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A Facile One-pot Process for the Synthesis of Stiripentol

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ABSTRACT

A facile one-pot synthesis of Stiripentol (STP) 1 in which Initially 3,4-dihydroxy benzaldehyde 13 is treated with methylene diiodide using base KOH to get **2** which undergoes *In situ* Knoevenagel condensation with 3,3-dimethyl 2-butanone using catalytic Phase Transfer Catalyst i.e. Tetrabutylammonium bromide (TBAB) and K_2CO_3 to get **4** which undergo Regioselective Luche reduction of α-$\beta\beta$unsaturated ketone with $NaBH_4$ and Cerium(III) chloride ($CeCl_3$) to get pure Stiripentol **1** which is commercially viable and eco-friendly.

Keywords: Tetrabutyl ammonium bromide, 3,4 dihydroxy benzaldehyde, Knoevenagel condensation, Antiepileptic, Regioselective Luche reduction, Commercially feasible.

INTRODUCTION

Globally 50 million peoples affected by neurological disorder i.e. epilepsy. Nearly 80% of people living with epilepsy are in low and middle-income countries. Globally estimated 5 million people are diagnosed with epilepsy each year.[1] γ-aminobutyric acid is the neurotransmitter of the brain which controls neuronal excitability and deficiency that cause epilepsy. During such treatment, several antiepileptic drugs have been developed to increase the level of GABA and among them, Stiripentol (STP) is one of the drug produced by Biocodex.[2] It is an orally active drug sold by the brand name Diacomit and available in 250 mg and 500 mg capsules.[3,4] Stiripentol increases $\beta\gamma$-aminobutyric acid (GABA) levels in the brain which major inhibitory neurotransmitter in the brain.[5]

It inhibits enzyme lactose dehydrogenase[6] European Medical agency granted Stiripentol an orphan drug status for the treatment of epilepsy in 2001 and gave marketing Authorisation for use in 2007.[7] It was approved in Canada in 2013 and 2017 approved in Japan.[8,9] In 2018 approved by US FDA as therapy for Dravet Syndrom.[10]

Stiripentol **1** synthesis reported in the prior art as under.

Synthesis of stiripentol was first disclosed in US patent 3910959 by Vallet F.M.J.[11] as shown in Scheme 1 below.

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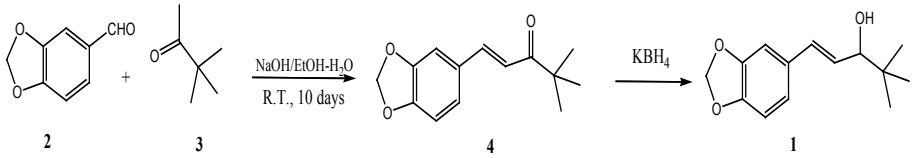
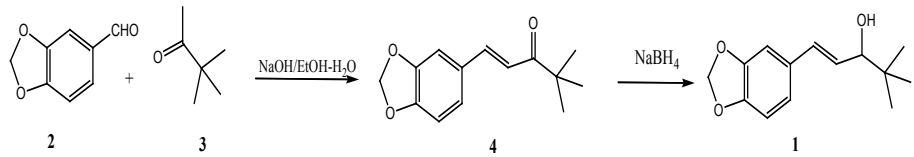


Scheme 1.

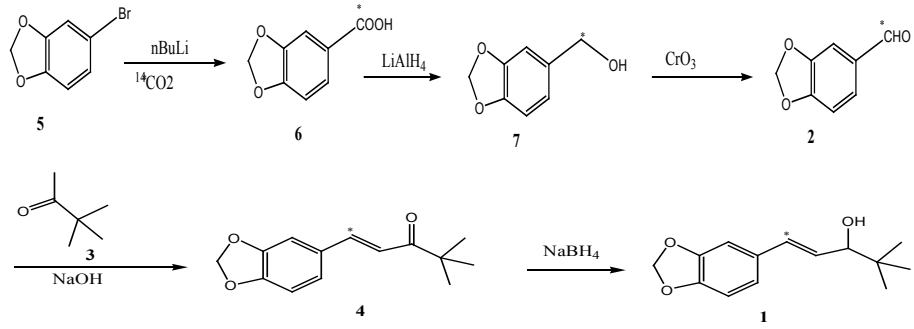
Astoin, J.[12] disclosed synthesis of stiripentol **1** by condensation of Piperonal **2** with tertiary butyl ketone **3** get unsaturated ketone **4**, further on reduction to get desired product **1** as shown in Scheme 2 below.



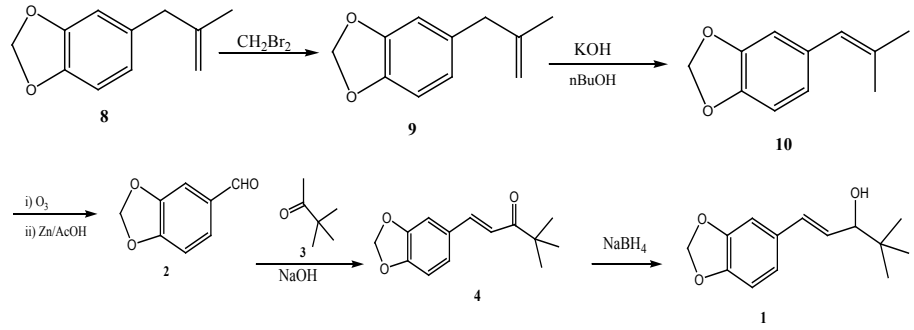
Scheme 2.

Lepage F.[13] disclosed synthesis of [14]-labeled stiripentol using Bromo Piperonal **5** as shown in Scheme 3 below.

Chinese patent CN 102690252[14] disclosed the synthesis of stiripentol **1** from 4-(2-methyl allyl)-1, 2-dihydroxybenzene as per Scheme 4 below.

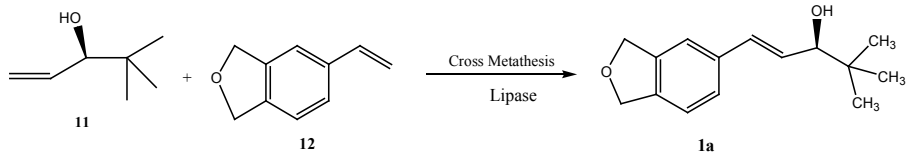


Scheme 3.



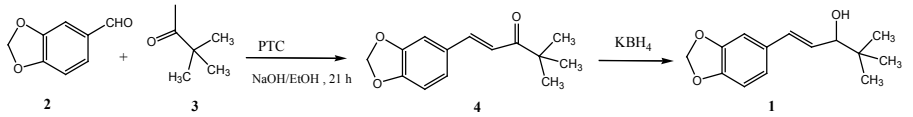
Scheme 4.

Mohammed F.E.B.[15] disclosed preparation of (R)-Stiripentol **1a** as per belows Scheme 5.



Scheme 5.

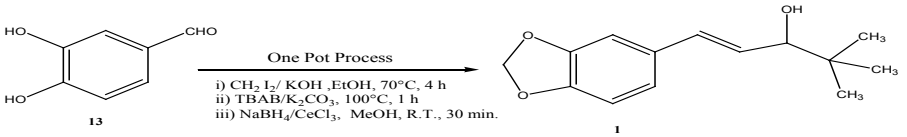
Chinese patent CN102391242[16] disclosed a method for stiripentol synthesis from piperaldehyde using PTC (quaternary ammonium salts and crown ether) at 40°C but too much time required to complete the reaction i.e. 21 h-108 hours. Further isolated ketone reduced with sodium borohydride.



Scheme 6.

All the above processes are multistep synthesis, not eco-friendly and not commercially viable.

Need to develop a facile and commercially useful process for the synthesis of stiripentol **1**. We report an facile and commercially useful one-pot process for preparation of Stiripentol **1** as shown in Scheme 7 below.

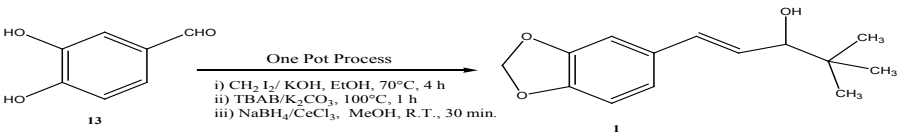


Scheme 7.

RESULTS AND DISCUSSION

Initially, 3,4-dihydroxy benzaldehyde **13** reacts with ethylene diiodide in presence of base KOH to get residue **2** which undergoes in situ Knoevenagel condensation with 3,3 dimethyl 2-butanone using catalytic Phase Transfer Catalyst i.e. Tetrabutylammonium bromide (TBAB) and potassium carbonate to get residue **4** which undergo in situ Luche reduction i.e. regioselective reduction of the α-β unsaturated ketone to allylic alcohol with $NaBH_4$ and Cerium(III) chloride ($CeCl_3$) to get pure Stiripentol **1** (HPLC Purity: >99%), characterized by CMR and PMR studies.

Reported processes are multistep synthesis, time-consuming, not eco-friendly and commercially not viable. To overcome this, we report a commercially viable facile one-pot process for the synthesis of Stiripentol **1**. We studied the effect of different bases and catalyst (PTC) concentrations for our below one-pot process.



Scheme 8.

Table 1: Testing various bases (step ii) and observed yield of Stiripentol 1

Entry	Base	Concentration (mmol)	Yield (%)[1]
1	Ammonium hydroxide	120	35
2	Lithium hydroxide	120	56
3	Sodium hydroxide	120	48
4	Potassium hydroxide	120	64
5	Sodium carbonate	120	45
6	Potassium carbonate	120	71
7	Potassium carbonate	115	78
8	Potassium carbonate	110	90
9	Potassium carbonate	105	52

Reaction Conditions: Piperonal (*In situ*), 3,3 dimethyl-2-butanone, TBAB (0.90 mmol), **1** isolated yield at 100°C for 1 hours

Testing various bases (step ii) and observed yield of Stiripentol **1**. In Knoevenagel condensation, TBAB is used as a PTC which is superior to get maximum output[17]. We used different bases i.e. NH_4OH, LiOH, NaOH, KOH, Na_2CO_3 and K_2CO_3 (Table 1), got 35%, 56%, 48%, 64%, and 45%, yield respectively. Potassium carbonate was observed suitable base and investigated at four different concentrations (105, 110, 115 and 120 mmol). By use of a 110 mmol concentration of potassium carbonate got an excellent yield of 90% (Table 1, entry 8).

We study the Effect of different concentrations of catalytic PTC (TBAB) (0, 0.10, 0.20, 0.30, 0.40, 0.50, 0.60, 0.70) and examined the yield of Stiripentol **1**. Without PTC we got a trace amount of product. We got 15%, 32%, 43%, 55%, 68%, 80%, and 90% yield of Stiripentol **1** respectively.

Further increasing concentration of PTC and same reaction time yield is same. But by decreasing reaction time yield decreased as shown in Table 2.

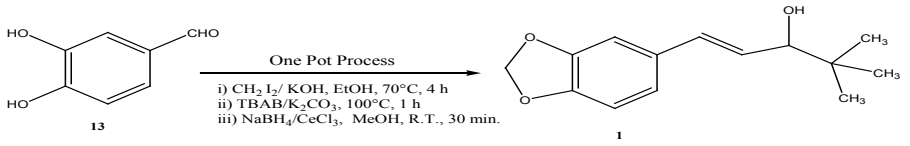
We study the reaction progress on TLC at different temp. And maintaining time (step ii) (Table 3). Different reactions were carried out from R.T. to 100°C. We observed that at 100°C temp. and 1 h maintaining complete conversion of starting spot. (Table 3, entry-10)

Our optimized one-pot process of Stiripentol **1**

Table 2: Effect of different concentrations (step-ii) of catalytic PTC (TBAB) on the yield of Stiripentol 1

Entry	Conc. of TBAB (mmol)	Time (h)	Stiripentol Yield (%) 1
1	0	12	Trace
2	0.10	10	15
3	0.20	8	32
4	0.30	6	43
5	0.40	4	55
6	0.50	3	68
7	0.60	1	80
8	0.70	1	90
9	0.80	1	90
10	0.90	1	90
11	1.00	0.5	82

Reaction Conditions: Piperonal (*In situ*), 3,3 dimethyl -2-butanone, K_2CO_3 (110 mmol), **1** isolated yield at 100°C



Scheme 9.

Table 3: Testing of reaction conditions (step ii) in situ by TLC

Entry	TBAB in (mmol)	Temp. (°C)	Maintaining Time (h)	Observations on TLC
1	0.70	10	24	No conversion
2	0.70	20	18	No conversion
3	0.70	30	12	No conversion
4	0.70	40	8	Starting conversion starts
5	0.70	50	6	Progress of reaction
6	0.70	60	5	Progress of reaction
7	0.70	70	4	Starting spot seen
8	0.70	80	3	Starting spot seen
9	0.70	90	2	Slight Starting Observed
10	0.70	100	1	Starting completely Nil

Reaction Conditions: Piperonal (*In situ*), 3, 3 dimethyl, 2-butanone, K_2CO_3 (110 mmol), TBAB (0.70 mmol)[1] isolated yield at 100°C

Merits of our process i.e.

i) Capital investment is low.
ii) Minimum material handling steps.
iii) Shorter reaction time.
iv) Commercially viable process.
v) Multistep reactions in one vessel without any workup.
vi) Environmentally viable process.

EXPERIMENTAL

Materials

All chemicals used from analytical grade (A.R.) and purchased from Sigma Aldrich. 3, 4-dihydroxy benzaldehyde, methylene diiodide, Potassium hydroxide, TBAB, Potassium carbonate, sodium borohydride, cerium trichloride. Thin Layer

Chromatography was (TLC) used for the progress of the reaction.

Instrumentation

The PMR and CMR spectra recorded on 400 MHz and 100 MHz using a Brucker instrument in DMSO/$CDCl_3$. The chemical shift is recorded in ppm scale (δ) using TMS as reference standard.

One-Pot Process for synthesis of Siripentol (1)

A solution of 3, 4-dihydroxy benzaldehyde 13 (72 mmol), methylene diiodide (72 mmol), KOH (144 mmol) and ethanol (100 mL). The mixture stirred and boiled at 70°C for 4 h; after completion of reaction Cool, filter and distill filtrate to get crude **2**. Add DCM and water (30:30 mL). Stirr for 10-15 minute. remove aq. Layer and concentrate organic layer. Then in the same flask add 3,3,dimethyl 2-butanone (99 mmol), potassium carbonate (110 mmol) and add PTC i.e. TBAB (0.70 mmol and heat for 1 h at 100°C. Reaction completion detected on TLC. Add DCM and water (50:50 mL) and remove aq. Layer and concentrate the DCM layer under reduced pressure to get residue **4**. Then add a solution of $CeCl_3.7H_2O$ (18 mmol) in MeOH (30 mL). Cool to 0 to 5°C. Dissolve $NaBH_4$ (72 mmol) in MeOH (50 mL) and add dropwise in 5 minutes. After the addition of $NaBH_4$ solution over then remove the cooling and stir the reaction mixture at R.T. After 30 minute. TLC shows (Hexane: Ethyl acetate=8:2) complete conversion of starting material. For work-up add 50 mL, 2 N HCl stirred for 30 minute. Cool to 10°C and precipitate is formed filtered and dried to get pure Stiripentol **1** (90.62%). 74- 75°C (lit.11: 74°C); HPLC Purity:>99%; PMR ($CDCl_3$, δppm):0.98 (singlet, 9H), 1.54 (singlet, 1H) 3.9 (m, 1H), 5.98 (singlet, 2H), 6.17 (dd, 1H), 6.51 (doublet, 1H), 6.78 (doublet, 1H), 6.84 (doublet, 1H), 6.96 (doublet, 1H); ^{13}C NMR, 125 MHz, $CDCl_3$): δ 25.96, 33.23, 33.50, 34.98, 79.17, 100.73,108.16, 108.95,121.14, 136.31,145.58, 147.57

CONCLUSION

We have developed a facile one-pot process for the synthesis of Stiripentol **1** in which multicomponent reactions are carried out in one vessel which is commercially viable and ecofriendly with higher yield and purity.

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Conflict of interest

All authors declare that no any financial funding received.

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