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An Efficient Method for the Synthesis of 4,5-Disubstituted Catechols

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4,5-Disubstituted catechols were prepared in high yields via successive Friedel-Crafts acylation in the presence of a Ti(IV) catalyst or I_2 and reduction with triethylsilane of veratroles. This method provides an effective and well-regulated synthetic strategy toward catechol derivatives having a variety of substituents at the 4- and 5- positions.

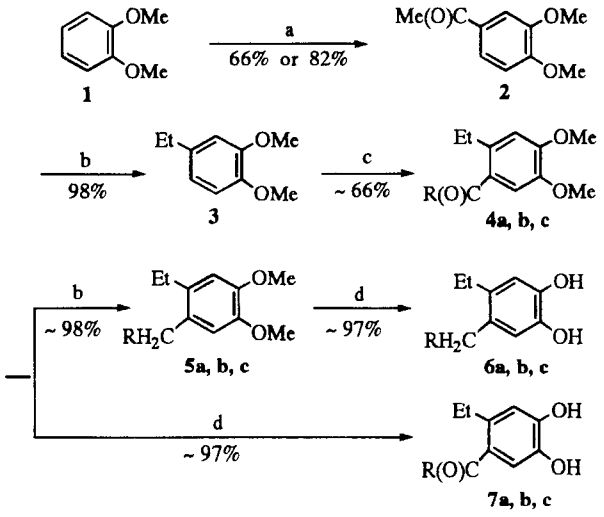
Catechol and its derivatives are powerful bidentate chelating agents, having particular affinity for metal ions in higher oxidation states or those showing higher ratios of the charge/metal ion radius.[1] On the other hand, catechol derivatives possess diverse biological activity, such as hyperglycemic,[2] antimutagenic,[3] antibiotic, and cytotoxic activities.[4] For these reasons, the role of catechol derivatives has become a topic of increased study in recent years. However, in spite of their chemical and biological importance, very limited studies have thus far been reported on the synthesis of catechol derivatives. As for the synthetic procedures for alkylcatechols, they are usually obtained from their corresponding phenols or benzoquinones, as reported concerning the synthesis of 4-alkylcatechols and 3,5-di-*t*-butylcatechol.[5] Recently, Siddiqui et al. prepared a series of alkylcatechols through the Friedel–Crafts alkylation of catechol with alkyl halides and diethyl ether–boron trifluoride (1/1) used as a catalyst;[4] however, there has been no report on the synthesis of 4,5-diethylcatechol. The disadvantage of this method is a polysubstitution reaction, which results in a lowering of the yields of the target compounds. Another problem concerning Friedel–Crafts alkylation is that only dialkylcatechols with the same alkyl substituents are accessible. Our interest in the reactivity and chemical and biological properties of catechols led us to explore a reliable and rational synthetic route toward 4,5-dialkylcatechols, including 4,5-diethylcatechol and asymmetrically substituted derivatives, which have not been synthesized and have not been evaluated concerning their chemical and biological properties. In this paper, we describe the synthesis of novel 4,5-disubstituted catechols. Our synthetic strategy is depicted in Scheme 1.

We took advantage of Friedel–Crafts acylation; the reaction introduces only one acyl group into an aromatic ring at one time. In the case of 1,2-dimethoxybenzene (veratrole) (**1**), 4-acetylveratrole (**2**) was obtained in 82% yield by using a combined catalyst system of titanium(IV) chloride tris(trifluoromethanesulfonate) and trifluoromethanesulfonic acid ($TiCl(OTf)_3$/TfOH).[7]

The reaction using I_2 as a catalyst gave a lower yield of the product (66%). Compound **2** was converted to 4-ethylveratrole (**3**) quantitatively by reduction with triethylsilane (Et_3SiH) in CF_3COOH. The ethylation of **1** was attempted under the conventional Friedel–Crafts conditions, where ethylbromide (EtBr) and $AlCl_3$ were employed; however, regulation of the reaction toward monoethylation was not successful and polyalkylation was observed under severe conditions (excess amount of EtBr and excess of $AlCl_3$ used). This result indicates that the combination of acylation and hydrogenation by Et_3SiH is more effective and reasonable for regulating the alkylation of veratroles.

In order to prepare 4,5-diethylcatechol (**6a**), compound **3** was acylated by the same method using I_2 to obtain 4-acetyl-5-ethylveratrole (**4a**), followed by a reduction with Et_3SiH and deprotection of the methyl groups with BBr_3 in high yield. In this manipulation, the isolation of intermediates **3** and **4a** is not required, and the final distillation of the reaction mixture gave pure **5a**.

Novel asymmetrically substituted catechols, such as 4-benzyl-5-ethylcatechol (**6b**) and 4-benzyl-5-ethylcatechol (**6c**), were also afforded by using propionic anhydride and benzoyl chloride to react with **3**, respectively, along with the method described above. Generally, the introduction of alkyl groups longer than the ethyl group to aromatic rings



a: R = Me, **b**: R = Et, **c**: R = Ph
Reagents: a, Ac_2O, I_2 or $TiCl(OTf)_3$/TfOH; b, Et_3SiH/CF_3COOH; c, $(RCO)_2O$ or PhCOCl, I_2; d, BBr_3

Scheme 1.

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is known to be difficult to afford good yield; this is caused by rearrangements due to the stability of the corresponding carbocations derived from alkyl halides. 4-acyl-5-ethylcatechols (**7a—c**) were obtained by the deprotection of **4a—c** with BBr_3 in high yield. To our knowledge, this is the first report on the preparation of this type of catechol derivative.

In conclusion, we established an effective method for the synthesis of catechol derivatives containing a variety of alkyl and acyl substituents at the 4- and 5- positions.

Experimental

All of the reagents were of commercial quality. Veratrole was obtained from Tokyo Kasei Kogyo Co., Ltd. The others were purchased from Wako Pure Chemical Industries, Ltd. Titanium(IV) chloride tris(trifluoromethanesulfonate) was prepared as described in the literature.[7]

The ^{1}H NMR spectra were measured at 295 K in $CDCl_3$ on JEOL GX 400 and EX 270 spectrometers at 400 MHz and 270 MHz, respectively. The chemical shifts were determined in ppm relative to TMS as an internal reference. The IR spectra (4000—400 cm^{-1}) were recorded on a Shimadzu FTIR-8000 Spectrometer. C, H, and N analyses were performed at the Service Center of the Elemental Analysis of Organic Compounds, Kyushu University.

The general experimental procedures are described as follows:

Acylation: Acylation reactions toward veratroles were carried out in accordance with two procedures by using I,[6] or $TiCl(OTf)_3$/TfOH[7] as catalyst.

Reduction: To a stirred solution of 4-acetylveratrole or 4-acyl-5-ethylveratrole (0.16 mol) in 75 ml trifluoroacetic acid, triethylsilane (0.38 mol) was added dropwise. After the addition, the solution was stirred for 12 h at room temperature. The obtained crude product was distilled under vacuum to give pure 4,5-dialkylveratroles in 94—98% yields.

Demethylation: To a solution of 4,5-dialkylveratrole or 4-acyl-5-ethylveratrole (77 mmol) in 60 ml of degassed CH_2Cl_2 at 0 °C, BBr_3 (100 mmol) was added. A yellow suspension was immediately formed, which was stirred for 12 h at ambient temperature. After the slow addition of water and the evaporation of CH_2Cl_2, the mixture was extracted with ether and the ether extract was washed with water three times. The ether was removed under reduced pressure to give a crude product; decolorization by activated charcoal or sublimation afforded a 4,5-dialkylcatechol or a 4-acyl-5-ethylcatechol as a colorless solid (95—97%, yields).

^{1}H NMR, IR, and elemental analyses for the products in each step are given as follows.

3: Bp 115 °C/10 mmHg (1 mmHg = 133.322 Pa); ^{1}H NMR δ = 6.70—6.80 (3H, m Ar–H), 3.86 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 2.56 (2H, q, J = 8 Hz, CH_2), 1.22 (3H, t, J = 8 Hz, CH_3). Anal. ($C_{10}H_{14}O_2$) C, H.

4a: Bp 104—108 °C/10 mmHg; IR (KBr) 1663, 1267, 1061, 1030 cm^{-1}; ^{1}H NMR δ = 7.20 (1H, s, Ar–H), 6.74 (1H, s, Ar–H) 3.94 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 2.57 (3H, s, $COCH_3$), 2.88 (2H, q, J = 8 Hz, CH_2), 1.22 (3H, t, J = 8 Hz, CH_3). Anal. ($C_{12}H_{16}O_3$) C, H.

4b: Bp 95—101 °C/2 mmHg; IR (CCl_4) 1684, 1263, 1076, 1009 cm^{-1}; ^{1}H NMR δ = 7.15 (1H, s, Ar–H), 6.74 (1H, s, Ar–H), 3.93 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 2.89—2.86 (4H, m, CH_2), 1.19—1.17 (6H, m, CH_3). Anal. ($C_{13}H_{18}O_3$) C, H.

4c: Bp 137—140 °C/2 mmHg; ^{1}H NMR δ = 8.12—8.07 (2H, m, Ar—H), 7.66—7.62 (1H, m, Ar–H), 7.52—7.50 (2H, m, Ar–H), 6.84 (1H, s, Ar–H), 6.82 (1H, s, Ar–H), 3.93 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 2.64 (2H, q, J = 8 Hz, CH_2), 0.93 (3H, t, J = 8 Hz, CH_3). Anal. ($C_{17}H_{18}O_3$) C, H.

5a: Bp 110 °C/7.5 mmHg; IR (CCl_4) 1211, 1059 cm^{-1}; ^{1}H NMR δ = 6.69 (2H, s, Ar–H), 3.87 (6H, s, OCH_3), 2.60 (4H, q, J = 8 Hz, CH_2), 1.20 (6H, t, J = 8 Hz, CH_3). Anal. ($C_{12}H_{18}O_2$) C, H.

5b: Bp 92—95 °C/2 mmHg; IR (CCl_4) 1223, 1069 cm^{-1}; ^{1}H NMR δ = 6.68 (1H, s, Ar–H), 6.66 (1H, s, Ar–H), 3.86 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 2.62—2.49 (4H, m, CH_2CH_2), 1.60 (2H, q, J = 8 Hz, CH_2), 1.17 (3H, t, J = 8 Hz, CH_3), 0.98 (3H, t, J = 8 Hz, CH_3). Anal. ($C_{13}H_{20}O_2$) C, H.

5c: Bp 130 °C/2 mmHg; IR (KBr) 1228, 1090 cm^{-1}; ^{1}H NMR δ = 8.08—8.12 (2H, m, Ar–H), 7.65—7.50 (1H, m, Ar–H), 7.47—7.38 (2H, m, Ar–H), 6.88 (1H, s, Ar–H), 6.79 (1H, s, Ar–H), 5.64 (2H, s, CH_2), 3.86 (3H, s, OCH_3), 3.64 (3H, s, OCH_3), 2.62 (2H, q, J = 8 Hz, CH_2), 1.05 (3H, t, J = 8 Hz, CH_3). Anal. ($C_{17}H_{20}O_2$) C, H.

6a: IR (KBr) 3460, 1221 cm^{-1}; ^{1}H NMR δ = 6.68 (2H, s, Ar–H), 4.89 (2H, br, OH), 2.55 (4H, q, J = 8 Hz, CH_2), 1.18 (6H, t, J = 8 Hz, CH_3). Anal. ($C_{10}H_{14}O_2$) C, H.

6b: IR (KBr) 3424, 1215 cm^{-1}; ^{1}H NMR δ = 6.69 (1H, s, Ar–H), 6.66 (1H, s, Ar–H), 4.70 (2H, br, OH), 2.60—2.50 (4H, m, CH_2CH_2), 1.59 (2H, q, J = 8 Hz, CH_2), 1.20 (3H, t, J = 8 Hz, CH_3). 0.98 (3H, t, J = 8 Hz, CH_3). Anal. ($C_{11}H_{16}O_2$) C, H.

6c: IR (KBr) 3423, 1229 cm^{-1}; ^{1}H NMR δ = 7.24—7.12 (5H, m, Ar–H), 6.73 (1H, s, Ar–H), 6.58 (1H, s, Ar–H), 5.02 (2H, br, OH), 3.89 (2H, s, CH_2), 2.50 (2H, q, J = 8 Hz, CH_2), 1.11 (3H, t, J = 8 Hz, CH_3). Anal. ($C_{15}H_{16}O_2$) C, H.

7a: IR (KBr) 3433, 1634, 1223 cm^{-1}; ^{1}H NMR δ = 7.28 (1H, s, Ar–H), 6.77 (1H, s, Ar–H), 6.00 (2H, br, OH), 2.85 (2H, q, J = 8 Hz, CH_2), 2.50 (3H, s, $COCH_3$), 1.19 (3H, t, J = 8 Hz, CH_3). Anal. ($C_{10}H_{12}O_3$) C, H.

7b: ^{1}H NMR δ = 7.21 (1H, s, Ar–H), 6.76 (1H, s, Ar–H), 5.62 (2H, br, OH), 2.88—2.73 (4H, m, CH_2), 1.14—1.12 (6H, m, CH_3). Anal. ($C_{11}H_{14}O_3$) C, H.

7c: ^{1}H NMR δ = 8.13—8.10 (2H, m, Ar–H), 7.59—7.50 (1H, m, Ar–H), 7.47—7.45 (2H, m, Ar–H), 5.40 (2H, br, OH), 2.62 (2H, q, J = 8 Hz, CH_2), 1.15 (3H, t, J = 8 Hz, CH_3). Anal. ($C_{15}H_{14}O_3$) C, H.

References

1 M. J. Kappel and K. N. Raymond, *Inorg. Chem.*, **21**, 3437 (1982).

2 L. Cavalca and F. Gilardi, *Atti Soc. Lomb. Sci. Med. Biol.*, **1955**, 154.

3 H. Winterhoff, H. G. Gumbinger, and H. Sourgens, *Planta Med.*, **54**, 101 (1988).

4 B. S. Siddiqui, Q. Adil, and S. Siddiqui, *Pak. J. Pharm. Sci.*, **6**, 53 (1993).

5 a) M. Masahiro, *Asahikawa Kogyo Semmmon Gakko Kenkyu Houbun*, **19**, 129 (1982). b) P. J. Bossermam and D. T. Sawyer, *Inorg. Chem.*, **21**, 1545 (1982).

6 D. E. Pearson and G. A. Buchler, *Synthesis*, **1972**, 533.

7 a) J. Izumi and T. Mukaiyama, *Chem. Lett.*, **1996**, 739. b) J. Izumi, I. Shiina, and T. Mukaiyama, *Chem. Lett.*, **1995**, 141.