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A Practical Synthesis of 3-*n*-Propylphenol, a Component of Tsetse Fly Attractant Blends

István Ujváry*,† and Gyula Mikite‡

Institute of Chemistry, Chemical Research Center, Hungarian Academy of Sciences, P.O. Box 17, H-1525 Budapest, Hungary, and ERCOM Ltd., Pusztaszeri út 59-67, H-1025 Budapest, Hungary

Abstract:

A practical synthesis of the tsetse fly attractant 3-*n*-propylphenol involves the Grignard reaction of 3-hydroxybenzaldehyde and ethylmagnesium bromide affording a benzylic alcohol-type phenol derivative that upon catalytic hydrogenation gives the title product in 75% overall yield. Selection of the right solvent mixture and temperature range for the Grignard reaction is crucial for the kilogram-scale preparation of the target compound.

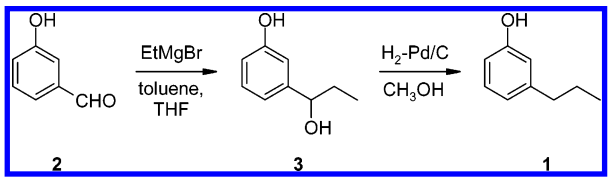
Introduction

The African trypanosomiases, sleeping sickness in humans and nagana in livestock, are devastating diseases in sub-Saharan Africa. The *Trypanosoma* parasites are transmitted between their vertebrate hosts by various tsetse fly (*Glossina*) species infesting 36 countries and a total area of at least 8.7 million km^2 in Africa. One of the current environmentally benign tsetse control methods is the use of traps baited with natural or artificial host odors. A large number of traps are used alone or in combination with chemical and nonchemical (e.g., sterile insect technique) tsetse control measures to monitor and reduce, even eradicate, local populations of the targeted *Glossina* species.

3-*n*-Propylphenol (**1**) is a synergistic component identified as one of the attractive phenols of buffalo and cattle urine.[1] This compound has been used extensively in artificial odor baits, such as acetone and the 8:4:1 combination of *p*-cresol, 1-octen-3-ol,[2] and **1** ("Zimbabwe mixture").

During our program to improve the efficiency of tsetse control and eradication campaigns,[3] we were prompted to develop an inexpensive and technically uncomplicated method for the large-scale production of phenol **1**. Previously known syntheses of **1** employed, as the key step, reduction of 3-hydroxypropiophenone,[4] reductive deoxygenation of safrole or isosafrole over Ni-catalyst[5] and of isosafrole with sodium metal,[6] Grignard reaction of 3-benzyloxybenzaldehyde with ethylmagnesium bromide (EtMgBr),[7] Wittig-reaction of 3-hydroxybenzaldehyde with ethyl(triphenyl)-phosphonium bromide,[1a] and transition metal-catalyzed C−C coupling of 3-bromoanisole and ethyl halide.[8] A multistep method based on the cyclocondensation of 3-oxohexanal with 1,3-acetonedicarboxylic acid esters has also been described.[9] Inspecting, and in some cases repeating on a small scale (<50 g), these methods revealed that they proceed in low yields and either use not readily accessible starting materials or involve reaction steps unsuitable for large-scale preparation of the target compound at acceptable cost. After some experimentation, involving optimization of reaction temperature and selection of solvent, we have devised a simple two-step procedure for the kilogram-scale production of **1** from the commercially available 3-hydroxybenzaldehyde (**2**), the details of which are described below (see Scheme 1).

Scheme 1



Results and Discussion

The reaction of aldehyde **2** with excess of EtMgBr in diethyl ether to give hydroxyphenol **3** has been described[10] with reported yields of 58−59%.[10b,c] Hydrogenolysis of the benzyl alcohol-type **3** was expected to readily provide the target phenol **1**. Thus, we set out to find conditions for the Grignard reaction feasible on a kilogram scale.

* Address correspondence to this author. Fax: 36-1-325-7554. E-mail: istvan@chemres.hu.

† Hungarian Academy of Sciences.

‡ ERCOM Ltd.

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(10) (a) von Auwers, K. *Ann. Chem.* **1917**, *413*, 253. This paper describes the preparation of hydroxyphenol **3** by using essentially the same procedure described herein, but no experimental details are given. (b) Another paper using von Auwers's method for the preparation of **3** gives no experimental details either: Pohl, L. R.; Haddock, R.; Garland, W. A.; Trager, W. F. *J. Med. Chem.* **1975**, *18*, 513. (c) A fully documented description of this method reports the use of diethyl ether as solvent and a 3.2-fold excess of the Grignard reagent, giving the target phenol **3** in 58% yield: Bird, T. G. C.; Bruneau, P.; Crawley, G. C.; Edwards, M. P.; Foster, S. J.; Girodeau, J.-M.; Kingston, J. F.; McMillan, R. M. *J. Med. Chem.* **1991**, *34*, 2176.

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For safety as well as solubility reasons the Grignard reaction was carried out in THF rather than in diethyl ether as reported earlier.[10] Because of the poor solubility of aldehyde **2** in THF the use of toluene as a cosolvent was found to be important.[11] In the event, a fine dispersion of aldehyde **2** in toluene−THF was reacted with 2.6 equiv[12] of EtMgBr to afford pure **3** in 80% yield after recrystallization. Small-scale experiments indicated that maintaining the reaction temperature around 20 °C during the addition of EtMgBr solution was optimal. At temperatures below 15 °C the solubility of the forming magnesium phenolate/alcoholate decreases making stirring difficult. At temperatures higher than 25 °C coloration, even charring, of the reaction mixture occurs, decreasing the yield and purity of the product. Recrystallization of the crude product from a minimum amount of EtOAc provided pure phenolic alcohol **3** free from any starting material in good yield. Unless these precautions (efficient stirring and maintaining the reaction temperature at 20 ± 5 °C) are taken, the product could contain up to 5% of the starting aldehyde **2** that, when carried over to the hydrogenation step, affords *m*-cresol, which could contaminate the final product. Since *m*-cresol is also behaviorally active for certain tsetse fly species the final product must be free from this homologue.

Finally, hydrogenolysis of **3** in methanol at atmospheric pressure using Pd-on-carbon catalyst gave **1** in nearly quantitative isolated yield. With smaller batches (<50 g) the reduction was typically performed at ambient temperature in ethanol with or without acid catalyst, but on a large scale it was preferably carried out in methanol in the presence of 70% aqueous $HClO_4$ (ca. 0.03% with regard to solvent) and at 40 °C with efficient magnetic stirring. Although acetic acid (up to 10% with regard to solvent) was also found to facilitate the reduction, its removal, for example by distillation or extraction, complicates workup.

Conclusions

The tsetse fly attractant component 3-*n*-propylphenol (**1**) has been prepared on a kilogram scale in two remarkable simple steps in 75% overall yield. The procedure described is applicable to the synthesis of other alkylated aromatics if the corresponding aldehyde is readily available (see, for example, ref 3).

Experimental Section

Proton and ^{13}C NMR spectra were recorded in $CDCl_3$ at 400 and 100 MHz, respectively, on a Varian spectrometer. Chemical shifts are expressed in ppm using the solvent signal ($CDCl_3$; $\delta = 7.26$ for ^1H and $\delta = 77.0$ for ^{13}C spectra, respectively) as internal reference. IR spectra were recorded on a Nicolet Magna-IR 750 spectrometer. Mass spectrometry was performed on a VG ZAB 2SEQ mass spectrometer in electron ionization mode. HPLC was performed on an ISCO 2350 system with UV detection at 220 nm through a Hypersil BDS C18 column (4.6 mm × 150 mm) using a 40:60 mixture of 0.05 M aqueous KH_2PO_4 buffer (pH = 3.5)−methanol as eluent (1 mL/min). Thin-layer chromatography used 0.25-mm thick silica gel plates (DC Alufolien Kieselgel 60, Merck KGaA, Darmstadt, Germany). The Pd-catalyst was from Merck, other reagents were purchased from Aldrich or Fluka, while solvents were from Reanal (Budapest, Hungary).

(±)-3-(1-Hydroxypropyl)phenol (3). Finely ground 3-hydroxybenzaldehyde (**2**, 1250 g, 10.2 mol) was dissolved in warm anhydrous toluene (2.2 L). The solution was then allowed to cool to ca. 30 °C, purged with dry argon gas and diluted with anhydrous THF (20 L) while stirring using mechanical stirrer. The effectively stirred suspension was then cooled to 10 °C, and a solution of EtMgBr, freshly prepared from ethyl bromide (1987 mL, 26.6 mol) and magnesium (648 g, 26.6 mol) in anhydrous THF (8.2 L), was added[13] over the course of 3 h while carefully maintaining the reaction temperature between 15 and 25 °C using water + dry ice as cooling bath. The thick reaction mixture was then stirred and refluxed for 2 h, cooled to 5 °C, quenched with cold water (1.0 L), and acidified with 5 M HCl solution (5.6 L). The phases were separated, and the aqueous layer was extracted with methyl *tert*-butyl ether (4 × 1.0 L).[14] The organic phases were combined, washed successively with water, saturated $NaHCO_3$ solution, and water (1.0−1.0 L), and dried ($MgSO_4$). The solvent was evaporated to give a thick oil (ca. 1600 g) that was briefly stirred with EtOAc (ca. 1.0 L) at 30 °C and then allowed to crystallize at 5 °C in a refrigerator over 14 h. The product (910 g) was collected by filtration. The mother liquor was concentrated, and a second crop of hydroxyphenol **3** was obtained by recrystallizing the residue from hexanes−EtOAc (60:40, by volume)[15] to give a total of 1250 g of **3** (80%) as white crystals; mp 106−107 °C (lit. mp 105−107 °C).[10b,c] Purity (HPLC): 99.0%.

(11) As in ref 10c, our initial small-scale preparations of **3** employed diethyl ether in which the starting aldehyde is more soluble than in THF although solutions more dilute than the one described here were needed. However, during the Mg-phenolate formation and subsequent Grignard reaction, stirring became a serious problem. This solubility problem, exacerbated by intensive cooling, should be the main reason for the earlier reported low (58%) yield of **3**: the Grignard adduct forms an ethyl ether-insoluble double salt covering the surface of unreacted Mg-phenolate precipitate, thus blocking complete consumption of the starting material. This could also explain why even a large, 3.2-fold excess (see ref 10c) of EtMgBr could not drive the reaction to completion. It is speculated that refluxing the reaction mixture after the completion of the addition breaks up the solid particles that include unreacted aldehyde phenolate.

(12) In preliminary experiments performed under various conditions on up to 50-g scales indicated (TLC) that the use of 2.2−2.4-fold excess of EtMgBr led to intermediate **3** that was contaminated with some unreacted starting material, the removal of which was cumbersome even by repeated recrystallization (attempted distillation of the crude product led to degradation of **3**). Furthermore, hydrogenation of the impure intermediate gave the target phenol contaminated with *m*-cresol resulting from the reductive deoxygenation of **2**. Acceptable yield (80%) and excellent purity of **3** was achieved when the excess of EtMgBr was increased to 2.6-fold, which is significantly less than the 3.2 equiv used in ref 10c.

(13) Because continuous addition of the suspension of **2** to the Grignard reagent presents some difficulties (clogging of the addition funnel), "inverse addition" of EtMgBr solution to the vigorously stirred dispersion of the aldehyde is preferred.

(14) Repeated extractions with 4 × 1 L methyl *tert*-butyl ether are necessary. Measuring the volume of each extract indicated substantial amounts of extractives present in the acidic aqueous phase: the volumes of the four subsequent extracts were 2. 5, 2.2, 2.0, and 1.8 L, respectively.

(15) TLC analysis indicated that the mother liquor of the second crop contained hydroxyphenol **3**, some starting material, and other unidentified contaminants.

TLC R_f: 0.19 (silica, toluene:methanol = 9:1 (v/v); for **2** R_f: 0.37.

IR (KBr): ν 3400, 1590, 1480, 1270, 1090, 950, 890, 790, 702 cm^{-1}.

^1H NMR: δ 0.95(t, J = 7.4 Hz, 3H), 1.77(m, 2H), 1.95-(s, 1H), 4.56(br t, J = 6.5 Hz, 1H), 5.18(s, 1H), 6.66(m, 1H), 6.86(m, 1H), 7.20(m, 1H). ^{13}C NMR: δ 155.8, 146.5, 129.6, 118.4, 114.5, 112.8, 75.8, 31.7, 10.0.

3-*n*-Propylphenol (1). A solution of **3** (381 g, 2.50 mol) in analytical grade methanol[16] (2.0 L) was added to a prehydrogenated suspension of 10% Pd-on-carbon[17] (28.0 g) and 70% aqueous $HClO_4$ (0.3 mL) in analytical grade methanol (1.3 L) while stirring, and then the reaction mixture was hydrogenated with vigorous magnetic stirring at 40 °C (water bath) from a 20-L gas buret until gas absorption ceased (ca. 60 L during 12 h). The suspension was filtered, and the catalyst was washed with a small amount of methanol and saved for further use. The filtrate was concentrated and the residue distilled in a vacuum. After a small forerun, 320 g (94%) of phenol **1** was collected as a colorless oil;[18] bp: 93−95 °C/2.3 mmHg (lit. bp 110 °C/10 mmHg).[6b] n_D (25 °C): 1.5236. Density: 0.9878 g/mL (24 °C). Purity (HPLC): 99.5%. Hydrogenation of two additional batches of **3** using recycled catalyst proceeded smoothly with similar results. The three distilled batches were then combined, giving a total of 995 g phenol **1** with 98.5% purity.

IR (film): ν 3300, 2960, 2925, 1575, 1496, 1260, 1155, 790, 695 cm^{-1}.

^1H NMR: δ 0.93(t, J = 7.4 Hz, 3H), 1.63(m, 2H), 2.53-(t, J = 7.4 Hz, 2H), 4.77(s, 1H), 6.64(m, 1H), 6.65(m, 1H), 6.75(m, 1H), 7.14(m, 1H). ^{13}C NMR: δ 155.2, 144.7, 129.4, 121.1, 115.4, 112.6, 37.8, 24.3, 13.8.

MS (EI^+): m/z 136 $[M]^+$ (45%), 121 (15%), 107 (100%), 77 (20%).

(16) As a rule, analytical grade methanol (>99.9%) is used at the pilot plant of ERCOM for the various syntheses. No other grades were tried, but ordinary methanol could also work. As mentioned earlier, laboratory-scale preparations of **3** also used 95% ethanol (with added acetic acid) successfully for the reduction. Due to the notoriously higher price of ethanol, its use on a larger scale was abandoned.

(17) In preliminary small-scale experiments reductions using 5% Pd/C from one supplier (Aldrich) were rather slow even in the presence of acetic acid. Note, however, that catalysts on various support—and even with the same support but from different sources—can vary in their efficiency. No other types of 5% Pd/C were tested.

(18) Although some references give a melting point of 26 °C for 3-propylphenol, our double-distilled product is a thick liquid at ambient temperature and remains as such even at ca. 5 °C (refrigerator).

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