

## An alternative synthesis of the CNS stimulant Prolintane

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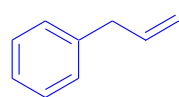
Received 04-08-2019

Accepted 05-14-2019

Published on line 06-02-2019

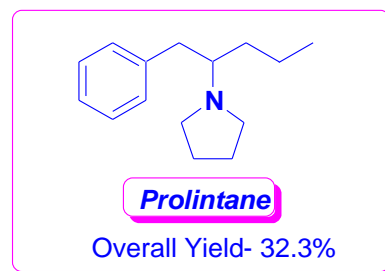
### Abstract

An alternative synthesis of prolintane, a CNS stimulant, is reported using commercially available allylbenzene in good overall yield (32.3%). The key transformations include epoxidation, Grignard reaction, Mitsunobu and reduction protocols.



Allyl benzene

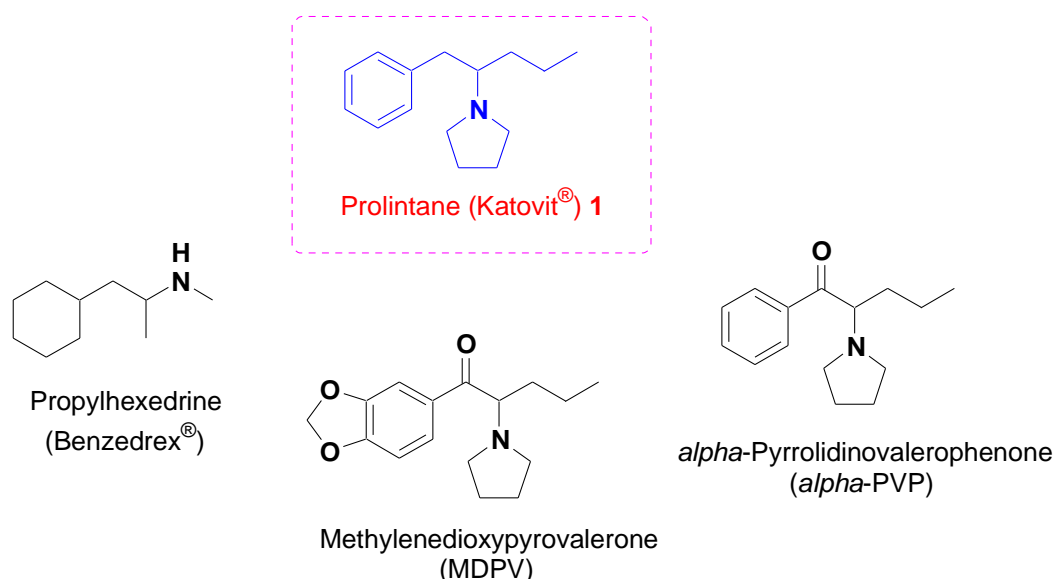
Five Steps



**Keywords:** Prolintane, epoxide, CNS stimulant, Mitsunobu reaction

## Introduction

Prolintane **1** (Katovit<sup>®</sup>) is a central nervous system (CNS) stimulant and norepinephrine-dopamine reuptake inhibitor developed in the 1950s.<sup>1</sup> Its chemical structure is closely related to other drugs such as  $\alpha$ -PVP, MDPV, and propylhexedrine (Fig. 1) and has a similar mechanism of action. It is also used in the treatment of blood pressure disregulation, circulatory disorders and impaired cardiac functions.<sup>2</sup> Very few methods are available for the preparation of prolintane **1**. In one of the methods the synthesis is accomplished by the reaction of 2-oxo-1-phenylpentane with pyrrolidine.<sup>3</sup> Though this method seems to be simple, but it requires the use of expensive starting material. Another method is based on Strecker's synthesis which includes the use of toxic potassium cyanide, thereby limiting the superiority of the method.<sup>4</sup> So, a method that can provide an easy access to prolintane **1** and its analogues is highly desirable. As part of our research interest in the development of new routes for the synthesis of various pharmaceuticals,<sup>5-8</sup> we have extended our efforts towards the synthesis of prolintane **1** using the cheap and readily available starting material allylbenzene.



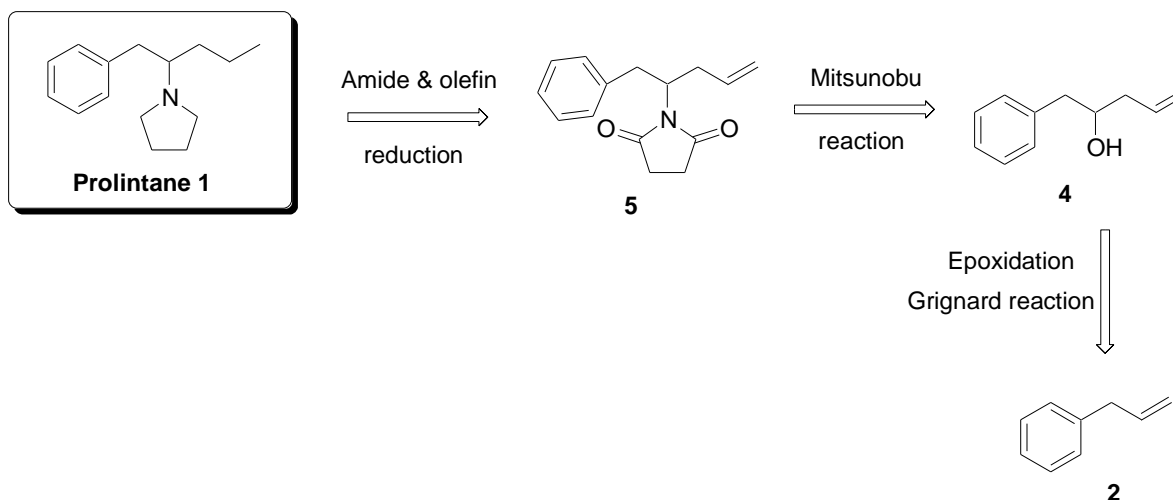
**Figure 1.** Examples of CNS stimulants.

## Results and Discussion

A retrosynthetic analysis of **1** is depicted in Scheme 1. We envisaged that the 1-Phenylpent-4-en-2-ol **4** would serve as a key intermediate for the synthesis that can be transformed to the final product via installation of a succinimide ring using the Mitsunobu reaction followed by amide and olefin reduction protocols. The key intermediate **4** in turn can be produced by epoxidation of allyl benzene followed by epoxide opening using a Grignard reagent.

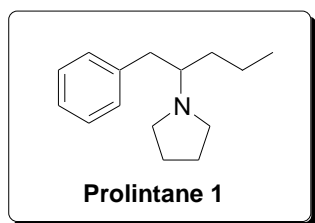
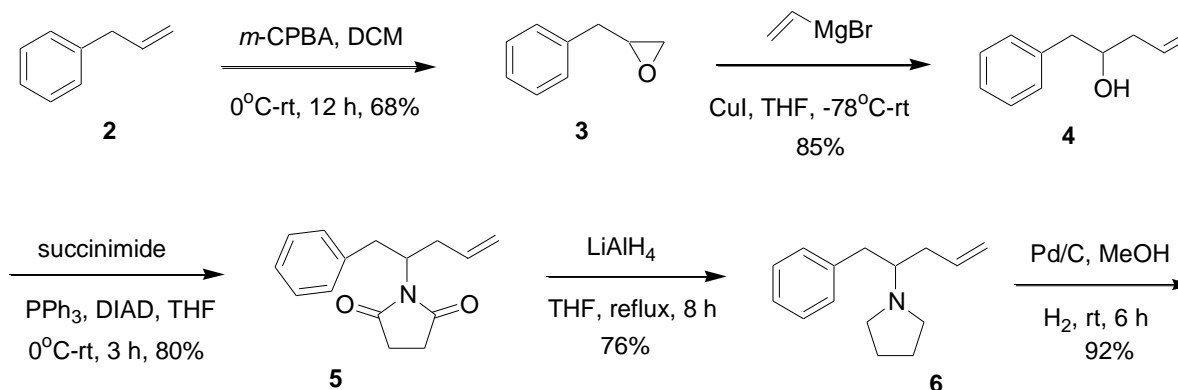
Accordingly, our synthesis commenced with commercially available allylbenzene **2**, which on epoxidation in presence of *meta*-perchlorobenzoic acid (*m*-CPBA) afforded epoxide **3** in 68% yield. Next, the epoxide **3** was subjected to a regioselective ring opening using vinyl magnesium bromide in presence of CuI to afford the required key intermediate 1-Phenylpent-4-en-2-ol **4** in 85% yield.<sup>9</sup> Installation of succinimide moiety on 1-Phenylpent-4-en-2-ol **4** was accomplished using Mitsunobu protocol<sup>10</sup> to furnish succinimido derivative **5** in 80%

yield. Subsequently, amide reduction of compound **5** was performed using lithium aluminium hydride



**Scheme 1.** Retrosynthetic analysis of prolintane **1**.

(LiAlH<sub>4</sub>) in THF under reflux condition to obtain pyrrolidine **6** in 76% yield. Finally, hydrogenation of **6** using catalytic amount of Pd/C in methanol afforded the targeted product prolintane **1** in 92% yield. The structure of prolintane **1** was confirmed by <sup>1</sup>H NMR, <sup>13</sup>C NMR and elemental analysis.



**Scheme 2.** Synthesis of prolintane **1**.

## Conclusions

In summary, we have demonstrated a new method for the preparation of central nervous system (CNS) stimulant prolintane **1**. Commercially available starting material, simple transformations and good overall yield are some of the salient features of this approach. Using this protocol, chiral analogues of the targeted compound can be prepared by employing hydrolytic kinetic resolution (HKR) strategy on intermediate **3**. We envisage that the present protocol may be useful for the synthesis of other prolintane analogues which may be required for extensive biological studies.

## Experimental Section

**General.** Solvents were purified and dried by standard procedures prior to use. IR spectra were obtained from Perkin–Elmer Spectrum One spectrophotometer.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were recorded on a Bruker AC-200 NMR spectrometer. Spectra were obtained in  $\text{CDCl}_3$ . Monitoring of reactions was carried out using TLC plates Merck Silica Gel 60 F254 and visualization with UV light (254 and 365 nm),  $\text{I}_2$  and anisaldehyde in ethanol as development reagents.

**2-Benzyloxirane (3).** To a solution of allylbenzene (**2**) (5.9 mL, 45.0 mmol) in DCM (200 mL) was added, 3-chloroperoxy benzoic acid (*m*-CPBA) (11.6 g, 67.5 mmol) slowly portionwise under vigorous stirring at  $0^\circ\text{C}$  within 30 min. The reaction mixture was allowed to attain room temperature and stirred for 12 h. After completion of the reaction, the resultant solution filtered under reduced pressure and neutralized by 200 mL sodium hydrogen carbonate solution (5.6 g, 67.5 mmol). The organic layer separated and washed with water ( $3 \times 50$  mL) then dried over anhydrous magnesium sulfate. Solvent was removed under reduced pressure and the crude mixture was purified over column chromatography (silica gel, petroleum ether/EtOAc, 96:4) to afford **3** as a colorless oil (4.1 g, 68%);  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  7.26–7.37 (m, 5H), 3.09–3.19 (m, 1H), 2.89–3.00 (m, 1H), 2.82–2.87 (m, 1H), 2.76–2.79 (m, 1H), 2.56 (dd, *J* 2.7, 5.1 Hz, 1H);  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  136.8, 128.9, 128.3, 126.3, 51.9, 46.5, 38.5; Anal. Calcd for  $\text{C}_9\text{H}_{10}\text{O}$  (134.18): C, 80.56; H, 7.51. Found C, 80.21; H, 7.43 %.

**1-Phenylpent-4-en-2-ol (4).** To a pre cooled ( $-20^\circ\text{C}$ ) solution of epoxide **3** (4.0 g, 29.8 mmol) and CuI (0.1 g) in dry THF (40 mL) was added vinyl magnesium chloride (1.0 M in THF, 40 mL, 32.8 mmol) in THF for about 30 min. Subsequently, the reaction mixture was allowed to attain ambient temperature and continued the stirring for additional 1 h. After completion of the reaction (indicated by TLC), aqueous  $\text{NH}_4\text{Cl}$  (20 mL) was added, after which the reaction mixture was filtered, and washed with ethyl acetate. The solvent was removed under reduced pressure and the crude product was subjected to column chromatography (silica gel, petroleum ether/ethyl acetate, 90:10) to yield compound **4** as a colorless oil (4.4 g; 85%);  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  7.31 - 7.39 (m, 2H), 7.20–7.30 (m, 3H), 5.87–5.92 (m, 1H), 5.14–5.24 (m, 2H), 3.90–3.93 (m, 1H), 2.86 (dd, *J* 13.4, 4.9 Hz, 1H), 2.76 (dd, *J* 13.4, 7.9 Hz, 1H), 2.32–2.43 (m, 1H), 2.21–2.32 (m, 1H), 1.87 (br. s, 1H);  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  138.4, 134.7, 129.4, 128.5, 126.4, 118.0, 71.6, 43.2, 41.1; Anal. Calcd for  $\text{C}_{11}\text{H}_{14}\text{O}$  (162.23): C, 81.44; H, 8.70. Found C, 81.21; H, 8.52 %.

**1-(1-Benzylbut-3-enyl)pyrrolidine-2,5-dione (5).** A solution of DIAD (5.3 mL, 26.6 mmol) in dry THF (5 mL) was added dropwise to a solution of compound **4** (3.9 g, 22.2 mmol), succinimide (2.64 g, 26.6 mmol) and triphenylphosphine (6.9 g, 26.6 mmol) in dry THF (60 mL) under  $\text{N}_2$  atmosphere at  $0^\circ\text{C}$ . The reaction mixture was stirred at ambient temperature for 5 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate, 85:15) to yield compound **5**

as a colorless oil. (4.0 g; 80%);  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  7.33-7.41 (m, 2H), 7.20-7.33 (m, 3H), 5.76-5.83 (m, 1H), 5.10-5.23 (m, 2H), 4.55-4.59 (m, 1H), 3.36 (dd,  $J$  13.7, 10.1 Hz, 1H), 3.16 (dd,  $J$  13.4, 6.1 Hz, 1H), 2.93 (dt,  $J$  14.0, 9.5 Hz, 1H), 2.49-2.66 (m, 5H);  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  177.3, 137.9, 134.4, 128.8, 128.3, 126.5, 117.8, 53.1, 37.2, 35.6, 27.6; Anal. Calcd for  $\text{C}_{15}\text{H}_{17}\text{NO}_2$  (243.30): C, 74.05; H, 7.04; N, 5.76. Found C, 73.90; H, 7.12; N, 5.92 %.

**1-(1-Benzylbut-3-enyl)pyrrolidine (6)**. A solution of compound 5 (1.2 g, 5.0 mmol) in dry THF (15 mL) was added dropwise to a suspension of  $\text{LiAlH}_4$  (1.0 g, 28.5 mmol) in dry THF (25 mL) at 0 °C. After being stirred at room temperature for 30 min, the mixture was refluxed for 6 h. After completion of the reaction, the mixture was allowed to cool to 0 °C and aq. KOH (10 mL) was added slowly followed by addition of ethyl acetate (30 mL). The residue filtered over celite and the filtrate was washed with water, brine and dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The crude product was purified over column chromatography (silica gel, petroleum ether/EtOAc, 75:25) so as to afford compound 6 as an oil (0.81 g, 76%);  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  7.30-7.38 (m, 2H), 7.22-7.29 (m, 3H), 5.93-6.0 (m, 1H), 5.04-5.16 (m, 2H), 3.05 (q,  $J$  8.5 Hz, 1H), 2.70-2.79 (m, 6H), 2.18-2.37 (m, 2H), 1.76-1.91 (m, 4H);  $^{13}\text{C}$  NMR(50 MHz,  $\text{CDCl}_3$ ): 140.3, 135.6, 129.3, 128.2, 125.8, 116.6, 64.8, 51.0, 37.6, 35.5, 23.5; Anal. Calcd for  $\text{C}_{15}\text{H}_{21}\text{N}$  (215.33): C, 83.67; H, 9.83; N, 6.50. Found C, 83.90; H, 9.62; N, 6.52 %.

**1-(1-Benzylbutyl)pyrrolidine (Prolintane) (1)**. To a solution of 6 (0.43 g, 2.0 mmol) in methanol (10 mL) was added palladium hydroxide (0.1 g, 10-20 wt %) and the reaction mixture was stirred under hydrogen (60 psi) for 12 h. After completion of the reaction (indicated by TLC), the catalyst was filtered over a plug of celite bed and the solvent was evaporated under reduced pressure to afford Prolintane 1 as a colorless oil. (0.40 g; 92 %):  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  7.30 - 7.39 (m, 2H), 7.27-7.25 (m, 3H), 3.05-3.06 (m, 1H), 2.62-2.83 (m, 6H), 1.86 (m, 4H), 1.36-1.53 (m, 4H), 0.88 (t,  $J$  6.4 Hz, 3H);  $^{13}\text{C}$  NMR(50 MHz,  $\text{CDCl}_3$ ): 140.7, 129.2, 128.2, 125.7, 64.4, 50.6, 37.6, 33.7, 23.5, 18.5, 14.4; Anal. Calcd for  $\text{C}_{15}\text{H}_{23}\text{N}$  (217.35): C, 82.89; H, 10.67; N, 6.44. Found C, 82.80; H, 10.48; N, 6.52 %.

## Acknowledgements

The authors thank Principal Dr. R. M. Bhise for constant encouragement and support.

## Supplementary Material

Supplementary information includes copies of  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR.

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