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Controlled Catalytic Reduction in Synthesising Pure Tetrahydrocurcumin

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Pd-Catalyzed hydrogenation process has been developed to synthesize tetrahydrocurcumin from synthetic curcumin. Use of diphenyl sulphide as catalyst poison is crucial for lowering the activity of the catalyst and thus reduces impurity formation. The process avoids column chromatography to achieve good quality tetrahydrocurcumin in cost effective manner. All the prepared compounds are characterized by FT-IR, ^{1}H NMR, mass and HPLC techniques.

Keywords: Curcumin; tetrahydrocurcumin; hydrogenation; poison catalyst; diphenylsulphide.

1. INTRODUCTION

Tetrahydrocurcumin **2a** is chemically known as 1,7-bis(4-hydroxy-3-methylphenyl)-3,5-heptanedione. Tetrahydrocurcumin is a metabolite of curcumin **1a** and is the most powerful antioxidant due to the free radical cleavage of the beta position of the gamma diketone moiety. Highly pure tetrahydrocurcumin **2a** is used in foods, alcohols, medicaments and cosmetics, etc., due to its excellent anti-oxidative properties. The inhibitory activity of **2a** is

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dependent on its keto-enol tautomer [1] **2a** is stronger antioxidant when compared with curcumin. Since **2a** is colourlessness and odourless [2], especially when colouring acts as an evil, it serves as a material which conquered the fault of the curcumin **1a**. **2a** also showed promising antibacterial activity and antifungal activity. The antioxidant property of **2a** has been further implicated in cancer, anti-inflamatory activities and in atherosclerotic lesion. In the present, herein we report a cost effective synthesis of tetrahydrocurcumin **2a** with commercial applicability [3-7].

Peter et al., [6] have reported the reduction of **1a** in acetone with Raney nickel. The main drawback of the method is that the catalyst is used in higher quantities and the product **2a** is obtained as a yellow coloured solid. Since yellow coloured compound **2a** has restricted use in cosmetics and foods, this process is not suitable for commercial scale manufacturing of **2a**.

Su-Lin et al*.,* have reported the reduction in ethyl acetate with 10% Pd/C [8]. We had tried this process in our hands to check its efficacy. The main limitation with this process is that the hydrogenation is not selective and formation of impurities **5** and **6** is high. Product **2a** was obtained in low yield of 14% due to repeated purifications.

Chatchwan et al., have reported the reduction in methanol with 10% Pt/C [9]. Isolated compound **2a** was contaminated with impurities **5**-**7**. The drawback of this method is cost of Pt/C catalyst and also compound **2a** is obtained with unwanted impurities **5**-**7**. Removal of these impurities required repeated purifications and compound **2a** was obtained in low yield.

The present article is directed towards developing a process for the preparation of pure compound **2a [**1] with impurities **5**-**7** in lower levels. We have attempted to slower the rate of hydrogenation by using sulphur related compound, for example diphenyl sulphide, and thus reducing the levels of impurities **5**-**6**.

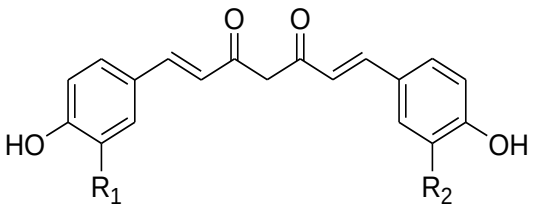
2. MATERIALS AND METHODS

2.1 Experimental Section

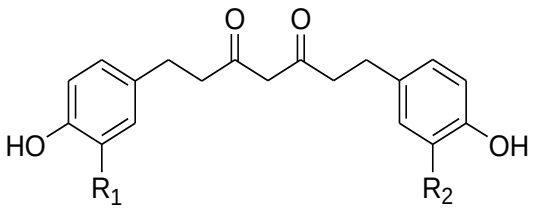
^{1}H NMR and DEPT spectral data were obtained in deuterated Chloroform ($CDCl_3$) and D_2O at 300MHz and 500MHz spectrometers. The chemical shift values were reported on the δ scale in parts per million (ppm), downfield from tetra methyl silane (TMS, δ = 0.0) as an internal standard. Spin multiplicities are given as s (singlet), d (doublet), dd (double of doublet), t (triplet) and m (multiplet) as well as broad (broad singlet). Coupling constants (J) are given in Hertz. IR spectra were recorded in the solid state as KBr dispersion using a PerkinElmer spectrum one Fourier transform (FT)-IR spectrophotometer. Mass spectrum was recorded using PerkinElmer PE SCIEX API 2000, equipped with an ESI source used online with an HPLC system after the ultraviolet (UV) detector. HPLC chromatographic purity was determined by using area normalization method.

2.2.1 Process for the preparation of Curcumin 1a [6]

Vanillin (60 g, 0.394 moles) was suspended in ethyl acetate (200 mL) at 25-30 °C. The reaction was stirred for 10 minutes. Tributyl borate (170.16 g, 0.74 moles), acetyl acetone (23.7 g, 0.237 moles) and boric anhydride (10 g, 0.142 moles) were added to the reaction mixture at 25-30 °C. Butyl amine (2.96 g, 0.04 moles) was



1a, $R_1 = R_2 = OCH_3$
1b, $R_1 = OCH_3$, $R_2 = H$
1c, $R_1 = R_2 = H$



2a, $R_1 = R_2 = OCH_3$
2b, $R_1 = OCH_3$, $R_2 = H$
2c, $R_1 = R_2 = H$

Fig. 1. Structures of curcumin (1a), curcuminoids (1b-c), tetrahydrocurcumin (2a) and tetrahydrocurcuminoids (2b-c)

added drop wise to the reaction mixture 25-30 °C and maintained for 40 hours. The reaction mass was quenched with 6 N aqueous hydrochloric acid and maintained at 25-30 °C for 1 hour. Ethyl acetate (400 mL) was added to the reaction mass and maintained at 25-30 °C for 2 hours. The reaction mass was filtered and washed with water (3x100 mL) and methanol (3x60 mL). The obtained solid was purified from aqueous methanol (990 mL) to produce title compound (51 g, 70%) with chromatography purity 95.33% performed by HPLC. **IR** (KBr, cm^{-1}); 3856, 3565, 2923, 2357, 2327, 1863, 1626, 1506, 1462, 1376, 1281, 1180, 1113, 1026, 986, 886, 783, 668; **^{1}H NMR** ($CdCl_3$, 500 MHz, δ): 3.95 (s, 6H), 5.80 (s,1H), 5.85 (s, 2H), 6.49 (d, 2H, j=8), 6.943 (d, 2H, j=2), 7.05(d, 2H, j=2.5), 7.11(d, 2H, j=2), 7.57 (d, 2H, j=15);.

2.2.2 Process for the preparation of tetrahydrocurcumin (2a) without using diphenyl sulphide [8]

Curcumin (20 g, 0.054 moles) was suspended in methanol (400 mL) at 25-30 °C in autoclave. 10% palladium/carbon (1 g, 5% w/w) was added to this reaction mass at 25-30 °C. Hydrogen pressure (10 kg) was applied and the reaction mass was maintained at 25-30 °C for 2 hours. After completion of the reaction, the catalyst was removed from the reaction mass. Carbon (2 g, 10% w/w) was added to the reaction mass and maintained for 1 hour at 25-30 °C. Carbon was also removed from the filtrate. The filtrate was concentrated and isolated from methyl tert butyl ether to produce title compound **2a** (9 g, 40%) with HPLC purity 74.33%. **IR** (KBr, cm^{-1}); 3854, 3420, 3065, 2948, 2133, 1901, 1740, 1610, 1548, 1414, 1326, 1265, 1156, 1032, 921, 837, 772, 681; **^{1}H NMR** ($CdCl_3$, 500 MHz, δ): 1.55 (t, 4H, j=7.5), 2.81 (t, 4H, j=7.5), 3.85 (s, 6H), 5.42 (s, 1H), 5.47 (s, 2H), 6.66 (d, 4H, j=5), 6.81 (d, 2H, j=10), 15.4(s, 1H).

2.2.3 Process for the preparation of tetrahydrocurcumin (2a) using diphenyl sulphide

Curcumin (50 g, 0.135 moles) was suspended in methanol (1000 mL) at 25-30 °C in autoclave. 10% Palladium/carbon (3.25 g, 6.5% w/w) was added, followed by diphenyl sulphide (65 mg, 0.13% w/w) and DM water (15 mL) were added to this reaction mass at 25-30°C. Hydrogen pressure (10 kg) was applied and the reaction mass was maintained at 40-45°C for 4 hours. After completion of the reaction, the catalyst was removed from the reaction mass. Carbon (5 g, 10% w/w) was added to the reaction mass and maintained for 1 hour at 25-30 °C. Carbon was also removed from the filtrate. The filtrate was concentrated and isolated from isopropyl alcohol (150 ml) to produce title compound (35.4 g, 70%) with HPLC purity 99.05%. **IR** (KBr, cm^{-1}); 3854, 3420, 3065, 2948, 2133, 1901, 1740, 1610, 1548, 1414, 1326, 1265, 1156, 1032, 921, 837, 772, 681; **^{1}H NMR** ($CDCl_3$, 500 MHz, δ): 1.55 (t, 4H, j=7.5 Hz), 2.81 (t, 4H, j=7.5 Hz), 3.85 (s, 6H), 5.42 (s, 1H), 5.47 (s, 2H), 6.66 (d, 4H, j=5 Hz), 6.81 (d, 2H, j=10 Hz), 15.4(s, 1H).

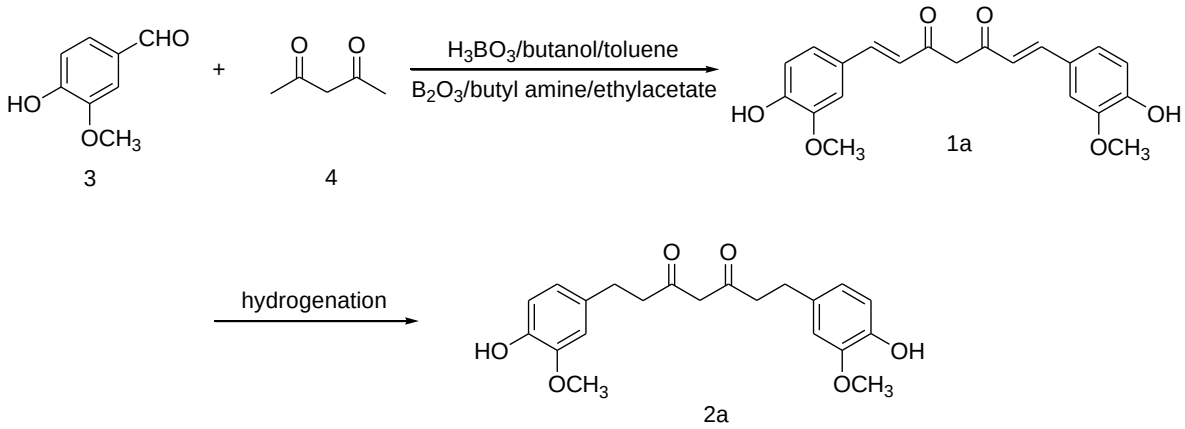
3. RESULT AND DISCUSSIONS

General literature for the synthesis of tetrahydrocurcumin **2a** from curcumin **1a** is provided in **Scheme 1** [7-14]. Compound **2a** was obtained from 1**a** by selective hydrogenation. Curcumin **1a** was synthesized from commercially available vanillin **3** and acetyl acetone **4** as per literature reported method (**Scheme 1**) [6]. The process comprised of condensing **3** and **4** in the presence of tributyl borate, boric anhydride and butyl amine. After the completion of the reaction, solvent was evaporated and product **1a** was precipitated using 10% aqueous acetic acid. Crude product **1a** was suspended in water and stirred at 70-80 °C for 1h. Reaction mass was subsequently cooled to 25-30 °C and pure compound **1a** was isolated by filtration and drying (**Scheme 1**).

The major disadvantage with the reported methods is formation of impurities, for example, hexahydrocurcumin **5**, desmethyl tetrahydrocurcumin **6** and octahydrocurcumin **7** (Fig. 2). These impurities are removed by column chromatography which limits the application of the process on large scale.

We had evaluated hydrogenation of **1a** to furnish **2a** under literature reported conditions. The rate of hydrogenation being fast under these conditions generated more impurities due to uncontrolled over reduction. Removal of impurities **5** and **6** required column purification which resulted in lower yield and also the method is non-viable on commercial scale.

In our study, use of Raney nickel provided **2a** in good yield and purity but yellow colour was still present in the product. So the method is not suitable for commercialization. Several purification techniques were tried but **2a** could not be isolated as off-white product (Table 1).



Scheme 1. Synthetic strategy for the preparation of tetrahydrocurcumin 2a

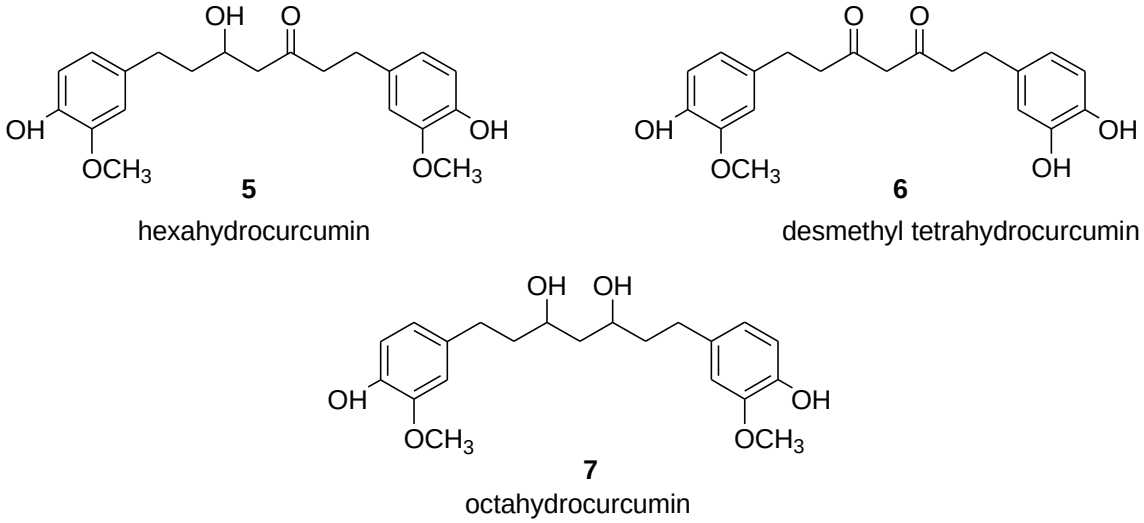


Fig. 2. Impurities (5-7) formed during synthesis of 2a from 1a

Table 1. Screening of Ph_2S catalyst poison for hydrogenation of 1a to give 2a

Entry	Catalyst	Molar ratio	Solvent	Ph_2S loading (%w/w)	Time (h)	Purity by HPLC (%)[a]	Yield (%)[b]
1	Raney Ni	0.3	Acetone	-	2	78.57	80
2	Raney Ni	0.2	Acetone	-	2	84.5	82
3	Raney Ni	0.1	Acetone	-	1	88.01	83.5
4	Raney Ni	0.1	Acetone	0.1	2.5	96.86	88
5	Raney Ni	ss0.1	Methanol	0.1	2	30.5	-

[a]reaction conversion during monitoring; [b]isolated yield

In further study, we have evaluated the conversion of **1a** to **2a** with variety of reducing agents (Table 2).

Among various tested reducing agents, we have observed that 10% Pd/C was best suited for this reduction. This is because of the faster rate of the reaction (less than 0.1% unreacted starting material was observed after 2 hours). Using other reducing agents, more than 0.1% of starting material was left unreacted even if the reaction was performed for more than 15 hours. Presence of more than 0.1% of starting material renders yellow colour to the product, which is undesirable and cannot be used in drug products and in food substances. On the other hand, when

PtO_2 was used as reducing agent, reaction completed in 2 hours (less than 0.1% of unreacted starting material was left out). But this reducing agent is highly expensive, which is not suitable for scale up and commercialization. Keeping in view of above facts, we concluded that 10% Pd/C should be the best reducing agent for this reaction.

Pd/C is known as the most universal catalyst for hydrogenation in synthetic organic chemistry because of its high catalyst activity, cost efficiency, easy separation from the reaction mixture and reusability [10]. Pd/C exhibits high catalytic activity and due to this reason its application to chemo selective hydrogenation between different types of reducible functionalities is very challenging. Highly active catalyst can lead to undesirable secondary reactions to generate undesired products. In some of these cases, the addition of small amount of a catalyst poison increase the yield of the desired product by lowering the catalyst activity and thus minimizing side reactions.

During our efforts to solve the problem, we found that the addition of a sulphur atom containing catalyst poison controls the activity of Pd/C for transformation of **1a** to **2a**. Herein, we describe the Pd/C catalyzed chemo selective hydrogenation using diphenylsulphide as a sulphur containing catalyst poison [15,16]. Further to reduce the impurity formation in the reaction, which are formed due to over reduction, we tried to limit the reaction rate by using various sulphur related catalytic poisons (Table 3). We found that diphenyl sulphide was the best catalytic poison for this reaction. When we used diphenyl sulphide as catalytic poison reaction completed in 24 hours at 45°C, the formation of impurities in the reaction were reduced from 25-30% to 2-3%. This shows the efficiency of diphenyl sulphide as catalytic poison.

We have further optimized the quantity of catalytic poison required to suppress impurity formation. Use of 0.5% w/w of the catalyst did not give good results and more than 0.1% of unreacted starting material was left out at 45°C even though few impurities were also present (Table 4, entries 1 & 2). Similarly, use of 0.05% w/w and 0.08% w/w did not furnished satisfactory results (Table 4, entries 3 & 4). On the other hand, use of 0.1% w/w of diphenyl sulphide (Table 4, entry 5) as poison yielded the product **2a** with a purity of more than 99%.

Table 2. Screening of catalysts/reagents for room temperature reduction of 1a to 2a in methanol

Entry	Catalyst/reagent	Time (h)	Loading (%w/w)	Purity by HPLC (%)[a]	Yield (%)[b]
1	10%Pd/C	2	5	76.31	40
2	10%Pd/C	20	2	79.24	41
3	$Pd/CaCO_3$	2	5	47.23	25
4	$NaBH_4$	1	2 moles	ND[c]	ND[c]
5	Pd/Al_2O_3	15	5	64.24	35
6	$Pd/C/AlCl_3$	10	5	ND[c]	ND[c]
7	PtO_2	2	5	54.99	30
8	5%Pd/C (Type-39)	1	5	55.67	30
9	10%Pd/C (Type 490 paste)	2	5	82.20	43

[a]conversion during monitoring; [b]isolated yield; [c]not detected

Table 3. Screening of catalyst poisons for conversion of 1a to 2a

Entry	Catalyst poison	Catalyst for reduction	Purity of 2a by HPLC (%)[a]
1	disodium sulphide	10% Pd/C	ND[b]
2	dimethyl sulfoxide	10% Pd/C	ND[b]
3	thioacetic acid	10% Pd/C	ND[b]
4	cyclopropyl mercaptoacid	10% Pd/C	ND[b]
5	diphenyl sulphide	10% Pd/C	96.44

[a]conversion during monitoring; [b]not detected

Table 4. Screening of optimum quantity of diphenyl sulphide catalyst poison for conversion of 1a to 2a

Entry	quantity of diphenyl sulphide (% w/w)	Temperature (°C)	Time (h)	Purity of 2a by HPLC (%)[a]
1	0.5	45	20	87.27
2	0.25	45	29	88.29
3	0.05	45	2	75.4
4	0.08	45	3	87.04
5	0.1	45	4	96.44

[a]*convertion during monitoring*

Next, we looked for the best solvent for this reaction (Table 5). Among the various tested solvents, we have observed methanol is best in attaining **2a** in good purity in lesser time with good yield. Also, methanol is less expensive solvent compared to ethanol and isopropyl alcohol (Table 5).

In the absence of the Ph_2S, purity level of **2a** is lower and impurities **5** & **6** are forming in higher amount (Table 6). On the basis of these results, we observed that the use of diphenyl sulphide poison would be crucial for the efficient and selective catalytic reduction of **1a**. Diphenyl sulphide acts as a poison which modulates the activity of palladium on carbon and thus minimizes impurity formation.

After the completion of the reaction, palladium on carbon is filtered through hyflo bed and residue was washed with methanol. Combined organics were evaporated in rotavap at 45-50 °C. Methyl tert-butyl ether was added to the resulting crude and stirred at 0-5 °C for 1h. Crystallized product was filtered to obtain compound **2a** in 60% yield and 98.4% HPLC purity. On the other hand, use of isopropyl alcohol instead of methyl tert-butyl ether furnished **2a** in 70% yield and 99.05% HPLC purity. Finally, the redesigned process furnished **2a** with an overall yield of 49% from vanillin over 2 steps with 99.05% HPLC purity**.**

Residual solvent and metal content analysis of **2a** was also performed and the values are well within regulatory requirements (Tables 7 & 8).

It has been observed that **2a** and **1a** obtained from synthetic routes are free from impurities **1b**-**c** and **4b**-**c**, respectively (Table 9).

Table 5. Screening of solvents for synthesis of 2a from 1a using 10% Pd/C (5% w/w) & Ph_2S (0.1% w/w)

Entry	Solvent	Time (h)	Purity of 2a by HPLC (%)[a]
1	Ethanol	20	75.76
2	Methanol	4	96.44
3	ethyl acetate	6	57.94
4	DCM	1	12.66
5	Acetonitrile	1	14.53
6	isopropyl alcohol	36	85.8

[a]*conversion during monitoring*

Table 6. Hydrogenation of 1a in the absence of diphenyl sulfide

Entry	Reducing agent	Solvent	Temperature (°C)	Time (h)	Purity of 2a by HPLC (%)[a]
1	10% Pd/C	acetone	27	2	20.1
2	5% Pd/C	methanol	27	1	29.3
3	10% Pd/C	methanol	50	2	21.30
4	$Pd/CaCO_3$	methanol	50	2	28.77
5	PtO_2	methanol	27	2	22.53
6	Raney-Ni/Ph_2s	methanol	27	2	66.29

[a]*conversion during monitoring*

Table 7. Residual solvent analysis of 2a

Entry	Purity by HPLC (%)		Residual solvents by GC (ppm)						Yield (%)
	1	V	Acetone	IPA	MeOH	Ethyl acetate	AcOH	Butanol	
1	99.29	0.57	ND	1201	170	ND	ND	ND	49.12
2	98.92	0.86	ND	1243	145	ND	ND	ND	49.09

Table 8. Heavy metals analysis of 2a by ICP-OES

Arsenic (ppm)	Cadmium (ppm)	Palladium (ppm)	Lead (ppm)
< 1.0	< 1.0	< 3.0	< 1.0

Table 9. HPLC purity of 2a obtained from synthetic and natural 1a

Entry	Source of 1a	1a (%)	1b (%)	1c (%)	2a (%)	2b (%)	2c (%)
1	synthetic	98.60	-	-	99.29	-	-
2	natural source	84.57	11.24	1.77	92.96	6.02	0.58

4. CONCLUSION

We have developed an improved process for synthesis of tetrahydrocurcumin **2a** by selective palladium-catalyzed hydrogenation of synthetic curcumin **1a**. The residual metal analysis of **2a** is well within allowed limits and the product meets the regulatory norms in terms of quality. Hydrogenation using 10% palladium on carbon in the presence of diphenyl sulphide catalyst-poison minimizes impurity generation and thus avoids column purification for the preparation of **2a**.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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