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Synthetic and mechanistic investigation of piperonyl butoxide from dihydrosafrole

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Abstract Piperonyl butoxide (PBO) **1** was prepared via the successive chloromethylation and etherification of dihydrosafrole **3**. In this work, during the chloromethylation of **3**, several by-products such as **5** (the isomer of chloromethyldihydrosafrole **4**), 6-propylpiperonyl alcohol **6**, bis(chloromethyl)-dihydrosafrole **7** and **8**, bis(2-propyl-4,5-methylenedioxyphenyl)methane **9** and di(2-propyl-4,5-methy lene-dioxybenzyl)ether **10** were found. However, it was found that **5**, **6**, **7**, and **8** could undergo a further reaction to the final product (PBO), rather than its derivatives, though the by-products **9** and **10** still existed. Based on these results, the plausible mechanism of the chloromethylation and etherification of **3** was proposed. Furthermore, the reliability of the plausible mechanism was verified by quantum chemical calculations using DFT. In addition, the final product (PBO) was produced with a high selectivity and yield by reducing the by-products **9** and **10**.

Keywords Piperonyl butoxide · Chloromethylation · Etherification · Dihydrosafrole · Density functional

Introduction

Piperonyl butoxide (PBO) **1**, a methylenedioxyphenyl compound, is the first major insecticide synergist and now used in a wide variety of pesticides, such as pyrethrins, pyrethroids, carbamates and so on [1, 2]. It was first synthesized in 1946

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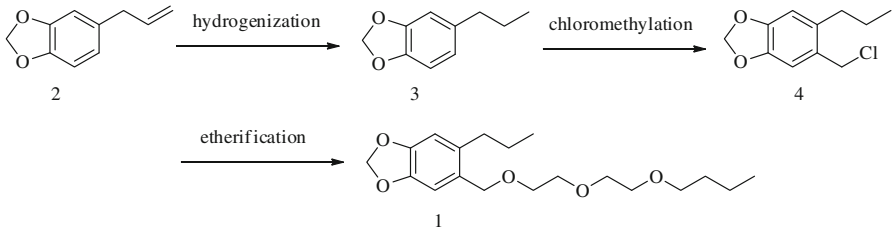


Scheme 1 Synthesis of PBO from Safrole **2**

by Wachs [3]. Since then, more interest centered around its preparation. It is generally prepared via the successive chloromethylation and etherification of dihydrosafrole **3** starting from naturally occurring safrole **2** (Scheme 1). The yield of PBO from **3** is relatively low, though the method of hydrogenation is mature. Previous research has mainly focused on the conditions of chloromethylation (reagent of chloromethylation, catalyst, reaction temperature or promoter) and etherification (solvent, reaction temperature, or base types) [4–10]. However, little information has been mentioned as to why the yield of the two steps is low, and the mechanism about the two steps has rarely been investigated. For these reasons, we have undertaken lots of experiments on the chloromethylation and etherification process with **3** as the starting material in order to understand the mechanism that might help to improve the total yield of PBO.

In this paper, we report the method to improve the yield of PBO and our observations on the mechanism of the chloromethylation and etherification of **3**. The plausible mechanism was also tested by quantum chemical calculations using density functional theory (DFT) with the program package DMol3 in Materials Studio of Accelrys Inc [11–13].

Results and discussion

Synthesis of chloromethyldihydrosafrole 4

The chloromethylation of aromatic hydrocarbons has been widely studied in the literature, and the most common procedures have been the use of hydrochloric acid and trioxane or paraformaldehyde as a formaldehyde precursor with Lewis acid as the catalyst [14, 15]. In our initial experiment, the chloromethylation of **3** was carried out in the presence of hydrochloric acid and paraformaldehyde according to the previous study [16, 17]. The analysis of the products was by GC–MS. To our disappointment, our attempts to reproduce the reported produce led to poor selectivity; multiple by-products were produced. Except for bis(2-propyl-4,5-methylenedioxyphenyl)methane **9**, other by-products, which were seldom reported like 4-chloromethyldihydrosafrole **5**, 6-propylpiperonyl alcohol **6**, 4,5-bis(chloromethyl)-6-propyl-1,3-benzodioxole **7**, 4,6-bis(chloromethyl)-5-propyl-1,3-benzodioxole **8**, and di(2-propyl-4,5-methy lene-dioxybenzyl)ether **10** were detected. Due

to the high activity of **3** (the methylenedioxy and *n*-propyl groups are both electron-donating), it is favorable for electrophilic substitution. In recent studies, the chloromethylation of aromatic compounds with hydrochloric acid, paraformaldehyde as well as catalysts such as phase-transfer catalysts [18–20], rare-earth metal triflates [21], and micellar catalysis in an oil/water biphasic system [22] are proved to be very promising methods. To enhance the selectivity and yield, lots of experiments on different reaction conditions were done on the base of the previous work and the results were shown in Table 1 (Fig. 1).

When no catalyst was used, the reaction rate of chloromethylation was relatively low (Table 1, entry 1–3), and with increase in temperature, yield of **7**, **8**, and **9** were also increased, while yield of **5** decreased (Table 1, entry 1–7). Perhaps at low temperature the effect of steric hindrance on the reaction is rather low, and activation energy of the reaction is the dominant factor. When Lewis acid was added, the reaction rate was increased, and furthermore, the by-products increased at the same time (Table 1, entry 5–7) because of the Friedel–Crafts alkylation catalyzed by the same Lewis acid. In the presence of a phase-transfer catalyst or rare-earth metal triflates, there was no obvious change in selectivity though the reaction rate could also be improved. Compared with Lewis acid, these catalysts are active at very low concentrations while a stoichiometric amount of Lewis acid catalyst to substrate is required, making the work-up procedure tedious. In an oil/water biphasic system with the addition of surfactant (CTAB), as the results shown in entry 10, the chloromethylation of **3** was also resulted in high conversion and high percent of by-products **7**, **8**, **9**, and **10**. Perhaps **3** was solubilized into micelles, resulting in a larger oil–water interfacial area, a higher reaction rate compared to the system without micelles and the decrease in selectivity, which was likely due to the subsequent chloromethylation of mono-chloromethyl products with the above by-products.

In summary, the results in Table 1 show that **3** could be reacted with high conversion and rapid reaction rate, but the selectivity is rather low even under various conditions. So the desired chloromethyldihydrosafrole **4** must be separated and purified by vacuum distillation before it can be reacted further to produce PBO **1**, but if such a method is used, the final yield of **1** would be no more than 75%.

Plausible mechanism of the chloromethylation and etherification of 3

Without considering the purification of **4**, we used the crude chloromethyldihydrosafrole as the starting material for etherification. To our surprise, the possible by-products **11**, **12**, **13** (Fig. 2) were not detected by GC–MS. The by-products of the chloromethylation step, **9** and **10** were still detected. The disappearance of **11** might be attributed to its isomerization to **1**, and the reason why **12** or **13** were not detected could be explained by Scheme 2. Based on this discovery, purification of chloromethyldihydrosafrole is no longer necessary. To increase the selectivity and yield of **1**, only **9** and **10** need to be decreased, which were produced during the chloromethylation of **3**.

During the chloromethylation of **3**, we found the intermediate **6**, so the plausible mechanism of chloromethylation can be presented as shown in Scheme 3. It mainly

Table 1 Results of the chloromethylation of **3** under different reaction conditions

Entry	Reaction time(h)	Reaction temperature (°C)	Catalyst	Conversion (%)	Selectivity %						
					(4)	(5)	(6)	(7)	(8)	(9)	(10)
1	6	90	None	98.3	72.2	10.4	1.2	2.3	4.4	4.8	1.6
2	6	70	None	98.1	71.6	13.8	1.1	2.1	4.0	3.7	1.5
3	6	50	None	95.1	71.4	14.6	1.2	2.1	3.8	3.5	1.5
4	14	10	None	32.4	66.7	23.3	1.1	1.6	3.0	2.5	0.9
5	4.5	70	$ZnCl_2$	98.0	71.8	13.5	1.2	2.2	3.8	3.9	1.5
6	4.5	50	$ZnCl_2$	95.2	71.5	14.5	1.1	2.2	3.9	3.6	1.4
7	14	10	$ZnCl_2$	41.5	65.9	23.5	1.1	1.5	3.2	2.8	0.8
8	5	70	Tetrabutylammonium chloride	98.1	71.5	13.5	1.2	2.1	3.8	3.7	1.5
9	4.5	70	$Sc(OTf)_3$	98.6	72.0	13.4	1.1	2.2	3.7	3.7	1.4
10	4	70	Micellar catalysis[a]	99.2	71.6	14.0	1.3	2.5	4.0	4.0	1.7

Reaction conditions: **3**, 25.0 g (0.15 mol); paraformaldehyde, 9.0 g (0.30 mol); conc. HCl, 30 mL; Conversions and selectivities are based on the GC with area normalization

[a] Micellar-catalyzed chloromethylation reaction of **3** was carried out in an oil–water biphasic system with the addition of surfactant (CTAB)

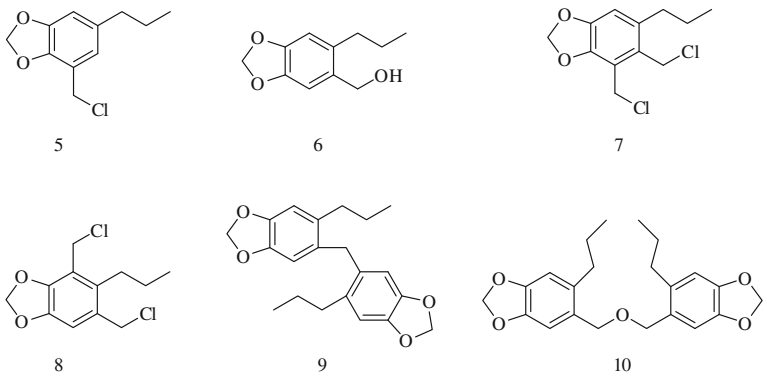


Fig. 1 By-products of the chloromethylation of dihydrosafrole **3**

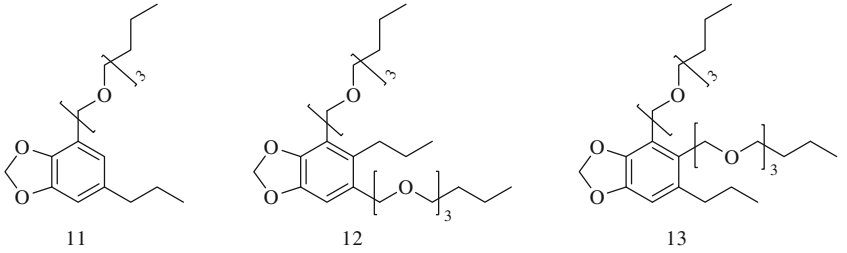
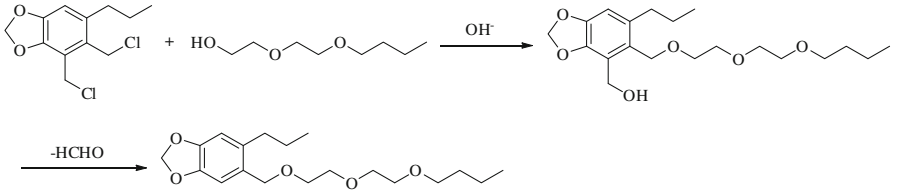


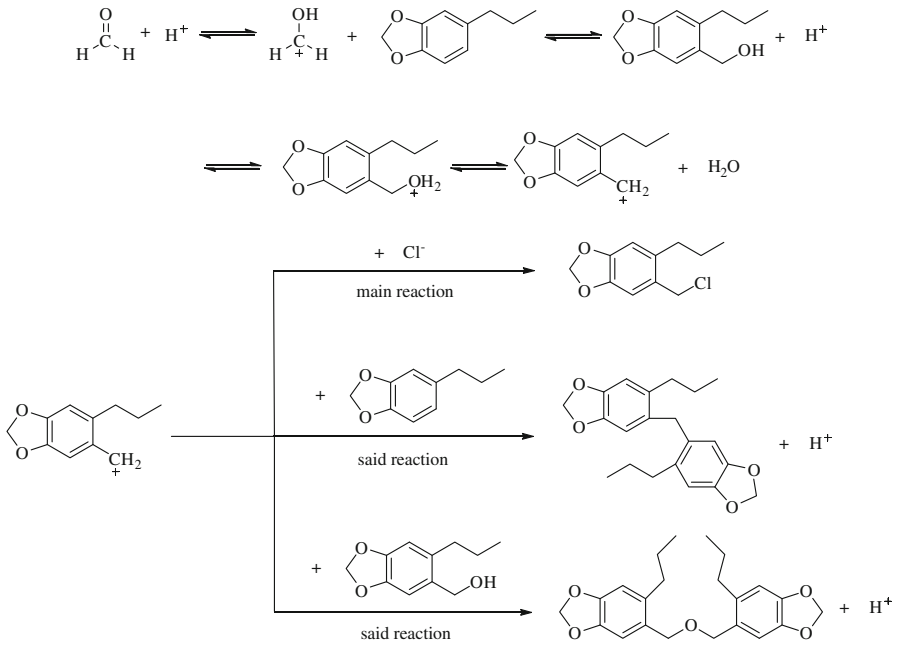
Fig. 2 The possible by-products of the etherification



Scheme 2 Plausible mechanism of the etherification

consists of two steps: electrophilic substitution and nucleophilic substitution, which can be expressed as follows:

Firstly, depolymerization of paraformaldehyde by acid catalysis of hydrochloric acid yields formaldehyde, which reacts with a proton (H^+) to give hydroxymethyl cation ($^+CH_2OH$) and the electrophilic substitution mainly occurs by subsequent attack of the $^+CH_2OH$ on benzene ring of **3** to give **4**; then the resulting alcohol under the action of acid gives a benzyl carbonium ion and water very rapidly; finally, the benzyl carbonium ion reacts with anions Cl^- to afford the desired product. Meanwhile, the benzyl carbonium ion can also react with benzene ring to give by-product **9**, or with **4** to give **10**. In addition, the production of by-products **5**, **7**, and **8** leads to the same product **4**.



Scheme 3 Plausible mechanism of the chloromethylation

As shown in Scheme 3, it is important to enhance the concentration of Cl^- and H^+, for more H^+ is advantageous to generate hydroxymethyl cation and benzyl carbonium ion, and more Cl^- is beneficial to produce the desired product and lessen the probability between benzyl carbonium ion and **3**, **4**, or **6**. So it is favorable to increase the concentration of hydrochloric acid, however, the concentration of hydrochloric acid decreased obviously with the consumption of hydrogen chloride and escape from the mixture at high temperature. In order to keep the hydrochloric acid concentration at a high level, we use a polymer of formaldehyde in the reaction system containing concentrated hydrochloric acid, instead of aqueous formaldehyde, or to bubble the gaseous hydrogen chloride at the end of the reaction. In this paper, the method of adding phosphorus trichloride dropwise was used. It not only produces hydrogen chloride but also consumes water. Also, the solvent must be considered, because it can reduce by-products by dispersing the starting material and products, decreasing their collision probability. The reaction temperature is also an important factor. At lower temperature, not only the reaction is slower but also the yield is poor. While at higher temperatures, the hydrogen chloride escapes and the by-products increase. Table 2 shows the effect of the above factors.

Without further purification, the products of the chloromethylation can directly react with the sodium salt of diethylene glycol monobutyl ether. This sort of ether preparation is known as the classical Williamson synthesis [23]. Generally, the influencing factors are the temperature and the catalyst type. In this paper, the reaction results at different reflux temperatures (cyclohexane, toluene, p-xylene, and mesitylene) and catalyzed by different bases (sodium hydroxide, potassium

Table 2 Effect of different factors for the chloromethylation of **3**

Entry	Reaction time(h)	Reaction temperature (°C)	Catalyst	Solvent	Conversion (%)	Selectivity %	
						(9)	(10)
1	6	70	None	None	98.1	3.7	1.5
2	6	70	PCl_3	None	98.5	2.1	0.9
3	6	70	PCl_3	Cyclohexane	98.3	1.8	0.7
4	6	50	PCl_3	Cyclohexane	96.3	1.8	0.7
5	6	90	PCl_3	None	98.8	2.8	1.2

Reaction conditions: **3**, 25.0 g (0.15 mol); paraformaldehyde, 9.0 g (0.3 mol); conc. HCl, 30 mL; cyclohexane, 40 mL; PCl_3, 8 mL, added dropwise after 4 h. Conversions and selectivities are based on the GC with area normalization. Selectivities of other products are not considerate because they can all be etherealizated to the final product (PBO)

hydroxide, and sodium carbonate) have indicated that the two factors have little effect. Since the chloromethylation was carried out using cyclohexane as solvent, the same solvent was used for the etherification.

Quantum chemical calculations on the synthesis of PBO

Computational method

In order to test the reliability of the plausible mechanism, DFT is used in this work to perform thermodynamic calculation for the proposed pathways. DFT has been very popular for calculations in chemistry since the 1970s, and it is now a widely used method for electronic calculations. Perdew and Wang's 1991 function (PW91) was used [24, 25]. A double-numeric polarized basis set (DNP) and truncate real-space cut-off of 4.0 Å were employed. These basis functions are numerically exact atomic orbitals, so that this quality of basis set gives rise to very little superposition effects [11].

The geometries of all the reactants, intermediates and products were optimized. The transition state (TS) search was performed with the linear and quadratic synchronous transit (LST/QST) complete search [26]. TS structures were verified using the TS confirmation tool. The solvent effect was estimated using the conductor-like screening model (COSMO) [27, 28], in which the solute molecules form a cavity within the dielectric continuum of permittivity ε. Compared to other continuum models, COSMO does not require complicated boundary conditions for a dielectric in order to obtain screening charges. It uses a simple boundary condition for a conductor.

Computational results and discussion

All the reactants, intermediates, and TS structures in the proposed reaction pathways are optimized firstly. Reaction Gibbs energy and barrier of every elementary

reaction are then calculated. The results are shown in Table 3. According to the reaction Gibbs energy of every elementary reaction in Table 3, Gibbs energy of the possible reactions was calculated as shown in Table 4.

Table 3 Gibbs energies and barriers of every elementary reaction

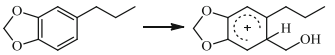
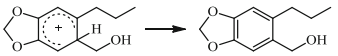
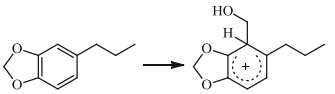
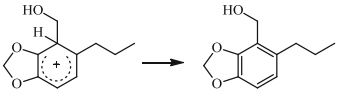
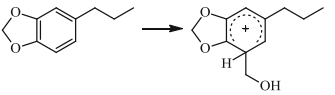
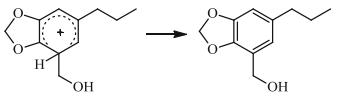
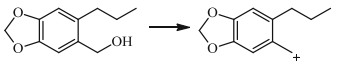
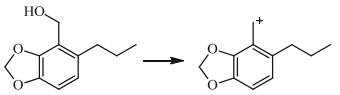
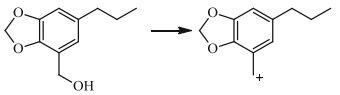
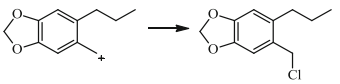
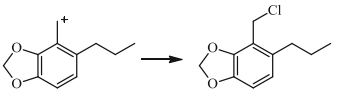
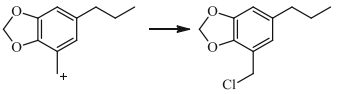
Entry	Reaction	Reaction Barrier (kJ/mol)	Reaction Gibbs energy (kJ/mol)
1		2.47	1.05
2		13.46	-13.01
3		8.45	7.14
4		18.42	-1.54
5		3.79	2.51
6		17.86	-7.72
7		8.00	-6.61
8		15.45	-1.34
9		10.24	-4.02
10		6.28	5.02
11		7.05	5.33
12		5.97	4.22

Table 3 continued

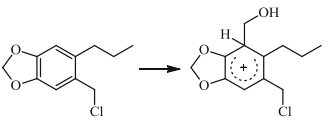
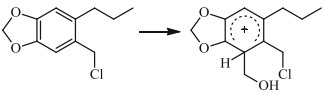
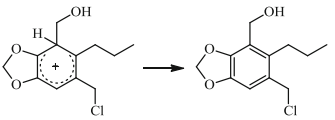
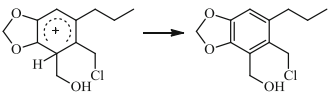
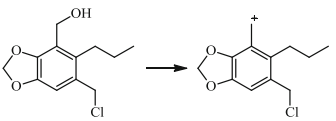
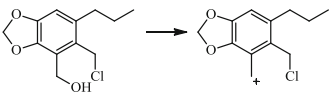
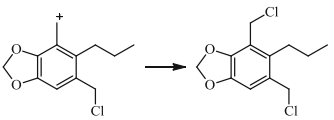
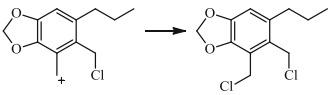
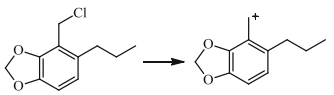
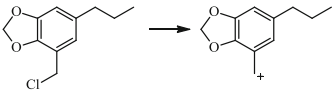
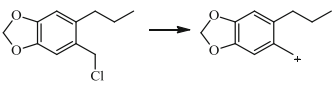
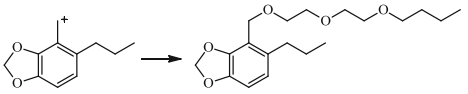
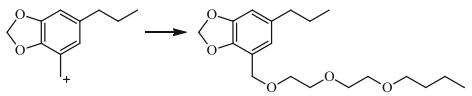
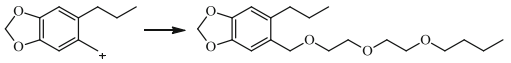
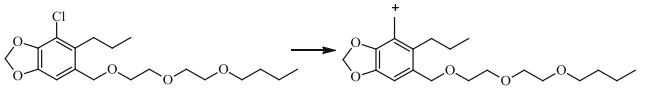
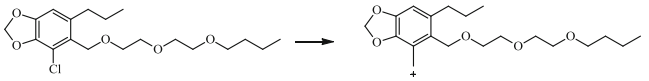
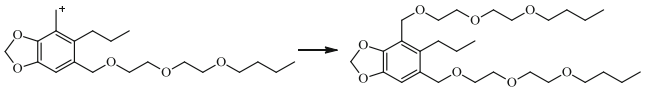
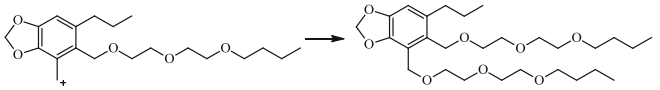
13		10.56	2.53
14		9.86	3.71
15		18.69	1.02
16		17.65	0.56
17		8.12	-2.55
18		7.95	-4.21
19		7.34	4.52
20		7.86	6.54
21		1.72	-5.33
22		1.75	-4.22
23		1.26	-5.02
24		12.39	2.54

Table 3 continued

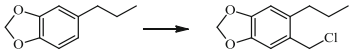
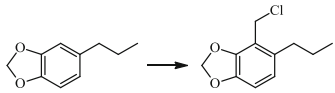
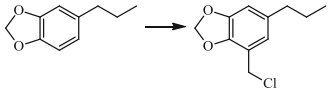
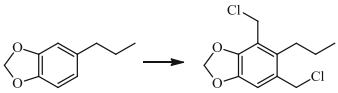
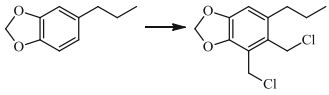
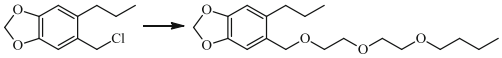
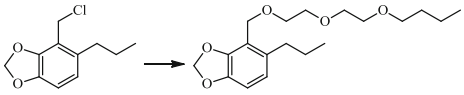
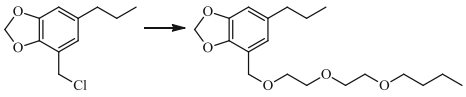
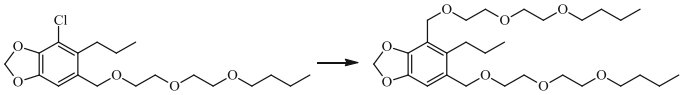
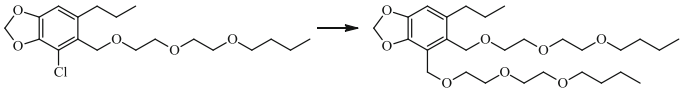
25		9.52	1.03
26		5.88	0.37
27		2.56	-1.05
28		2.74	-2.23
29		18.75	8.43
30		20.38	10.88

As shown in Table 4, the Gibbs energy of reaction 2 is the highest (Table 4, entry 1–5), and thus, it is hard to produce **14**, and indeed in the experiment two kinds of the mono-substituted chloromethyl substances were found, not three. Table 4 also contains the Gibbs energy of the etherification (entry 6–8). Obviously the Gibbs energy of reaction 6 is lowest, and the others are relatively higher, especially reactions 9 and 10. So it is possible that the by-products **11**, **12**, and **13** have not been found and they are likely to be converted to the desired product (PBO).

Conclusions

In summary, many by-products were found during the chloromethylation of dihydrosafrole, such as the isomer of chloromethyldihydrosafrole, 6-propyl piperonylic alcohol **6**, bis(chloromethyl)-dihydrosafrole **7** and **8**, the diphenylmethane derivative **9** and so on. In the experiment, **5**, **6**, **7**, and **8** could further react to give the final product (PBO), not the derivatives of PBO, though the by-products **9** and **10** still existed. So the main influencing factor of the selectivity and yield of PBO is how to reduce the by-products **9** and **10**. According to this result, the plausible mechanism of the chloromethylation and etherification of dihydrosafrole was put forward. Furthermore, the reliability of the plausible mechanism was tested by quantum chemical calculations using DFT. In addition, the method of adding dropwise phosphorus trichloride was used, and in this way the hydrochloric acid concentration was kept at a high level. The yield and selectivity of the final product (PBO) was rather high.

Table 4 Reaction energy of some possible reactions

Entry	Reaction	Reaction Gibbs energy (kJ/mol)
1		-13.55
2	 **(14)**	9.59
3		-5.01
4		-8.03
5		-6.95
6		-4.65
7		-2.79
8		-3.19
9		7.38
10		8.65

Experimental

Chemicals and instruments

Commercial reagents were used as received. ^{1}H NMR spectrum was recorded on a 400-MHz spectrometer with $CDCl_3$ as solvent and Me_4Si as an internal standard. The proton broadband decoupled ^{13}C NMR spectrum was recorded at 101 MHz.

$CDCl_3$ (Me_4Si as an internal standard) served as solvent. The following abbreviations were used to designate chemical shift multiplicities: s = singlet, d = doublet, t = triplet, m = multiple. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not easily be interpreted are designated as multiplet (m) or broad (br). IR spectra were recorded on an FTIR spectrometer. GC–MS analysis was carried out using an Agilent 6890 N gas chromatograph interfaced to a 5973 N mass selective detector. The column used was a HP-5 MS (5% phenylmethyl-polysiloxane) 30 m × 0.25 mm i.d. column, df = 0.25 μm. The GC conditions were as follows: injection port temperature was set at 280 °C and detector temperature at 300 °C, inlet pressures of nitrogen gas and hydrogen gas were 65 and 80 kPa, respectively, and the amount of test specimen was 0.1 μL. The temperature program started at 80 °C and maintained this temperature for 2 min, then ramped to 260 °C at 20°C/min followed by 25 min at 260 °C. The MSD parameters were electron impact in full scan mode.

General procedure for producing chloromethyldihydrosafrole 4

A visually clean, 250-mL three-neck round-bottom flask was charged with paraformaldehyde (9.00 g, 0.30 mol) and concentrated hydrochloric acid (38 wt%, 30 mL) and then heated to 40 °C with stirring until paraformaldehyde was completely dissolved to get a clear solution. The solvent cyclohexane (50 mL) and the starting material 3 (25.00 g, 0.15 mol) were then added, keeping the internal temperature at 70 °C. After 4 h, phosphorus trichloride (10 mL, 0.12 mol) was added dropwise over 3 h. The phases were allowed to separate when the mixture was cooled to room temperature. The organic layer was removed and the aqueous layer was back-extracted with cyclohexane (20 mL). The organic phases were combined and washed with half-brine (30 mL). Without further purification, the organic phase could be used directly in the next reaction. The mixture was analyzed by GC–MS. The conversion of **3** was 98.3%, and the selectivities of **9** and **10** were 1.8% and 0.7%. The main product **4** could be obtained at about 155 °C, at 10 mm of mercury when the above mixture was further distilled in vacuo. It is a colorless oil that is heavier than water. Chloromethyldihydrosafrole **4**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.80 (s, 1H), 6.67 (s, 1H), 5.91 (s, 2H), 4.55 (s, 2H), 2.61 (t, J = 6.8 Hz, 2H), 1.62 (m, J = 7.6 Hz, 2H), 0.99 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 147.9, 145.7, 135.7, 128.0, 110.1, 109.6, 101.1, 44.5, 34.2, 24.5, 13.9; IR (film) ν_{max}/cm^{-1} 2,962, 2,930, 2,875, 2,770, 1,620, 1,485, 1,379, 1,260, 1,170, 1,130, 1,040, 938, 866, 700, 645; MS (EI, 70 eV), *m/z* (relative abundance) 212 (M^+, 44), 183 (58), 177 (100), 149 (32), 119 (24), 89 (21), 77 (11), 63 (9), 51 (8), 39 (7).

Respective values for the by-products. 6-Propylpiperonyl alcohol **6**: MS (EI, 70 eV), *m/z* (rel abundance) 194 (M^+, 77), 176 (57), 165 (60), 149 (22), 135 (17), 107 (100), 91 (14), 77 (44); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.02 (s, 1H), 6.91 (s, 1H), 6.04 (s, 2H), 4.61 (s, 2H), 2.67 (t, 2H), 1.68 (m, 2H), 1.54 (s, 1H), 0.97 (t, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.8, 147.5, 137.1, 133.6, 108.8, 108.2, 101.4, 62.9, 37.5, 25.6, 14.1. 4,5-Bis(chloromethyl)-6-propyl-1,3-benzodioxole **7**: MS (EI,

70 eV), *m/z* (rel abundance) 260 (M^+, 28), 225 (100), 197 (24), 161 (23), 115 (11), 77 (16); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.89 (s, 1H), 6.02 (s, 2H), 4.89 (s, 4H), 2.61 (t, 2H), 1.61 (m, 2H), 0.99 (t, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.9, 146.5, 134.2, 130.8, 125.3, 108.6, 102.6, 62.9, 43.5, 38.7, 33.8, 25.2, 14.4. 4,6-Bis(chloromethyl)-5-propyl-1,3-benzodioxole **8**: MS (EI, 70 eV), *m/z* (rel abundance) 260 (M^+, 64), 231 (100), 225 (74), 189 (41), 159 (72), 131 (40), 115 (22), 91 (18), 77 (30); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.98 (s, 1H), 6.08 (s, 2H), 4.89 (s, 2H), 4.84 (s, 2H), 2.65 (t, 2H), 1.64 (m, 2H), 0.97 (t, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 146.2, 145.9, 133.1, 131.7, 127.0, 108.5, 102.3, 44.9, 39.8, 33.9, 24.7, 13.8. Bis(2-propyl-4,5-methylenedioxyphenyl)methane **9**: MS (EI, 70 eV), *m/z* (rel abundance) 340 (M^+, 57), 297 (5), 267 (13), 238 (9), 211 (11), 176 (100), 152 (9), 115 (6); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.01 (s, 2H), 6.97 (s, 2H), 6.09 (s, 4H), 4.04 (s, 2H), 2.63 (t, 4H), 1.68 (m, 4H), 0.99 (t, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 146.8, 146.6, 134.7, 133.0, 111.0, 107.7, 102.0, 39.2, 33.7, 24.6, 13.9. di(2-propyl-4,5-methylene-dioxybenzyl)ether **10**: MS (EI, 70 eV), *m/z* (rel abundance) 370 (M^+, 51), 176 (91), 150 (76), 135 (100), 119 (50), 91 (33); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.99 (s, 2H), 6.87 (s, 2H), 6.07 (s, 4H), 4.82 (s, 4H), 2.68 (t, 4H), 1.67 (m, 4H), 1.01 (t, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.5, 146.9, 135.7 134.6, 110.7, 108.5, 101.2, 71.6, 33.9, 24.8, 14.2.

General procedure for producing PBO 1

A visually clean, 250-mL three-neck round-bottom flask was charged with sodium hydroxide (15.00 g, 0.38 mol), water (10 mL) and diethylene glycol monobutyl ether (30.00 g, 0.19 mol) and then the mixture was refluxed using a water trap until no more water was collected (about 1 h). The solution was cooled to room temperature and the mixture of chloromethyl compounds (the organic phase obtained in the chloromethylation of **3**) was added. The mixture was then refluxed for 5 h. After cooling to room temperature, water (70 mL) was added until the salt dissolved. The layers were allowed to separate and the cyclohexane was distilled off. The remaining oil was distilled in vacuo. Some of the excess diethylene glycol monobutyl ether distilled over, and then PBO (48.65 g, 94.3%) of high purity (98.2%) was obtained, distilling at 230 °C at 10 mm of mercury. It is a colorless oil, soluble in benzene, cyclohexane, and most organic solvents. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.85 (s, 1H), 6.66 (s, 1H), 5.90 (s, 2H), 4.48 (s, 2H), 3.69–3.57 (m, 8H), 3.46 (t, $J = 6.8$ Hz, 2H), 2.54 (t, $J = 8.0$ Hz, 2H), 1.61–1.52 (m, 4H), 1.41–1.31 (m, 2H), 0.95 (t, $J = 7.2$ Hz, 3H), 0.91 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 146.9, 145.4, 135.0, 128.9, 109.4, 109.3, 100.7, 71.2, 70.8, 70.7, 70.6, 70.1, 69.3, 34.3, 31.7, 24.5, 19.2, 14.0, 13.9; IR (film) ν_{max}/cm^{-1} 2,960, 2,930, 2,870, 1,620, 1,485, 1,375, 1,259, 1,228, 1,105, 1,039, 935, 865; MS (EI, 70 eV), *m/z* (rel abundance) 338 (M^+, 10), 193 (15), 176 (100), 149 (42), 119 (22), 91 (13), 74 (8), 57 (25), 41 (13), 29 (8).

Similarly, experiments of chloromethylation and etherification under different conditions were carried out, and the results are shown in Tables 1 and 2.

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