8:<1
5	^{i}PrOH	7.5	$NaBH_4$ (1.1 equiv) Bu_3SnCl (0.05 equiv)	81%	75:10:6

tert-butyl alcohol containing AIBN, discovered by Stork,[4] has been applied to the cyclisation of an aryl bromide to give a tetrahydroquinoline derivative.[5]

Our initial goal was therefore to develop a process using a catalytic amount of tributyltin chloride in the presence of a relatively nontoxic reducing agent that was capable of producing a comparable yield of **2** to that obtained by the stoichiometric route, with a much reduced level of residual tin remaining in the recrystallised product. The process also had to have the potential to be scaled up in the pilot plant.

The initial experiments utilised the closely related *N*-ethyl tetrahydropyridine **5**[6] as the substrate, as large quantities of this intermediate were available at the time from a related project (Scheme 3).

The experiments were performed on a 1 mmol scale in the laboratory and are summarised below in Table 1.

The use of Stork's[4] conditions provided a starting point for our study (entry 1). Examination by HPLC of the reaction mixture revealed a 70:10:10 mixture of **6a:7a:5**, and after work-up, a 76% weight yield of product was isolated. This encouraging result led us to examine the use of modified Corey conditions (entry 2). This time analysis by HPLC showed a 78:13:2 mixture of **6a:7a:5**, although the addition of two further aliquots of $NaBH_4$ (2 × 1 equiv) after 1.5 and 2.5 h reflux was necessary to force the reaction towards completion. This gave rise to a 90% weight yield on work-up of material with the same HPLC profile. Replacing the solvent with 2-propanol, (in which sodium borohydride is much more stable) gave complete conversion to product in 81% weight yield (entry 3). HPLC analysis both before and after work-up showed an 80:12 mixture of **6a:7a**.

Reduction in the amount of sodium borohydride used (1.1 equiv, entry 4) led to an improved ratio of **6a:7a**, when examined by HPLC (85:8), with an 82% isolated yield on work-up of material with the same HPLC profile. An attempt to reduce the amount of tributyltin chloride to 0.05 equiv led to incomplete reaction. The product, obtained in 81% yield was an 75:10:6 mixture of **6a:7a:5** by HPLC (entry 5). The above results suggested that some development of a larger scale process would involve the use of at least 1.1 equiv of sodium borohydride in IPA.

With the above results providing some encouragement, it was desired to apply the results obtained to a large laboratory scale preparation of the *N*-methyl indoline **2**, which was needed at the time for our development programme. Accordingly, the procedure outlined in Scheme 4 (Method B) was adopted.

Using this methodology, a total of 785 g of the spirocylic piperidine **2** was prepared in 5 batches in 66−72% isolated yield with GC purity of 98.2−99.3% and a mean residual tin content of 18 ppm (range 17−25 ppm).

For further transfer to the pilot plant, however, there were some concerns from process safety:

1. In step (ii) of Scheme 4 (Method B), the evaporation of the crude reaction mixture after initial cyclisation and direct quenching with acid was highly undesirable.

2. A rate-controlled addition of sodium borohydride was required.

The process adopted to circumvent these problems is outlined in Scheme 4 (Method C).

In the initial step, a slurry of the bromo-ether **4** in 2-propanol (ca. 24 vol) was treated with tributyltin chloride

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(5) Clark, A. J.; Jones, K.; Storey, J. M. D.; McCarthy, C. *Tetrahedron Lett*. **1991** *32*, 7829.
(6) Gaster, L. M.; King, F. D.; Wyman, P. A. Patent WO 9619477, June 27, 1996; *Chem. Abstr*. **1996**, *125*, 142702

(0.14 equiv) and AIBN (0.23 equiv) and then heated to 80 °C, whereupon a solution of sodium borohydride (1.1 equiv) in ethanol containing 0.05 equiv of 10% aqueous sodium hydroxide solution (to stabilize the sodium borohydride solution) was added over 1 h. The reaction mixture was then maintained at reflux for a further 2 h, before HPLC analysis indicated complete conversion to product.

The reaction mixture was then quenched by the addition of water containing concentrated hydrochloric acid (1.1 equiv), and the IPA and ethanol were distilled out at atmospheric pressure, avoiding the unacceptable evaporation to dryness carried out on a smaller scale. The aqueous residue was then treated with further concentrated hydrochloric acid (14 equiv) and the resulting solution was washed with toluene and petrol (60−80), to remove organo-tin residues. The aqueous solution was then heated to reflux for 2 h and worked up as described by the conditions given in Scheme 2. The process was carried out on a 53.8 molar scale to give a 73% yield of the spirocycle **2**, with a GC purity of 97.4% and containing 15 ppm residual tin (ICP/AES).

In both the above cases, a good yield of the spirocycle **2** was isolated with acceptable GC purity and low residual tin.

In summary, we have developed known efficient catalytic tributyltin chloride process for the preparation of a key spirocycle **2**, giving rise to a product that is virtually tin free. We believe that this represents the first reported use of a catalytic amount of tributyltin chloride in the presence of sodium borohydride for the pilot plant preparation of a key pharmaceutical intermediate.

Experimental Section

General. Melting points were recorded on a capillary melting point apparatus and are uncorrected. ^{1}H NMR were recorded on a Bruker AC250 instrument. Chemical shifts for ^{1}H NMR are reported in ppm downfield (δ) relative to TMS as an internal standard in $CDCl_3$ or CD_3SOCD_3. Mass spectra were recorded on a Perkin-Elmer Sciex API-III instrument. GC analyses were performed on a Hewlett-Packard 5890 series II instrument, using a CPSIL 5CB (25 m × 0.32 mm) column, carrier gas He (2.0 mL/min at 200 °C), injection temperature 200 °C ramped to 320 °C at 8 °C/min, then held at 320 °C for 5 min, run time 20 min, detection by FID at 320 °C. Residual heavy metals were measured by inductively coupled plasma-atomic emission spectroscopy (ICP-AES) on a Jobin Yvon 24 spectrometer.

Reactions were monitored by HPLC analysis: YMC ODS C18 column 150 × 3.2 mm, gradient elution, $t = 0$ min, 80% aqueous TFA (0.1%): 20% MeCN, $t = 15$ min, 40% aqueous TFA (0.1%): 60% MeCN, UV detection at 260 nm, flow rate 1.0 mL/min.

Initial Catalytic Tin Experiments-Table 1: General Method. A stirred suspension of the *N*-ethyltetrahydropyridine **5** (0.365 g, 1.0 mmol) in the solvent (20 mL) was treated with the reducing agent (2.0 mmol), AIBN (0.025 g, 0.015 mmol), and tributyltin chloride (0.027 mL, 0.1 mmol) and the suspension heated to reflux under nitrogen for the specified period. The suspension produced was analysed by HPLC, before being evaporated under reduced pressure to give a yellow solid. The solid obtained was partitioned between 5 M HCl (15 mL) and toluene (15 mL). The aqueous layer was basified to pH 9 using solid sodium carbonate, and the suspension produced was extracted with dichloromethane (2 × 25 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the product as a beige solid.

1′-Methyl-2,3,6,7-tetrahydrofuro[2,3-f]indole-3-spiro-4′-piperidine (2). Method A: Stoichiometric Tributyltin Hydride Cyclisation Procedure. A stirred solution of the tetrahydropyridine **4** (67.3 g, 0.185 mol) in toluene (1750 mL) at 80 °C under nitrogen was treated with a solution of tributyltin hydride (70.0 mL, 0.260 mol) in toluene containing azo-bis(isobutyronitrile) (7.00 g, 0.043 mol) over a period of 3 h. The reaction mixture was analysed by HPLC, and was allowed to cool to 30 °C. The solution was extracted with a solution of concentrated HCl (200 mL) in water (400 mL), followed by 5 M HCl (100 mL). The acidic aqueous extracts were combined and washed with hexane (1000 mL), before being heated to reflux under nitrogen. After 3 h, the reaction mixture was allowed to cool to room temperature, and was treated with toluene (850 mL). The resulting biphasic mixture was carefully treated with 40% sodium hydroxide solution (280 mL) to pH 14. The biphasic mixture was filtered through a small pad of Celite, and the Celite pad was washed with warm (45 °C) toluene (850 mL). The organic layer was separated, and the aqueous layer was further extracted with warm (45 °C) toluene (500 mL). The combined organic layers were washed with water (500 mL) before being dried (Na_2SO_4) and evaporated under reduced pressure to give a pale brown solid which was dried in vacuo (38.9 g). The solid was recrystallised from refluxing cyclohexane (1200 mL). The product obtained was filtered, washed with cyclohexane (4 × 80 mL) and dried in vacuo to give the title compound **2** as a beige solid (29.74 g, 66%): mp 167−168 °C, δ ($CDCl_3$) 1.70 (m, 2H), 1.98 (m, 4H), 2.30 (s, 3H), 2.82 (m, 2H), 2.95 (t, 2H, $J = 6.6$ Hz), 3.52 (t, 3H, $J = 6.6$ Hz), 4.30 (s, 2H), 6.45 (s, 1H), 6.62 (s, 1H); MS *m*/*z* 244 (MH^+, 100%), ICP/AES 193 ppm Sn.

Method B: Initial Scale-Up of Catalytic Tin Process to Prepare 2. To a stirred suspension of the tetrahydropyridine **4** (338.0 g, 0.93 mol) in 2-propanol (9.2 L) under nitrogen was added AIBN (35.2 g, 0.21 mol) and sodium borohydride (38.2 g, 0.99 mol). Tributyltin chloride (34.2 mL, 0.126 mmol) was added over 5 min and the resultant suspension heated to reflux. After 5 h, the reaction mixture was allowed to cool to room temperature. Analysis by HPLC revealed an 85:6:2 mixture of **6b:7b:4.** The reaction mixture was evaporated under reduced pressure to give a beige solid. The beige solid was dissolved with stirring in 5 M hydrochloric acid (3.1 L) under a stream of nitrogen. The cloudy orange solution produced was washed with toluene (2 × 10 L) and 60−80 petroleum ether (1 × 10 L) before being heated to reflux under nitrogen. After 6 h at reflux, the reaction mixture was allowed to cool to room temperature and was treated with toluene (5 L), followed by 40% sodium hydroxide solution. The resulting warm (50 °C) biphasic mixture was filtered through a bed of Celite (400 g) and the Celite bed was washed with hot (60 °C) toluene (2.5 L).

The aqueous layer was separated off, and the organic layer was washed with hot (60 °C) water (1 × 2 L). The combined aqueous layers were extracted with hot (60 °C) toluene (1 × 2.5 L), and this toluene extract was washed with warm (40 °C) water (1 × 0.5 L). The toluene extracts were combined and evaporated under reduced pressure to give a light brown solid which was dried in vacuo. The brown solid was treated with hot (60 °C) cyclohexane (2.5 L) and was transferred to a 10 L flask. Further cyclohexane (3.1 L) was added, and the slurry obtained was heated to reflux under nitrogen to give a dark brown solution. The solution was allowed to cool to room temperature and was stirred overnight before the slurry was filtered and washed with cyclohexane (4 × 0.4 L) to give the title compound **2** as pale brown crystals (157.2 g, 72%). GC 99.06%, ICP/AES, 15 ppm Sn.

Method C: Pilot Plant Preparation of the Spirocycle 2. A solution of sodium borohydride (2.30 kg, 60.7 mol at 99.8%) in ethanol (74 L) stabilised with 32% w/w sodium hydroxide solution (0.25 L) and water (0.9 L) was added to a suspension of the tetrahydropyridine **4** (20.16 kg, 53.8 mol at 97.4%), AIBN (2.08 kg, 12.3 mol at 97.0%) and tributyltin chloride (2.52 kg, 8.5 mol at 97.6%) in 2-propanol (295 L) at 79 °C over 1 h maintaining the temperature at 79−82 °C. The mixture was stirred for a further 1.5 h, maintaining the temperature at 79−82 °C after which time HPLC analysis showed an 85:8:0.8 ratio of **6b:7b:4**. The mixture was cooled to 44 °C, and a solution of aqueous hydrochloric acid (5.7 L of concentrated hydrochloric acid in 138 L of water) was added over 17 min at 40−44 °C. The solution was heated to reflux, and ethanol/2-propanol/water distilled from the mixture at 76−92 °C over 3.5 h. The mixture was cooled to 38 °C, and concentrated hydrochloric acid (66 L) was added over 20 min at 30 to 38 °C. The resulting solution was washed with toluene (2 × 276 L) and hexane (2 × 276 L). The aqueous acidic solution was heated to 100 °C and stirred at this temperature for 2 h, after which time HPLC analysis showed the de-acetylation to be complete. Toluene (322 L) was added, and the mixture was basified by addition of 32% w/w sodium hydroxide solution (99 L) over 37 min, allowing the temperature to rise to 50 °C. The biphasic mixture was filtered through Celite (2 kg), and the filter bed was washed with warm (55 °C) toluene (147 L). While the temperature was maintained at ∼50 °C, the mixture was separated and the aqueous phase extracted with further toluene (147 L). The combined toluene extracts were washed with water (64 L), again while the temperature was maintained at ∼50 °C, and then the extracts were evaporated to dryness in vacuo. The residue was dissolved in cyclohexane (306 L), heating to reflux (81 °C). The solution was cooled to 20 °C to crystallize the product and stirred at 14 to 20 °C for 18 h. The resulting product was filtered and washed with cyclohexane (96 L), before being dried in vacuo at 36−45 °C for 20 h to give the **title compound 2** as a beige solid (9.81 kg, 73%). GC 97.4%, ICP/AES 15 ppm Sn.

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