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TOTAL SYNTHESIS OF TROPINONE USING 1,3-DIPOLAR CYCLOADDITION OF CYCLIC AZOMETHINE YLIDE AND PHENYL VINYL SULFONE AS THE KEY STEP

Joydev K. Laha

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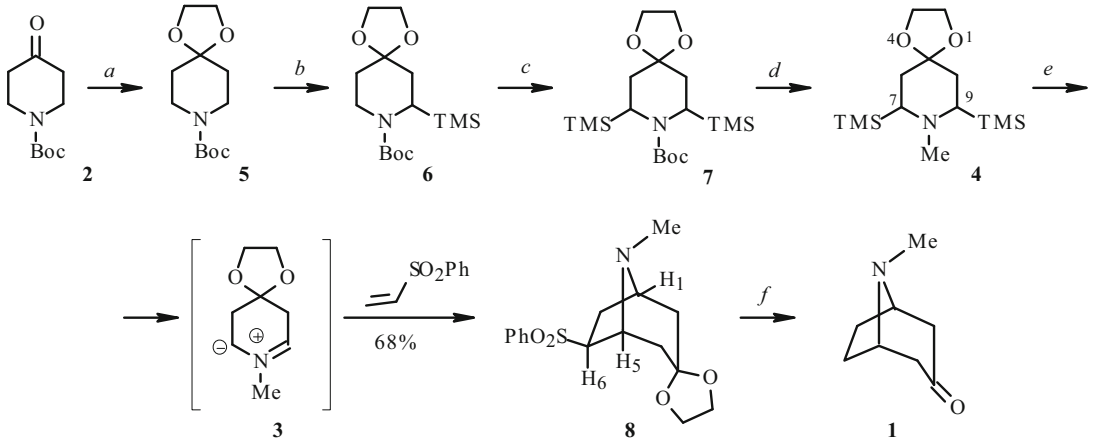
*Total synthesis of tropinone from the readily available piperidone **2** is described. The rapid assembly of the tropane skeleton was achieved by 1,3-dipolar cycloaddition of cyclic azomethine ylide **3** to phenyl vinyl sulfone.*

Keywords: tropane alkaloids, tropinone, phenyl vinyl sulfone, 1,3-dipolar cycloaddition, cyclic azomethine ylide.

Tropane alkaloids possessing the intriguing structural feature of the 8-azabicyclo[3.2.1]octane (tropane) skeleton are endowed with a variety of biological activities [1]. The first synthesis of tropinone (**1**), a simple tropane alkaloid, was reported by Willstatter in an extended series of transformations starting from cycloheptanone [2]. Soon thereafter, Robinson devised an efficient, elegant approach involving the condensation of succinaldehyde, methylamine, and the calcium salt of 1,3-acetone dicarboxylic acid affording **1** in 42% yield [3]. Recently, Mikami et al. reported the synthesis of **1** *via* a tandem (domino) ene-type reaction of acetone silyl enol ether with an imminium ion [4].

Our continued efforts to develop an efficient route to the stereoselective construction of the tropane skeleton by 1,3-dipolar cycloaddition of endocyclic non-stabilized azomethine ylide to a racemic [5] or chiral [6] dipolarophile provided a unique platform to apply this methodology to the total synthesis of tropane alkaloids. Herein, we describe the synthesis of **1** from an inexpensive piperidone **2** using 1,3-dipolar cycloaddition of a suitably functionalized cyclic azomethine ylide **3**, generated *in situ* from α,α'-bis(trimethylsilyl)-*N*-methylpiperidine **4** by treatment with Ag(I)F, to phenyl vinyl sulfone as the key step [7].



a. ethylene glycol, PPTS, benzene reflux, 87%; *b*. TMEDA, *s*-BuLi, TMSCl, –78°C, 86%; *c*. TMEDA, *s*-BuLi, TMSCl, –40°C, 62%; *d*. 1. TFA, CH_2Cl_2, room temperature, 2. HCHO, $NaBH_3CN$, gl CH_3COOH, room temperature, 66%; *e*. Ag(I)F, CH_2Cl_2, room temperature; *f*. 6% Na–Hg, $Na_2HPO_4 \cdot H_2O$, MeOH, room temperature, 65%

Scheme 1

Division of Organic Chemistry (Synthesis), National Chemical Laboratory, Pune-411008, India, e-mail: jlaha@rics.bwh.harvard.edu. Published in Khimiya Prirodnykh Soedinenii, No. 2, pp. 213–215, March–April, 2010. Original article submitted September 12, 2008.

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The synthesis of **1** from the commercially available piperidone **2** is shown in Scheme 1. Refluxing a mixture of **2**, ethylene glycol, and pyridinium *p*-toluene sulfonate (PPTS) in benzene gave **5** in 87% isolated yield.

Following our previous protocol [6b], treatment of **5** with *s*-BuLi at –78°C for 2 h in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), followed by the addition of TMSCl, gave **6** in 86% isolated yield. Several experiments were carried out to optimize the synthesis of **7**. The best condition entails treatment of **6** with *s*-BuLi at –40°C for 1 h, followed by the addition of TMSCl, yielding **7** in 62% isolated yield. Treatment of **7** with TFA in CH_2Cl_2 at room temperature afforded the free-base crude amine, which was subjected to reductive methylation with 37% aqueous formaldehyde in the presence of $NaBH_3CN$ and glacial acetic acid. Thus, compound **4** was obtained from **7** in 66% isolated yield (two steps). The effective generation of cyclic azomethine ylide **3** and subsequent cycloaddition to the dipolarophile involved addition of a solution of **4** in anhydrous CH_2Cl_2 to a stirred mixture of Ag(I)F and phenyl vinyl sulfone in anhydrous CH_2Cl_2 under argon. Upon flash chromatography of the crude mixture, only cycloadduct **8** was isolated in 68% yield. In the ^1H NMR spectra of **8**, the H-6 *endo*-proton appeared at δ 3.90 as a doublet of a doublet (J = 10.7, 5.9 Hz,), which is indicative of *exo*-orientation of the sulfonyl functionality. Furthermore, this assignment was confirmed by 2D ^1H–^1H COSY experiment. Desulfonylation of **8**, carried out by stirring a buffered solution of **8** and 6% sodium-amalgam in methanol, and subsequent *in situ* deprotection of the ketal group afforded **1** in 65% isolated yield.

In conclusion, we have synthesized tropinone (**1**) in a short sequence of steps using a novel 1,3-dipolar cycloaddition chemistry involving a cyclic azomethine ylide **3** and phenyl vinyl sulfone. The methodology is sufficiently flexible to initiate a complex total synthesis of tropane alkaloids.

EXPERIMENTAL

8-Methyl-7,9-bis(trimethylsilyl)-1,4-dioxa-8-azaspiro[4.5]decane (4). A stirred solution of **7** (3.88 g, 10.0 mmoL) in anhydrous CH_2Cl_2 (40 mL) was treated dropwise with TFA (5.70 g, 50.0 mmoL) at 0°C over 30 min. After stirring at room temperature for 4 h, the reaction mixture was basified with 10% aqueous NaOH solution under ice-cold conditions. The organic layer was separated, washed with brine, dried (Na_2SO_4), and concentrated to give a crude amine that was utilized in the next step. A stirred solution of the crude amine in CH_3CN (120 mL) was treated with 37% aqueous formalin (1.5 mL) followed by $NaBH_3CN$ (1.71 g, 27.3 mmoL). After stirring at room temperature for 15 min, the reaction mixture was neutralized with glacial acetic acid followed by basification with NH_4OH, affording a solution which upon extraction with hexane gave a yellow liquid. Chromatographic purification of the crude product [silica, ethyl acetate–hexane (3:97)] gave a colorless viscous liquid (2.00 g, 66% yield). $C_{14}H_{31}NO_2Si_2$. IR ($CHCl_3$, ν_{max}, cm^{-1}): 2940, 1263; ^1H NMR (200 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.12 (18H, s), 1.72 (4H, d, J = 7.2), 2.45 (3H, s), 2.48 (2H, t, J = 5.8), 3.92 (4H, s); ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 28.6, 28.7, 42.1, 52.8, 64.1, 108.4; mass (*m/z*): 301 (M^+); FAB-MS: obsd 301.1889, calcd 301.1893.

***tert*-Butyl-1,4-dioxa-8-azaspiro[4.5]decane-8-carboxylate (5).** A mixture of **2** (10.0 g, 50.2 mmoL), ethylene glycol (3.70 g, 60.3 mmoL), and PPTS (1.20 g, 5.02 mmoL) was refluxed in benzene for 8 h under Dean-Stark conditions. The solvent was evaporated, and the residue thus obtained was dissolved in excess ethyl acetate. The solution was washed with water, brine, and dried (Na_2SO_4). Chromatographic purification of the crude reaction mixture [silica, hexane–EtOAc (2.5:1.5)] afforded a viscous liquid (10.6 g, 87% yield). $C_{12}H_{21}NO_4$. IR ($CHCl_3$, ν_{max}, cm^{-1}): 2974, 1697, 1421; ^1H NMR (200 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.45 (9H, s), 1.70 (4H, t, J = 5.6), 3.50 (4H, t, J = 6.2), 3.98 (4H, s); ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 28.1, 34.7, 41.6, 64.0, 79.0, 106.8, 154.3; Mass (*m/z*): 243 (M^+).

***tert*-Butyl-7-(trimethylsilyl)-1,4-dioxa-8-azaspiro-[4.5]decane-8-carboxylate (6).** A solution of **5** (4.90 g, 20.1 mmoL) in anhydrous ether (40 mL) was treated with TMEDA (2.79 g, 24.1 mmoL) followed by *s*-BuLi (1.5 M solution in cyclohexane, 16.1 mL, 24.1 mmoL) at –78°C over 15 min. After stirring the reaction mixture at –78°C for 2 h, TMSCl (2.61 g, 24.1 mmoL) was added and the reaction mixture was allowed to warm to room temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl followed by the usual work up, affording a crude mixture which upon distillation (bp 75–80°C/0.5 mm) gave a colorless oil (5.45 g, 86% yield). IR ($CHCl_3$, ν_{max}, cm^{-1}): 2940, 1691, 1423; ^1H NMR (200 MHz, $CDCl_3$, δ, ppm): 0.10 (9H, s), 1.45 (9H, s), 1.58–1.62 (2H, m), 1.70–1.80 (2H, m), 3.50–3.75 (3H, m), 4.02 (4H, s); ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): –0.9, 28.3, 35.4, 35.5, 44.1, 45.2, 64.0, 64.3, 78.9, 107.3, 154.7; mass (*m/z*): 316 (M+H); FAB-MS: obsd 315.1861, calcd 315.1866 ($C_{15}H_{29}NO_4Si$).

***tert*-Butyl-7,9-bis(trimethylsilyl)-1,4-dioxa-8-azaspiro[4.5]decane-8-carboxylate (7).** A solution of **6** (3.66 g, 11.6 mmoL) in anhydrous ether (30 mL) was treated dropwise with TMEDA (1.60 g, 13.9 mmoL) followed by *s*-BuLi (1.5 M in cyclohexane, 9.3 mL, 13.9 mmoL) at –78°C over 15 min. After 15 min, the temperature was raised to –40°C over 30 min.

After stirring for 1 h at this temperature, TMSCl (1.50 g, 13.9 mmoL) was added. Work-up followed by chromatography of the crude mixture gave a colorless liquid (2.80 g, 62% yield). IR ($CHCl_3$, ν_{max}, cm^{-1}): 2973, 1692, 1430; ^1H NMR (200 MHz, $CDCl_3$, δ, ppm): 0.15 (18H, s), 1.40 (9H, s), 1.60–1.80 (4H, m), 2.50–2.60 (2H, m), 3.85 (4H, s); ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): –1.32, –0.68, 28.47, 35.11, 36.07, 45.06, 46.07, 64.26, 79.04, 108.22, 155.86; mass (*m/z*): 388 (M + H); FAB-MS: obsd 387.2256, calcd 387.2261 ($C_{18}H_{37}NO_4Si_2$).

8-Methyl-6-(phenylsulfonyl)-8-azaspiro-[bicyclo[3.2.1]octane-3,2′-[1,3]dioxolane] (**8**). A stirred suspension of Ag(I)F (1.50 g, 0.010 moL) (previously dried under vacuum at 40°C) and phenyl vinyl sulfone (1.00 g, 5.90 mmoL) in anhydrous CH_2Cl_2 (15 mL) was treated dropwise with a solution of **4** (1.50 g, 5.00 mmoL) in CH_2Cl_2 (30 mL) over 15 min. Chromatographic purification of the crude residue [silica, $CHCl_3$–methanol 98:2] gave a yellow solid (1.10 g, 68% yield). Mp 165–167°C; IR ($CHCl_3$, ν_{max}, cm^{-1}): 2925, 1275, 1125; ^1H NMR (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.50–1.60 (2H, m), 2.10–2.20 (2H, m), 2.25–2.45 (2H, m), 2.45 (3H, s), 3.40 (1H, m), 3.65 (4H, m), 3.90 (1H, dd, J = 10.7, 5.9), 4.20 (1H, t, J = 8.0), 7.55 (2H, t, J = 7.8), 7.65 (1H, t, J = 7.8), 7.90 (2H, d, J = 7.8); ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 30.5, 35.9, 36.1, 37.1, 59.5, 60.2, 63.6, 64.9, 67.2, 107.1, 128.3, 129.3, 133.7, 139.3; mass (*m/z*): 323 (M^+); FAB-MS obsd 323.1196, calcd 323.1191 ($C_{16}H_{21}NO_4S$).

8-Methyl-8-azabicyclo[3.2.1]octan-3-one (**1**). A solution of **8** (0.500 g, 1.54 mmoL) and $NaH_2PO_4 \cdot H_2O$ (0.700 g, 6.19 mmoL) in anhydrous methanol (15 mL) was treated with 6% sodium amalgam (1.5 g). After stirring at room temperature for 2 h, the reaction mixture was poured into water and the aqueous layer was extracted with $CHCl_3$. Chromatographic purification of the crude mixture [silica, $CHCl_3$–methanol 98:2] gave a brown solid (0.14 g, 65% yield). Mp 40°C (lit. [3] mp 42.5°C). $C_8H_{13}NO$. IR ($CHCl_3$, ν_{max}, cm^{-1}): 3018, 2952, 1714; ^1H NMR (200 MHz, $CDCl_3$, δ, ppm): 1.50–1.65 (2H, m), 2.05–2.20 (4H, m), 2.45 (3H, s), 2.55–2.70 (2H, m), 3.35–3.50 (2H, m); ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 27.4, 37.9, 47.2, 60.5, 208.8.

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