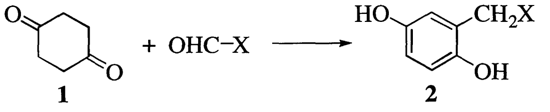
A New Approach to 5-Hydroxyindoles from 1,4-Cyclohexanedione

Yutaka Ozaki,* Kyouko Okamura, Ayako Hosoya, and Sang-Won Kim*
Faculty of Pharmaceutical Sciences, Josai University, Keyakidai, Sakado, Saitama 350-02

(Received March 27, 1997; CL-970226)

Several kinds of 2-substituted 5-hydroxyindoles were prepared by the procedure starting from the condensation of 1,4-cyclohexanedione with *N*-protected α-amino aldehydes in the presence of lithium chloride. The substitutent on 2-position of the indole ring system depends on that of the α-amino acid which was converted to the aldehyde.

The indole ring system is found in a wide range of compounds, from naturally occurring compounds such as various indole alkaloids to important synthetic compounds such as indomethacin and other indole-3-acetic acid derivatives. Many of these chemicals have attracted great chemical and biochemical interests.[1] For these reasons, numerous synthetic methods of indole derivatives have been investigated continuously.[2] Especially, the preparation of 5-hydroxyindole derivatives is one of the most significant syntheses owing to the powerful biological actions of the target compounds. These derivatives have been constructed by several pathways such as the Nenitzescu synthesis,[3] the Fisher synthesis,[2,4] and the oxidative cyclization reaction[5] of 2-(1,4-dihydroxyphenyl)ethylamine systems. The Nenitzescu synthesis gives 5-hydroxyindole-3-carboxylic esters or 3-acyl-5-hydroxyindoles in one step by employing *p*-benzoquinones as key compounds to the indole synthesis. This procedure, as well as the Fisher synthesis, have been employed frequently. The oxidative cyclization method of the amines has been less used because it requires multistage reactions to earn the amines from starting aromatic compounds. In this communication, we report a practical synthesis of the 5-hydroxyindoles by a procedure starting from 1,4-cyclohexanedione and α-amino aldehydes followed by the oxidative cyclization.



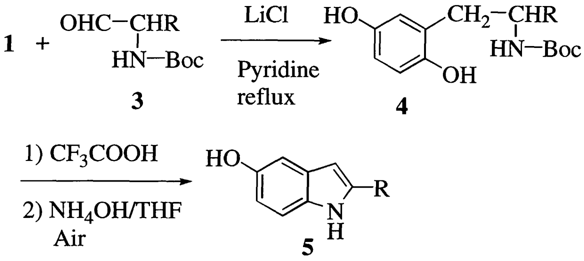
X: alkyl or aryl group

Scheme 1.

In connection with our interest to synthesize aromatic compounds, we have reported a new approach to 2-substituted 1,4-benzenediols (**2**) by the reaction of 1,4-cyclohexanedione (**1**) with a variety of aldehydes (Scheme 1).[6] This synthetic method was found to be applicable to the preparation of the 2-(1,4-dihydroxyphenyl)ethylamine derivatives (**4**) by using a-(*t*-butoxycarbonylamino)aldehydes (**3**) instead of the simple aldehydes (Scheme 2). The compounds **3** were derived from α-amino acids according to the procedure of the literature.[7] The condensation of **1** with **3** in the presence of lithium chloride in refluxing pyridine gave *N*-protected 2-(1,4-dihydroxyphenyl)-ethylamine systems (**4**) in moderate yields as shown in Table 1.[8,9] After removal of the protective group of **4** by trifluoroacetic acid, the resulting amines were stirred with aqueous 28% NH$_3$ under the atmosphere at room temperature to give 2-substituted 5-hydroxyindoles (**5**).[10] The yields of compound **5** from **4** are shown in Table 1. The variation of the alkyl or aryl groups on 2-position of the indoles depends on the structure of the α-amino acids employed for the aldehyde synthesis.

Table 1. Preparation of 1,4-benzenediols (**4**) and 5-hydroxyindoles (**5**)

Run	R	**4** Yield / %	**5** Yield / %
1	$(CH_3)_2CH$-	67	73
2	$PhCH_2$-	49	65
3	$(CH_3)_2CHCH_2$-	51	72
4	$CH_3CH_2(CH_3)CH$-	66	52
5	CH_3-	37	51
6	Ph-	43	47



Scheme 2.

In conclusion, 2-substituted 5-hydroxyindoles were prepared by the procedure starting from 1,4-cyclohexanedione and aldehydes derived from α-amino acids. The 1,4-cyclohexanedione is a key compound to the novel 5-hydroxyindole synthesis as well as the *p*-benzoquinones in the Nenitzescu indole synthesis.

References and Notes

1 See for example: T. Y. Shen, C. A. Winetr, in "Advance in Drug Research," ed by A. B. Simmons, Academic Press, New York (1977), Vol. 12, p. 89; P. M. Vanhoutte, in "Serotonin and the Cardiovascular System," Raven Press, New York (1985), p. 280.

2 See for example: R. T. Brown, J. A. Joule, and P. G. Sammes, in "Comprehensive Organic Chemistry," ed by P. G. Sammes, Pergamon Press, Oxford (1979), Vol. 4, p.411; U. Pindur and R. Adam, *J. Heterocyclic Chem.*, **25**, 1

(1988); J. Bosch and M. Bennasar, *Synlett*, **1995**, 587; E. D. Cox and J. M. Cook, *Chem. Rev.*, **95**, 1797 (1995).

3 See for example: G. R. Allen, Jr., in "Organic Reactions," ed by W. G. Dauben, John Wiley & Sons, New York (1973), Vol. 20, Chap. 3, p. 337; J. M. Pawlak, V. V. Khau, D. R. Hutchison, and M. J. Martinelli, *J. Org. Chem.*, **61**, 9055 (1996); R. M. Coates, P. A. MacManus, *J. Org. Chem.*, **24**, 4822 (1982); J. F. Poleto, G. R. Allen, Jr., A. E. Sloboda, and M. J. Weiss, *J. Med. Chem.*, **16**, 757 (1973).

4 See for example: R. D. Clark, J. M. Muchowski, L. E. Fisher, L. A. Flippin, D. B. Repke, and M. Souchet, *Synthesis*, **1991**, 871; E. Shaw, *J. Am. Chem. Soc.*, **77**, 4319 (1955).

5 See for example: J. S. Zweig and N. Castagnoli, Jr., *J. Med. Chem.*, **17**, 747 (1974); J. S. Zweig and N. Castagnoli, Jr., *J. Med. Chem.*, **20**, 414 (1977); P. Jacob III, T. Kline, and N. Castagnoli, Jr., *J. Med. Chem.*, **22**, 662 (1979).

6 Presented at the 117th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, March 1997; Y. Ozaki, A. Hosoya, K. Okamura, and S. Kim, *Synlett.*, accepted.

7 J. Fehrentz and B. Castro, *Synthesis*, **1983**, 676.

8 Typical procedure to **4**: A mixture of 1,4-cyclohexanedione (**1**) (5 mmol), a-(*t*-butoxycarbonylamino)-aldehyde (**3**) (5 mmol), and lithium chloride (5 mmol) in pyridine (2 ml) was heated under reflux for 1 h. After evaporation of the solvent *in vacuo*, the residue was poured into water. The mixture was acidified with diluted HCl and the product was extracted with EtOAc. The organic extract was washed with water, aqueous NaHCO$_3$, water, and brine, and then dried over MgSO$_4$. After evaporation of the solvent, the residue was purified by column chromatography to give 1,4-benzenediol derivatives (**4**).

9 Although optically active aldehydes (**3**) [R = (CH$_3$)$_2$CH-, (CH$_3$)$_2$CHCH$_2$-] were used in these reactions, the earned 1,4-benzenediols (**4**) [R = (CH$_3$)$_2$CH-, (CH$_3$)$_2$CHCH$_2$-] were optically inactive. These results indicated that racemization occurred during the condensations.

10 Typical procedure to **5**: To a solution of **4** (0.5 g) in methylene chloride (5 ml) was added trifluoroacetic acid (2.5 ml) with stirring. The stirring was continued for 2 h at room temperature. After evaporation of volatile components *in vacuo*, the residue was subjected to column chromatography on silica gel with EtOAc to give the amine which was exposed to the next reaction without further purification. A mixture of the amine and 28% aqueous NH$_3$ (30 ml) in THF (5 ml) was stirred under the atmosphere at ambient temperature for 16 h. The product was extracted with EtOAc, and the organic extract was washed with brine, dried, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with n-hexane/EtOAc (7 : 3) to afford the 5-hydroxyindole derivatives (**5**). Inspection of ^{1}H-NMR spectra of these indole derivatives indicated the presence of C-3 protons along with other aromatic protons. The former were found in the range of δ 6.1 to δ 6.7.