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A FACILE AND EFFICIENT SYNTHESIS OF (±)-TROPAN-2-ONE

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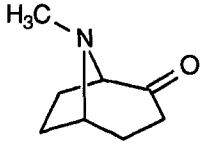
Abstract: The facile and efficient multigram synthesis of (±)-tropan-2-one **1** was achieved in six steps (65% overall yield) from *N*-methyl-3-oxopyridyl hydroiodide **3**.

The tropane ring system (8-methyl-8-azabicyclo[3.2.1]octane) is an important structural unit in a number of natural products and synthetic compounds of biological importance.[1] As part of a program aimed at the synthesis of a variety of substituted tropanes, it became necessary to develop a rapid yet versatile synthesis of (±)-tropan-2-one **1**.



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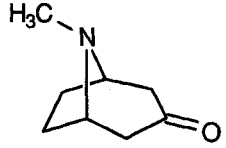

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Despite numerous procedures reported in the literature for the preparation of the meso-derivative tropinone **2**,[2] only a few methods exist for the preparation of tropan-2-one **1**.[3] From a survey of the literature, the 1,3-dipolar

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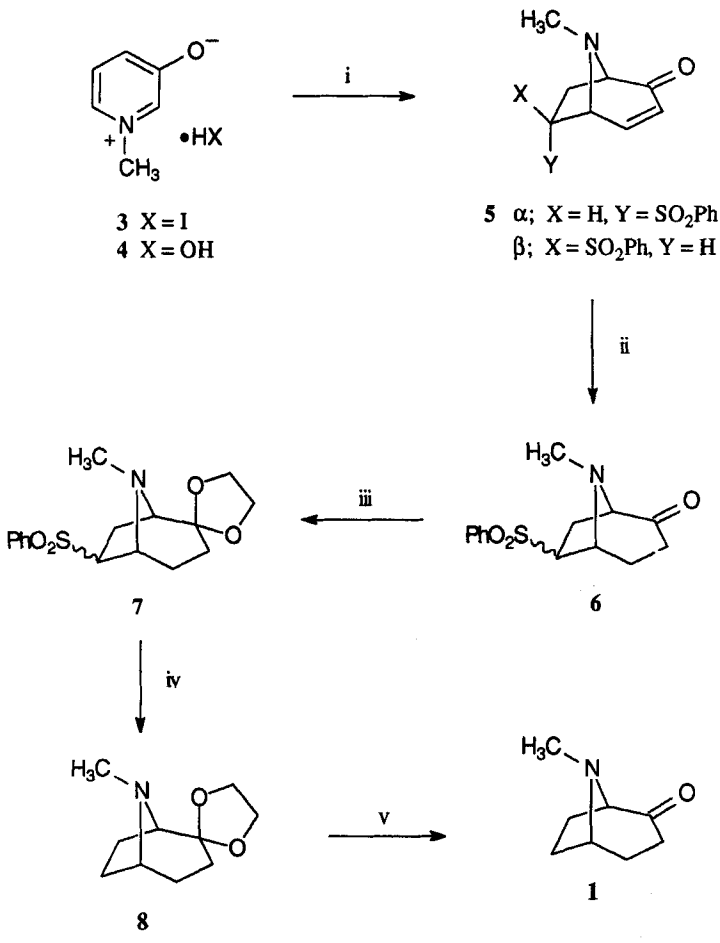
cycloaddition of pyridinium betaines with electron deficient alkenes, initially developed by Katritzky *et al*, is ideally suited for the construction of the bicyclic ring system of **1**.[4-7] The 1,3-dipolar cycloaddition of pyridinium betaines has recently been exploited for the synthesis of a number of 2,6-disubstituted tropanes.[8] Herein we wish to report the further development of this method for the multigram synthesis of (±)-tropan-2-one **1**.[9]

As illustrated in Scheme 1, the construction of (±)-tropan-2-one **1** was achieved by the 1,3-dipolar cycloaddition of a betaine **4** and phenyl vinyl sulfone, in similar fashion to the work described by Lallemand *et al.*[7] The betaine **4** was generated by passing *N*-methyl-3-oxopyridyl hydroiodide **3**[10] through a prepared ion exchange column (IRA 401, $^{-}$OH).[4a] Removal of excess water afforded the betaine **4** which presumably existed as the monohydrate.[4a] The air sensitive betaine **4** was then immediately added to a solution of phenyl vinyl sulfone in THF. Routinely, a stoichiometric ratio of 1.5:1 of betaine **4** to sulfone was employed to ensure complete conversion of the sulfone into the cycloaddition product. The 1,3-dipolar cycloaddition reaction was performed at reflux over 18 h and provided the 6-benzenesulfonyl-8-methyl-8-azabicyclo[3.2.1]oct-3-en-2-one **5** as a mixture of isomers (*endo*:*exo*, 7:1) in 97% yield. The major *endo*-isomer **5α** was obtained in pure form by recrystallization of the mixture from ethyl acetate. Alternatively, the minor *exo*-isomer **5β** was obtained in pure form by column chromatography. However, subsequent reactions were usually carried out with the mixture of isomers without further purification.

Hydrogenation (45 psi) of alkene **5** over 10% palladium on carbon in ethanol/chloroform (1:1) furnished the saturated derivative **6** in quantitative yield. The carbonyl moiety of **6** was then protected as the ethylene ketal **7**. This furnished the ketal derivative **7** in 81% overall yield from **5**.



Reagents: i) Phenyl vinyl sulfone, THF, Δ, 18 h. ii) 10% Pd/C, H_2 (45 psi), EtOH/$CHCl_3$. iii) $(CH_2OH)_2$, *p*-TsOH, benzene, Δ. iv) 40% Na(Hg), Na_2HPO_4, MeOH, THF, 1:1. v) 3N $HClO_4$, 90 °C.

Scheme 1

The desulfonation of the ketal derivative **7** was found to be most effective with freshly prepared 40% Na(Hg)[11] in a sodium phosphate (dibasic) buffered methanol/THF (1:1) solution. This procedure kept the mercury waste to a minimum, reaction times short and resulted in the clean and efficient desulfonation to give the ketal **8** in 85% yield.

Finally, deprotection of the ketal moiety was achieved in 3N perchloric acid at 90 °C. A number of methods were explored for the deprotection step.[12] Only perchloric acid was found to affect the hydrolysis of the ketal cleanly and furnished tropan-2-one **1** in 94% yield. However, this reaction was found to be very sensitive to temperature. Reaction temperatures below 90 °C resulted in incomplete conversion while temperatures above 95 °C resulted in lower yields due to decomposition of material.

In summary, the synthetic procedure reported herein provides a rapid and efficient synthesis of (±)-tropan-2-one **1** in 65% overall yield from **3**. In addition, several of the intermediates described herein are currently being exploited for the synthesis of highly functionalized tropane derivatives. The results of these studies will be reported in due course.

Experimental Section

All chemicals and reagents not otherwise noted were purchased from Aldrich Chemical Co. Tetrahydrofuran was dried by distillation from Na/benzophenone ketyl. Methanol was dried by distillation from $CaSO_4$. Chromatography solvents ethyl acetate (E.M. Science) and 30–60 °C petroleum ether (E.M. Science) were distilled prior to use. Flash silica gel (Silica Gel 60, E.M. Science, 230–400 mesh) and TLC plates (E.M. Science, Kiesel gel 60, F_{254}, 0.2 mm layer, glassback) were purchased from Curtin–Matheson Scientific. NMR

spectra were recorded using a Varian Gemini 300 MHz spectrometer. IR spectra were recorded on a Perkin–Elmer 2000 FT–IR spectrometer. Melting points were recorded on a Mel–Temp apparatus and are uncorrected. Elemental analyses were obtained from Atlantic Microlab, Inc., Norcross, GA.

6-Benzenesulfonyl-8-methyl-8-azabicyclo[3.2.1]oct-3-en-2-one (**5**).

N-Methyl-3-oxypyridyl betaine hydroiodide **3**[10] (64.0 g, 0.27 mol) was dissolved in water (50 mL) and eluted through an ion exchange column (IRA 401, 800 g) with water.[4a] The excess water was removed under reduced pressure until a constant weight was obtained. This afforded betaine **4** (32.5 g, 95%) as a yellow oil. A solution of phenyl vinyl sulfone (30.0 g, 0.18 mol, Lancaster Synthesis Inc.) in THF (200 mL) was added immediately to **4** and the heterogenous mixture was heated to reflux overnight. The yellow reaction mixture was allowed to cool to room temperature and poured into water (100 mL). The organic layer was removed and the aqueous portion was extracted with ethyl acetate (3 × 100 mL). The combined organic portions were washed with brine and dried (Na_2SO_4). The solvent was removed under reduced pressure to give **5** (46.8 g, 97%) as a mixture of isomers (**5α**:**5β**, 7:1). The material was usually pure enough at this point to carry on to the next step. However the major *endo*-isomer **5α** could be obtained in pure form by a single recrystallization of the mixture from ethyl acetate. The minor *exo*-isomer **5β** could be obtained in pure form by chromatography (SiO_2, ethyl acetate/petroleum ether, 8:2). **5α**: yellow solid, mp 118 – 120 °C; ^{1}H NMR ($CDCl_3$) δ 7.89 (d, J = 7.6 Hz, 2H, *o*-Ph), 7.65 (m, 1H, *p*-Ph), 7.58 (m, 2H, *m*-Ph), 6.92 (dd, J = 9.7 Hz, 4.9 Hz, 1H, *H-4*), 6.03 (d, J = 9.8 Hz, 1H, *H-3*), 4.21 (d, J = 4.8 Hz, 1H, *H-5*), 3.53 (m, 2H, *H-6*, *H-1*), 2.75 (m, 1H, *H-7*α), 2.35 (s, 3H, *CH*$_3$), 1.90 (dd, J = 12.0 Hz, 6.0 Hz, 1H, *H-7*β). ^{13}C NMR ($CDCl_3$) δ 197.5, 145.5, 138.1, 134.0, 129.3, 128.7, 128.5, 70.2, 67.8, 60.4, 34.7, 27.9. **5β**: white

solid, mp 122 – 124 °C; ^{1}H NMR ($CDCl_3$) δ 7.91 (d, J = 7.5 Hz, 2H, *o*-Ph), 7.65 (m, 1H, *p*-Ph), 7.59 (m, 2H, *m*-Ph), 6.96 (dd, J = 9.7 Hz, 4.8 Hz, 1H, *H-4*), 5.92 (d, J = 10.0 Hz, 1H, *H-3*), 3.85 (m, 2H, *H-1*, *H-6*), 3.44 (t, J = 7.9 Hz, 1H, *H-5*), 2.71 (m, 1H, *H-7*α), 2.46 (s, 3H, CH_3), 2.09 (dd, J = 10.5 Hz, 6.03 Hz, 1H, *H-7*β). ^{13}C NMR ($CDCl_3$) δ 194.6, 149.4, 134.1, 129.5, 128.3, 126.6, 71.5, 64.4, 60.6, 38.1, 31.2.

Anal. Calcd. for $C_{14}H_{15}NO_3S$: C, 60.63; H, 5.45; N, 5.05. Found: C, 60.59; H, 5.44; N, 4.89.

6-Benzenesulfonyl-8-methyl-8-azabicyclo[3.2.1]octan-2-one (**6**).

To a solution of 10% Pd/C (4.7 g) in ethanol (100 mL) was added a solution of **5** [47 g, 0.17 mol, in chloroform (100 mL)]. The mixture was hydrogenated on a Parr Hydrogenation apparatus at 45 psi for 2 h. The catalyst was removed by filtration through a pad of celite. The filter cake was rinsed with chloroform (50 mL) and the combined organic portions were concentrated under reduced pressure. This afforded **6** (46.8 g, 99%) as a mixture of isomers. The colorless oil was generally found to be of sufficient purity to carry on to the next step. However, the major *endo*-isomer **6**α could be obtained in pure form by a single recrystallization from ethyl acetate. The minor *exo*-isomer **6**β could be obtained in pure form by column chromatography (SiO_2, ethyl acetate/petroleum ether, 8:2). **6**α: white solid, mp 119 – 121 °C; ^{1}H NMR ($CDCl_3$) δ 7.89 (d, J = 7.7 Hz, 2H, *o*-Ph), 7.63 (m, 1H, *p*-Ph), 7.56 (m, 2H, *m*-Ph), 3.82 (s, 1H), 3.62 (dd, J = 6.9 Hz, 6.8 Hz, 1H), 3.33 (d, J = 7.0 Hz, 1H), 2.50 (m, 1H), 2.40 (s, 3H, CH_3), 2.27 (m, 3H), 1.98 (m, 1H), 1.78 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 208.5, 138.2, 133.8, 129.2, 128.4, 71.0, 67.4, 59.5, 36.1, 32.7, 29.7, 27.9. **6**β: oil; ^{1}H NMR ($CDCl_3$) δ 7.79 (d, J = 7.6 Hz, 2H, *o*-Ph), 7.55 (m, 1H, *p*-Ph), 7.48 (m, 2H, *m*-Ph), 3.56 (m, 2H), 3.34 (s, 1H), 2.56 (m, 1H), 2.3 (s, 3H, CH_3), 2.24 (m, 3H),

1.96 (m, 1H), 1.65 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 205.2, 137.9, 133.6, 129.0, 128.1, 71.0, 65.7, 58.7, 36.4, 32.8, 30.5, 27.7.

Anal. Calcd. for $C_{14}H_{17}NO_3S$: C, 60.19; H, 6.13; N, 5.01. Found: C, 60.32; H, 6.11; N, 5.08.

6-Benzenesulfonyl-8-methyl-8-azabicyclo[3.2.1]octan-2-one ethylene ketal (**7**).

A solution of **6** (46.0 g, 0.16 mol), ethylene glycol (51 g, 0.82 mol) and *p*-toluenesulfonic acid monohydrate (36.1 g, 0.19 mol) in benzene (200 mL) was heated to reflux for 8 h with azeotropic removal of water by a Dean–Stark trap. The reaction mixture was allowed to cool to room temperature and was poured into a solution of 7% ammonium hydroxide (100 mL). The organic portion was removed and the aqueous solution was extracted with ethyl acetate (3 × 100 mL). The combined organic portions were washed with brine and dried (Na_2SO_4). The solvent was removed under reduced pressure and the resultant oil chromatographed (SiO_2, ethyl acetate). This furnished **7** as oil (46.1 g, 84%), **7α**: white solid, mp 111–113 °C. ^1H NMR ($CDCl_3$) δ 7.85 (d, J = 7.6 Hz, 2H, *o*-Ph), 7.59 – 7.49 (m, 3H, *m*-, *p*-Ph), 3.95–3.70 (m, 5H, *H-5*, $-OCH_2$-), 3.41 (t, J = 6.0 Hz, 1H, *H-6*), 2.96 (d, J = 6.0 Hz, 1H, *H-1*), 2.48 (s, 3H, CH_3), 2.32 (m, 1H), 1.92 (m, 2H), 1.59 (m, 1H), 1.39 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 139.5, 133.4, 129.1, 127.9, 106.9, 68.4, 68.0, 64.8, 64.2, 61.7, 40.3, 28.5, 27.9, 27.7. **7β**: ^1H NMR ($CDCl_3$) δ 7.63 (d, J = 7.5 Hz, 2H, *o*-Ph), 7.29 (m, 3H, *m*-, *p*-Ph), 3.76 – 3.46 (m, 4H, $-OCH_2$-), 3.30 (m, 1H), 3.25 (m, 2H), 2.23 (s, 3H, CH_3), 1.75 – 1.57 (m, 3H), 1.35 – 1.16 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 138.8, 132.7, 128.5, 127.4, 106.4, 67.4, 66.5, 64.4, 63.7, 60.7, 39.9, 27.6, 27.4, 27.0.

Anal. Calcd. for $C_{16}H_{21}NO_4S$: C, 59.42; H, 6.54; N, 4.33. Found: C, 59.22; H, 6.49; N, 4.39.

8-Methyl-8-azabicyclo[3.2.1]octan-2-one ethylene ketal (**8**).

To a 2 L three-neck flask fitted with a thermometer, a powder funnel and a mechanical stirrer was added anhydrous Na_2HPO_4 (108 g, 0.62 mol) and dry methanol (100 mL). A solution of **8** (20.0 g, 0.062 mol) in dry THF (100 mL) was then added. 40% Na(Hg)[11] (40 g) was pipetted portionwise (~ 2 g) into the slurry over 2 h. The rate of addition of the amalgam was controlled such that the reaction temperature did not exceed 50 °C. After all the amalgam had been added (reaction complete by TLC) the reaction mixture was quenched with methanol (50 mL) and allowed to cool to room temperature. The organic solution was carefully decanted away from the inorganic residue. The inorganic material was then rinsed with THF (3 × 100 mL). The combined organic portions were then concentrated under reduced pressure. The resultant slurry was then dissolved in water (400 mL) and extracted with dichloromethane (4 × 200 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). The solvent was removed under reduced pressure and the resultant oil was purified by bulb-to-bulb distillation to give **8** as a colorless liquid (9.6 g, 85%), bp 80–85 °C (0.1 mm Hg). ^{1}H NMR ($CDCl_3$) δ 3.95–3.74 (m, 4H, *OCH*$_2$), 3.01 (t, J = 2.7 Hz, 1H, *H-5*), 2.78 (d, J = 6.2 Hz, 1H, *H-1*), 2.18 (s, 3H, *CH*$_3$), 1.09 (m, 2H), 1.75 – 1.60 (m, 2H), 1.49 – 1.31 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 108.8, 68.0, 64.6, 64.0, 60.6, 41.3, 29.8, 26.7, 23.9, 23.2.

Anal. Calcd. for $C_{10}H_{17}NO_2 \bullet HCl \bullet ½H_2O$: C, 52.51; H, 8.37; N, 6.12. Found: C, 52.48; H, 8.32; N, 6.09.

(±)-Tropan-2-one (**1**).[9]

A solution of ketal **8** (8.0 g, 0.044 mol) in 3N $HClO_4$ (300 mL, 20 equiv.) at 90 °C was stirred overnight. The reaction mixture was allowed to cool to room

temperature and poured into an ice-cold solution of 3N NaOH (310 mL). The alkaline aqueous mixture was extracted with dichloromethane (3 × 200 mL). The combined organic fractions were washed with brine (300 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the resultant oil was purified by bulb-to-bulb distillation. This furnished (±)-tropan-2-one **1** as a slightly yellow liquid (5.8 g, 94%), bp 50–53 °C (0.5 mm Hg) [lit. bp[3], 99–99.5 °C (11 mm Hg)]. ^{1}H NMR ($CDCl_3$) δ 3.31 (brs, 1H, *H-5*), 3.25 (d, J = 6.2 Hz, 1H, *H-1*), 2.38 (s, 3H, *CH_3*), 2.30–2.17 (m, 5H), 1.81–1.68 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 209.7, 71.3, 58.7, 37.3, 32.3, 29.2, 26.6, 26.4. IR (NaCl) 1705 cm^{-1}.

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