Res. Chem. Intermed., Vol. 33, No. 6, pp. 535–540 (2007)

Also available online - www.brill.nl/rci

New process for the preparation of 3,5-dihydroxy-1-pentylbenzene

LONG ZHANG [1,2,*], ZHIQIANG LIU [2], YULUN XU [1] and SHUYING LIU [2]

[1] *School of Chemical Engineering, Changchun University of Technology, Changchun, Jilin 130012, P. R. China*
[2] *Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, Chanchun, Jilin 130021, P. R. China*

Received 30 August 2006; accepted 19 January 2007

Abstract—A new process for the preparation of 3,5-dihydroxy-1-pentylbenzene, which is used as medicinal intermediate and raw material for the synthesis of HIV restrainer, is proposed in this paper. Technical 3,5-dimethoxybenzoic acid reacted with lithium hydride to form a salt (I) which acylated n-butyllithium directly to give 1-(3,5-dimethoxyphenyl)-1-pentanone (II) in 85.06% yield. Then (II) was reduced through a Wolff-K-Huangminglong reaction at 210°C to give 3,5-dimethoxy-1-pentylbenzene (III). Finally, (III) refluxed with melt pyridine hydrochloride at 200°C for 2 h to afford the target product 3,5-dihydroxy-1-pentylbenzene (IV). The total yield of (IV) amounted to 61.50% and its mass percentage was 98.22%. The products were characterized by means of IR, ^{1}H-NMR, GC and HLPC-MS. The results indicated that this synthetic route was feasible, characterized by simple process and higher yield, and superior to the published ones.

Keywords: HIV restrainer; 3,5-dihydroxy-1-pentylbenzene; 3,5-dimethoxybenzoic acid; acylation; Wolff-K-Huangminglong reaction; demethylation.

INTRODUCTION

3,5-dihydroxy-1-pentylbenzene (Olivetol) is an important medical intermediate. Since its inhibition of human immune disease had been discovered in the 1980s, it has gained wider application in this field. Itself combined with other anti-immune dysfunction drugs can lead to effective drugs to cure HIVs, tumors and cancers [1]. Moreover, Olivetol is also employed as the raw material to prepare analgesics, pain-killing agents, sedatives and antihypertensive agents [2]. Research on its preparation has gained more and more attention. Korte *et al*. [3] proposed

*To whom correspondence should be addressed. Tel.: (86-431) 571-6785;
e-mail: zhanglongzhl@163.com

the preparation of Olivetol by the following reaction comprising the reaction of 1-alkynyl-methyl ketones with sodium malonic acid diethyl ester to 4-alkyl-6-methyl-2-oxo-2H-pyrane-3-carboxylic acid ethyl esters, followed by rearrangement and decarbethoxylation to form the corresponding 5-alkyl-resorcinols by heating with potassium hydroxide. However, the required alkynyl methyl ketone is not readily available. Kato and Hoizumi [4] reported that acetoacetic acid ethyl ester reacts with diketene in the presence of sodium hydride in THF to obtain 2,4-dihydroxy-6-methyl-benzoic acid ethyl ester which can be converted into the desired product, but the by-reaction results in lower yield. The latest preparation method is reported by Gosteli [5]. It employs 3-oxoglutaric acid dimethyl ester and 2-octynoic acid methyl ester as raw material, the raw materials react with NaH to form 2,4-dihydroxy-6-pentylisophthalic acid dimethyl ester (I) post-treatment. (I) is refluxed in sodium hydroxide solution and acidified to form 2,4-dihydroxy-6-pentylisophthalic acid (II). (II) is dissolved in diluted sulphuric acid, refluxed, extracted in sodium hydroxide solution and acidified with concentrated hydrochloric acid and purified by distillation in high vacuum. The total yield of olivetol is 57.12%. All the above-mentioned methods have the shortcoming of involving complex reactions, lower yield and employing no-easily available and expensive material. The development of a new preparation method is of great interest. This paper puts forward a new process for the preparation of olivetol employing easily available 3,5-dimethoxy benzoic acid as raw material. The experimental results are reported below.

EXPERIMENTAL

We used 3,5-dimethoxybenzoic acid (Industry grade, 99%), lithium hydride (Industry grade, 99%), n-butyllithium (Industry grade, 20% in n-hexane solution), sodium hydroxide (AR), pyridine (AR), concentrated hydrochloride (AR) and diethylene glycol (CR). The structure and composition of the intermediates and products prepared were determined on a Nicolet 360 FI-IR spectrometer, Agilent 1100-1946C HPLC-MS spectrometer, Shimadzu GC-14C Gas chromatograph and Varia FT-80 A NMR spectrometer. An X-4 melting point measurement apparatus was employed to determine the melting point of the solid substances; the yield of product is calculated by the following formula:

$$Y = \frac{m_1/M_2}{m_2 P/M_2} \times 100\%,$$

where Y is yield of product (in %), m_1 mass of product (in g), m_2 mass of raw material (in g); M_1 molar mass of product (in g/mol), M_2 molar mass of raw material (in g/mol) and P the mass fraction of raw material (in %).

The synthetic route for the preparation is shown in Fig. 1.

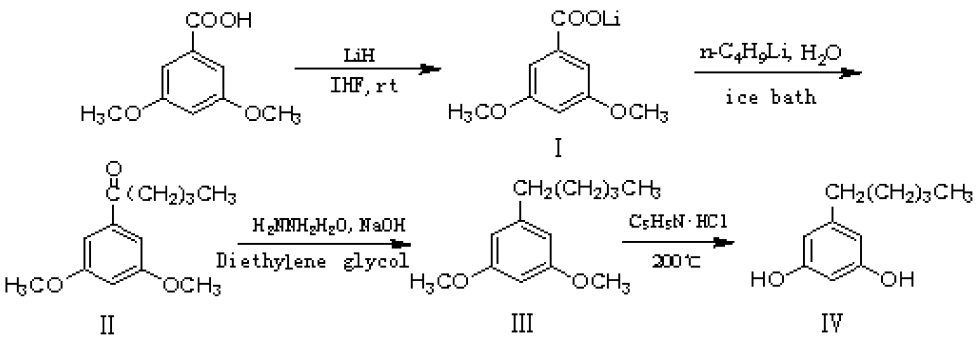

Figure 1. Synthesis of olivetol.

Synthesis of 3,5-dimethoxyphenyl-1-pentanone

In a 1000-ml four-necked flask with stirrer, temperature controller and an inner gas inlet was added 36.40 g (0.2 mol) 3,5-dihydroxy benzoic acid that was dissolved in 400 ml THF under stirring. Then 1.68 g (0.21 mol) LiH was added to react for 10 h at room temperature, followed by heating to reflux for 0.5 h to form benzoate. The product was cooled and put in an ice bath, n-butyllithium in hexane solution (mass fraction 20.05%) was added portion-wise and the reaction was continued until a Gilman test [6] could be performed. After that the reaction mixture was pour into 500 ml iced water to stir to hydrolyze it, settling in a tap funnel to separate the organic phase. The organic phase was washed 3 times with distillated water, dried by $MgSO_4$ and purified by distillation in vacuum. The distillate at the bottom was diluted with anhydrous alcohol and put into a refrigerator for a day. The crystal appeared next day and was recrystalized in the mother liquor to obtain a white crystal (II), 37.80 g, yield 85.06%, its melting point was 42–44°C. ^{1}H-NMR ($CDCl_3$): δ 7.09 (d, 2H), 6.64 (t, 1H), 3.82 (s, 6H), 2.91 (t, 2H), 2.1–0.7 (broad, m, 7H). IR (ν^{-1}): 2956.6, 2872.3, 2839.3, 1656, 1593, 1206.1, 846.6 and 732.8 cm^{-1}, conform the standard data. The white crystal was proven to be 3,5-dimethoxyphenyl-1-pentanone.

Preparation of 3,5-dimethoxy-1-pentylbenzene

In a 500-ml four-necked flask with stirrer, temperature controller and an inner gas inlet, was added 100 ml diethylene glycol, 22.00 g (0.10 mol) 3,5-dimethoxyphenyl-1-pentanone, 30 ml (0.50 mol) hydrazine hydrate. The mixture was heated and refluxed for 2 h, then the temperature was decreased and the water-separator set to distill off the water formed and unreacted hydrazine hydrate at 180°C, followed by cooling the reaction mixture to 30°C, again refluxed for 3 h, and cooled to room temperature. Then the reaction mixture was poured into 200 ml iced water and extracted 3 times with 100 ml petro ether; the extract was dried over anhydrous $MgSO_4$ and distilled by reduced pressure at 144–148°C and 1 kPa, gathering the pale yellow distillate III, 18.12 g, yield 90.5%, GC analysis shows the mass fraction

is 99.2%. IR (ν^{-1}): 2955.2, 2931.0, 2857.1, 1596.0, 1460.2, 1205.3, 828.7, 693.7, conform the standard IR data.

Preparation of 3,5-dihydroxyphenyl-pentane

In a 500-ml four-necked flask with stirrer, temperature controller and an inner gas inlet, was added 125 ml hydrochloride (10 M) and 100 ml pyridine. The mixture was heated to 200°C to remove the water in the system, then cooled to 130°C, after which 10.40 g (0.02 mol) 3,5-dimethoxyphenyl-pentane was added. This mixture was heated to reflux for 2 h to end the reaction, the mixture was cooled to 80°C and 200 ml iced water was added, followed by two extractions with dichloromethane in a tap funnel, then the extract was washed with anhydrous $MgSO_4$, distilled under reduced pressure and the distillate was collected at 168–170°C and 400–570 Pa. It is a yellow viscous liquid that becomes a transparent crystal (III) under N_2 protection at 10°C. Its weight is 7.65 g, yield 80.4%, melting point 46–48°C, mass fraction is 98.22%. IR (ν^{-1}) 3415.2, 2930.7, 2857.6, 1596.8, 1460.7, 831.2 and 730.4 cm^{-1}, MS (m/z) = 181.1, conform the standard data. Analysis proved it was the desired product 3,5-dihydroxyphenyl-pentane, with a total yield of 61.5%.

RESULTS AND DISCUSSION

Effect of portionwise speed of n-butyllithium on the yield of 3,5-dimethoxyphenyl-pentanone

In the alt-forming reaction the molar ratio of LiH to 3,5-dimethoxy benzoic acid was kept at 1.05, reaction temperature 20°C, reaction time 10 h. In the acylation process, the reaction proceeded in an ice bath under N_2 protection. Experiments have been conducted to investigate the effect of n-butyllithium portion-wise addtion speed on the yield of 3,5-dimethoxyphenyl-pentanone. The results are listed in Table 1.

The results demonstrate that the yield of 3,5-dimethoxyphenyl-pentanone increases as the adding speed of n-butyllithium decreases and that increasing speed causes a temperature rise. This will hinder the nucleophilic reaction to proceed, resulting in the by-reaction; therefore, the speed should be strictly controlled and the reaction be carried out at lower temperature. A shorter reaction time is suggested. In view of the above considerations, the optimal portion-wise speed is suggested as 0.40–0.60 ml/min.

Table 1.
Effect of adding speed of n-butyllithium on the yield of (3,5-dimethoyphenyl)-1-pentanone

Adding speed (ml/min)	1.20	1.00	0.80	0.60	0.40	0.20
Yield (%)	78.62	80.3	82.24	84.78	85.12	85.36

Table 2.
Effect of reflux time on the yield of 3,5-dihydroxy-1-pentylbenzene

Reflux time (h)	1.00	1.50	2.00	2.50	3.00	3.50
Yield (%)	68.85	76.28	80.42	79.16	76.83	72.24

Reflux temperature, 200°C, N_2 protection.

Posttreatment of 3,5-dimethoxyphenyl pentane

In the preparation of 3,5-dimethoxyphenyl pentane, the product is analyzed as a mixture of dimethylether and methylether. It is suggested that dimethylether of olivetol demethylated to the methylether of olivetol at higher reaction temperature. Methylether of olivetol can be converted to 3,5-dimethoxyphenyl pentane by adding proper amount of dimethyl sulfate in the reaction. By doing so, the content of 3,5-dimethoxyphenyl pentane in the product is 98.54 wt%. This can be directly employed as the raw material for the successive reaction without any purification.

Effect of reflux time on the yield of 3,5-dihydroxy-1-pentylbenzene

The effect of reflux time on the yield of 3,5-dihydroxy-1-pentylbenze has been investigated and the results are shown in Table 2.

The results show that the yield of 3,5-dihydroxy-1-pentylbenzene increases first and then decrease as the reflux time increases. This is because that pyridine hydrochloride is a very strong demethylation agent. Prolonging reflux time will result in the carbonization of the product and correspondingly decrease the yield. Therefore, 2 h is recommended as a suitable reflux time.

CONCLUSIONS

A new preparation process for olivetol is proposed. It comprises technical 3,5-dimethoxybenzoic acid reacted with lithium hydride to form benzoate which acylated n-butyllithium directly to give 3,5-dimethoyphenyl-1-pentanone, it is reduced by a Wolff-K-Huangminglong reaction to give 3,5-dimethoxy-1-pentylbenzene. Finally it is refluxed with melt pyridine hydrochloride to afford the target product 3,5-dihydroxy-1-pentylbenzene with total yield of 61.5% and mass percentage 98.22%. Suitable reaction parameters for each reaction have been determined and the intermediates and product was confirmed by means of IR. ^{1}H-NMR, GC-MS and HPLC-MS. The results indicated that the new synthetic route was feasible, characterized by simple process and higher yield, and superior to the published ones.

REFERENCES

1. A. Travis, US Patent 6,274,635 (2001).
2. E. A. Formukong, A. T. Evans and F. J. Evans, *Inflammation* **12**, 361 (1988).

3. F. Korte and H. Sieper, *Justus Liebigs Ann. Chem*. **71**, 603 (1960).
4. T. Kato and T. Hozumi, *Chem. Pharm. Bull*. **20**, 1574 (1972).
5. B. Gosteli, US Patent 4,249,027 (1981).
6. H. Gilman and F. Schultze, *J. Am. Chem. Soc.* **47**, 2002 (1925).