Alternative Synthesis of Septic Shock Candidate 3,4-Dihydro-3,3-dimethylisoquinoline *N*-Oxide (MDL 101002) Utilizing an Improved Pictet−Spengler Reaction

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A series of compounds incorporating a dihydroisoquinoline-based nitrone has drawn particular interest for the treatment of stroke and septic shock.[1] One in particular, 3,4-dihydro-3,3-dimethylisoquinoline *N*-oxide (MDL 101002, **6**), has previously been synthesized utilizing a modified Bischler−Napieralski reaction. The key reaction to form the quinoline ring system via this route is shown in Scheme 1.[1b] This reaction proved to be very tedious and gave poor results on a larger scale. It became clear that alternative chemistry needed to be investigated if larger quantities of material were to be obtained.

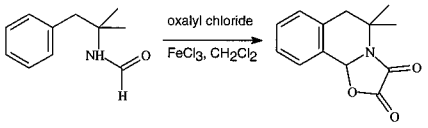
A more direct route could be envisioned utilizing a Pictet−Spengler reaction on phentermine hydrochloride (**1**). Although there has been limited success, the difficulty with which unsubstituted aromatic phenethylamines undergo the Pictet−Spengler reaction is well-recognized.[2]

In 1977, Ito and Tanaka reported the ease at which *N*-sulfonylphenethylamines underwent cyclization in the presence of 37% formaldehyde and boron trifluoride diethyl etherate.[3] We report herein an alternative synthesis of MDL 101002 (**6**) via a *modified Pictet−Spengler reaction following the Ito−Tanaka protocol*, a highly efficient procedure having the potential of readily producing kilogram quantities of MDL 101002.

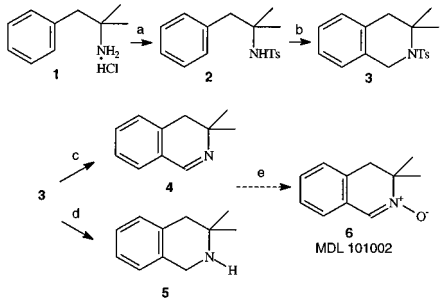
Results

Scheme 2 summarizes the synthesis of MDL 101002 (**6**). Commercially available phentermine hydrochloride (**1**) was transformed into *N*-(1,1-dimethyl-2-phenylethyl)-4-methylbenzenesulfonamide (**2**) using standard tosylation conditions.[3] Any attempt to directly cyclize **1** under original Pictet−Spengler conditions (HCl, "methylal") failed to produce a tetrahydroisoquinoline in reasonable amounts.[2]

Scheme 1



Scheme 2[a]



[a] (a) *p*-TsCl, NEt_3, CH_2Cl_2 (99%); (b) $BF_3.OEt_2$, DMM (99%); (c) KOH, MeOH, reflux (90%); (d) Na, naphthalene, DMF (86%); (e) H_2O_2, Na_2WO_4.[1a,b]

Treating **2** in dimethoxymethane (DMM) with boron trifluoride diethyl etherate produced 1,2,3,4-tetrahydro-3,3-dimethyl-2-[(4-methylphenyl)sulfonyl]isoquinoline (**3**) in an isolated yield of 99%. The DMM serves as the solvent as well as the formaldehyde source, while the boron trifluoride diethyl etherate facilitates formaldehyde formation and Pictet−Spengler cyclization. It is quite unusual for the solvent and catalyst both to serve two unique and essential functions resulting in such an efficient reaction. It should also be noted that the reaction does not proceed in the absence of the tosylate functionality.[2,3]

Removal of the tosylate can be accomplished in two fashions: Refluxing potassium hydroxide in methanol will afford the elimination product 3,4-dihydro-3,3-dimethylisoquinoline (**4**) in 90% yield.[4] Alternatively, treatment of **3** with sodium naphthalenide[5] gives the 1,2,3,4-tetrahydro-3,3-dimethylisoquinoline (**5**) in 86% yield containing 14% of the elimination product **4** as well. Reacting compound **4** or **5** with sodium tungstate will afford the desired MDL 101002 as previously reported.[1a,b]

Although there are other limited examples[2] of unsubstituted aromatic phenethylamines undergoing the Pictet−Spengler reaction in modest yields, we feel this modified Itom−Tanaka reaction may have some minor advantages. The ability to mildly generate formaldehyde in an anhydrous environment, thus limiting human exposure, is always advantageous. The *extreme efficiency* of this example has potential for rapid access into larger quantities of MDL 101002 as well as analogues of dihydroisoquinoline-based nitrones from nonactivated phenethylamines.

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Experimental Section

General. NMR spectra were recorded on Varian XL 300 and/or Varian GEMINI-300 spectrometers at 300 MHz for ^{1}H and 75 MHz for ^{13}C. GC conditions: injector temperature, 250 °C; detector temperature, 250 °C; program, 50 °C for 2 min, then heated to 250 °C at 20 °C/min; column, HP-1 methyl silicone gum, 10-m × 0.53-mm × 2.65-mm film thickness. Spectral and elemental analyses were performed by the Analytical and Structural Sciences Department, Hoechst Marion Roussel Research Institute, Cincinnati Center.

***N*-(1,1-Dimethyl-2-phenylethyl)-4-methylbenzenesulfonamide (2).** To a nitrogen-blanketed solution of **1** (3.56 g, 0.019 mol), CH_2Cl_2 (20 mL), and triethylamine (8.01 mL, 0.058 mol) was added *p*-TsCl (4.39 g, 0.023 mol). The mixture was stirred at room temperature for 12 h while monitoring by GC; t_R of **1**(free base)= 4.1 min, t_R of **2** = 11.2 min. The reaction mixture was partitioned between CH_2Cl_2 (100 mL) and water (100 mL), and the organic layer was separated and dried over Na_2SO_4. The drying agent was filtered off, and the filtrate was concentrated to give 5.73 g of compound **2** (99%): IR (KBr, cm^{-1}) 3443, 3283, 1311, 1097; ^{1}H NMR ($CDCl_3$) d 7.72 (m, 2H), 7.21−7.35 (m, 7H), 4.50(bs, 1H), 2.83 (s, 2H), 2.40 (s, 3H), 1.18 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 142.8, 140.6, 136.6, 130.8, 129.4, 128.2, 126.9, 126.7, 56.9, 49.0, 27.4, 21.5; MS *m*/*z* (M^+) calcd 303.4, obsd 304.

Anal. Calcd for $C_{17}H_{21}NO_2S$: C, 67.30; H, 6.98; N, 4.62. Found: C, 67.23; H, 6.90; N, 4.55.

1,2,3,4-Tetrahydro-3,3-dimethyl-2-[(4-methylphenyl)sulfonyl]isoquinoline (3). To a nitrogen-blanketed mixture of compound **2** (8.30 g, 0.027 mol) in DMM (50 mL) was added BF_3·OEt_2 (9.9 mL, 0.081 mol). The mixture was stirred at room temperature for 12 h while monitoring by GC; t_R of **2** = 11.2 min, t_R of **3** = 11.5 min. The reaction mixture was partitioned between ethyl acetate (100 mL) and water (100 mL). The layers were separated, and the organic layer was washed with saturated sodium bicarbonate (2 × 100 mL) and dried over Na_2SO_4. The drying agent was filtered off, and the filtrate was concentrated at 40 °C/50 Torr to give 8.55 g of compound **3** (99%): IR (KBr, cm^{-1}) 3441, 2984, 1338, 1159; ^{1}H NMR ($CDCl_3$) δ 7.65 (m, 2H), 7.05−7.25 (m, 6H), 4.59 (s, 2H), 2.70 (s,2H), 2.39 (s, 3H), 1.40 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 142.7, 139.7, 134.5, 133.6, 129.4, 128.1, 127.2, 126.9, 126.4, 125.4, 58.1, 46.9, 44.9, 27.7, 21.4; MS *m*/*z* (M^+) calcd 315.4, obsd 315. *Anal.* Calcd for $C_{18}H_{21}NO_2S$: C, 68.54; H, 6.71; N, 4.44. Found: C, 68.14; H, 6.70; N, 4.37.

3,4-Dihydro-3,3-dimethylisoquinoline (4). To a nitrogen-blanketed mixture of KOH (30 g) and MeOH (60 mL) was added compound **3** (4.0 g, 0.013 mol). The reaction mixture was heated at reflux for 17 h, and the reaction was followed by GC; t_R of **3** = 11.5 min, t_R of **4** = 5.0 min. The reaction mixture was cooled to ambient temperature, the reaction was quenched with water (100 mL), and 10% HCl was slowly added until a pH = 7 was reached. The aqueous mixture was extracted with CH_2Cl_2 (3 × 100 mL), and the organic layers were combined and stirred with charcoal and Na_2SO_4. The solution was filtered through Celite, and the filtrate was concentrated (25 °C/150 Torr) to give 1.79 g of compound **4** (90%) (lit.[1a]). *Caution*: Compound **4** is volatile. IR (neat, cm^{-1}) 3389, 2966, 1628; ^{1}H NMR ($CDCl_3$) δ 8.23 (s, 1H), 7.40−7.15 (m, 4H), 2.72 (s, 2H), 1.25 (s, 6H);^{13}C NMR ($CDCl_3$) δ 157.4, 135.6, 131.0, 128.0, 127.5, 127.0, 126.9, 54.7, 37.9, 28.0; MS *m*/*z* (M^+) calcd 159.23, obsd 159.

1,2,3,4-Tetrahydro-3,3-dimethylisoquinoline (5). To a stirred solution of naphthalene (5.8 g, 0.045 mol) in dimethoxymethane (DME) (50 mL) was added sodium (1.09 g, 0.039 mol). The mixture was allowed to stir for 4 h until a dark green color persisted. To this solution was added **3** (5.0 g, 0.016 mol) in 20 mL of DME. The reaction was monitored by GC; t_R of **3** = 11.5 min, t_R of **5** = 5.3 min. When the reaction was complete (2 h), the reaction was quenched with saturated NaCl (70 mL). The mixture was partitioned between ethyl acetate (250 mL) and 10% HCl (250 mL), and the organic layer was discarded; 10% NaOH was added to the aqueous layer until a pH = 7 was reached. The mixture was extracted with CH_2Cl_2 (2 × 100 mL), dried ($MgSO_4$), filtered, and concentrated (25 °C/150 Torr) to produce 2.2 g (86%) of **5** (lit.[1a]). *Caution*: Compound **5** is volatile. There was 14% of **4** present which can be quantitatively reduced with $NaBH_4$ in ethanol if desired. **5**: IR (neat, cm^{-1}) 3043, 2897, 744; ^{1}H NMR ($CDCl_3$) δ 7.14−7.00 (m, 4H), 4.02 (s, 2H), 2.61 (s, 2H), 1.58 (bs, 1H), 1.19 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 134.5, 134.4, 129.5, 125.9, 125.6, 125.5, 48.6, 44.3, 41.5, 27.7; MS *m*/*z* (M^+) calcd 161.24, obsd 161.

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