SYNTHESIS OF 5-HYDROXYOXAINDAN-2-ONES AND INDOL-5-OLS FROM 1,4-CYCLOHEXANEDIONE

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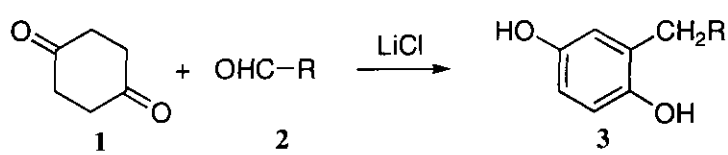
Abstract - 1,4-Cyclohexanedione reacted with 2-oxocarboxylic acids to give 5-hydroxyoxaindan-2-ones including homogentisic lactone in one pot. The obtained aromatic compounds were transformed into indol-5-ols in a few steps. The sequential reactions showed a significance of 1,4-cyclohexanedione as a starting material in aromatic synthesis and an alternative access to the indol-5-ols.

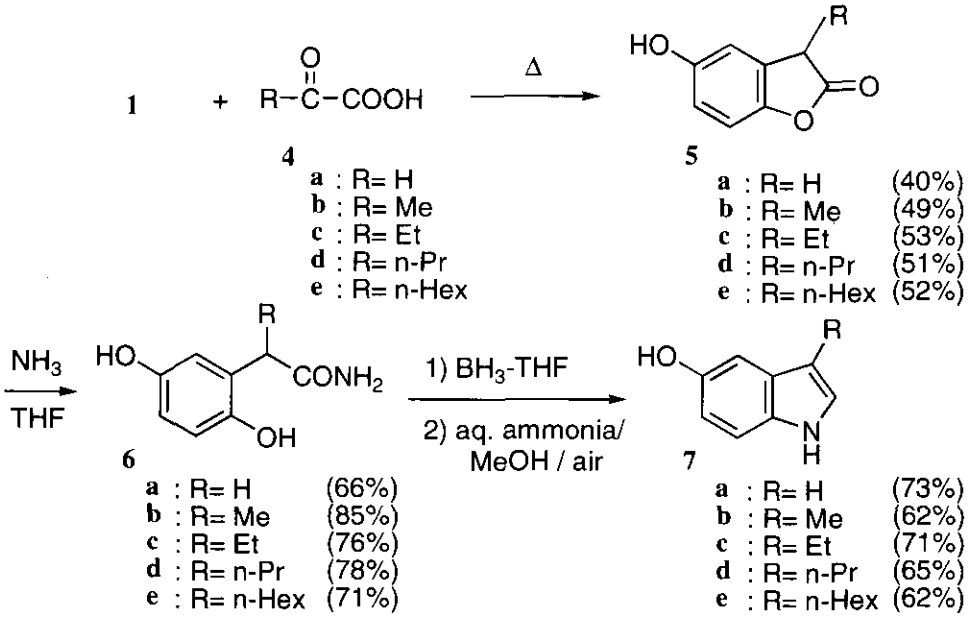
Synthesis of aromatic compounds is a major goal of organic synthesis and construction of phenolic compounds is an important area because of their utility in various fields. For example, chromans bearing a phenolic hydroxyl group display distinctive biological activity,[1] cannabinoids contain 1,3-benzenediol structure,[2] and 1.4-benzenediol derivatives have been studied as anti-oxydant chemicals, photo-industory materials, and polymer materials.[3] The new approach to the phenolic compounds is the continuous main target in this laboratory[4] as many biologically active aromatic compounds are categorized in phenolic compound groups.[1-3] In the course of our investigation on the aromatic synthesis, we disclosed a new route to 1,4-benzenediols using the condensation of 1,4-cyclohexanedione (**1**) with a variety of aldehydes.[5] The procedure was further applied to the preparation of 2-alkylated indol-5-ols.[6] In this communication, we report a new synthesis of 5-hydroxyoxaindan-2-ones and 3-alkylated indol-5-ols starting from the reaction of 1,4-cyclohexanedione with α-keto acids.



1 **2** **3**

Scheme 1

The reaction of 1,4-cyclohexanedione (**1**) with aldehydes (**2**) converted the aliphatic six-membered ring into the aromatic ring to give 2-substituted 1,4-benzenediols (**3**) as shown in Scheme 1.[5] The employed aldehydes contained aliphatic, aromatic and heteroaromatic aldehydes. However, the reactions of **1** with simple ketones such as cyclohexanone or 3-pentanone instead of the aldehyde under the similar conditions gave no satisfactory result. The simple ketones were not so reactive as the aldehydes in this reaction. Investigation of both the reaction conditions and the substrates revealed that the condensation of α-keto acids (**4**) with **1** gave 5-hydroxyoxaindan-2-ones (**5**) as follows. A neat mixture of pyruvic acid (**4b**) and **1** was heated to 160-170°C with stirring for 3 h. The mixture melted in liquid and the carboxylic acid offered a role of acidic catalyst to push forward the condensation between **1** and the pyruvic acid. After drying under reduced pressure at ambient temperature, the reaction mixture was subjected to a SiO_2 column eluted with AcOEt / hexane (3:7) to give 5-hydroxy-3-methyloxaindan-2-one (**5b**) in 49% yield.



Scheme 2

The structure of the product was confirmed by the observation of signals of three aromatic protons and those of a methyl group on the lactone ring in ^{1}H-NMR together with other spectral data.[7] The carbonyl group of pyruvic acid has the lowered electron density owing to its neighbored electron withdrawing carboxylic acid group and, further, the intramolecular hydrogen bonding can be formed in this compound. These structural advantages over the simple ketones accelerate the nucleophilic attack of **1** against **4b**.

Thus, the aldol condensation between 1,4-cyclohexanedione and the α-keto acid gave the α,β-unsaturated γ-keto acid, which has the structure easy to isomerize to furnish the stable aromatic

compound. Other α-keto acids such as 2-oxobutyric acid (**4c**), 2-oxopentanoic acid (**4d**) and 2-oxooctanoic acid (**4e**) were also transformed into the corresponding 3-alkyl-5-hydroxyoxaindan-2-ones (**5c-e**) as shown in Scheme 2.

Glyoxylic acid (**4a**) was used as the smallest 2-oxocarboxylic acid to the condensation reaction with **1**. The similar reaction procedure and subsequent purification afforded compound (**5a**) in 40% yield.[8] The IR and NMR spectral data of the lactone were the same as those of the commercially available homogentisic lactone.[9] This compound, 5-hydroxyoxaindan-2-one (**5a**), is a synthetic precursor of homogentisic acid which is an important intermediate in the metabolism of phenylalanine and tyrosine.[10] The reported preparations of homogentisic lactone in the literature employed 1,4-benzenediol or 1,4-benzoquinone as the starting material and the lactone was obtained in several steps under the various reaction conditions.[11] Compared to these reported procedures including anhydrous environment or strong acidic conditions, our one-pot synthesis from 1,4-cyclohexanedione is desirable to the mass production of the lactone (**5a**).

The framework of constructed homogentisic lactone and its derivatives (**5**) contains both the 1,4-benzenediol structure and the side chain. The conversion of the side chain into 2-aminoethyl group was anticipated to give the indol-5-ols (**7**) since it was reported that the oxidative cyclization of 2-(2,5-dihydroxyphenyl)ethylamines afforded the indole derivatives.[12] The lactone (**5a**) was converted into the amide (**6a**) by treatment with ammonia in THF. The converted amide was reduced by BH_3-THF to amine that was exposed to the atmosphere in aqueous ammonia/MeOH without purification. The sequential reactions starting from **5a** gave indol-5-ol (**7a**). Other lactones (**5b-e**) gave indoles (**7b-e**) in the same manner. The yields of the amides (**6**) and the indoles (**7**) are shown in Scheme 2.

The reported preparation of indol-5-ols was carried out by the Fischer synthesis,[13] the Nenitzecu synthesis,[14] above oxidative cyclization, etc.[15] The oxidative one has been not so frequently used as the Fischer synthesis because the synthetic intermediates such as 2-(2,5-dihydroxyphenyl)ethylamines have been supplied by only a few procedure.[12] Therefore, the proposed simple preparation of homogentisic lactone and its analogue (**5**) can be utilized to an alternative approach to indol-5-ols (**7**), whose structure is found in biologically important compounds such as serotonin, indomethacin, and melatonin.[16]

In conclusion, the reaction of 1,4-cyclohexanedione (**1**) with 2-oxocarboxylic acids (**4**) was found to give 5-hydroxyoxaindan-2-ones (**5**). The transformation of the lactones into the indol-5-ols (**7**) showed an alternative route to the indol-5-ols starting from aliphatic compounds.

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7. ^{1}H-NMR ($CDCl_3$) δ: 1.54 (3H, d, J = 8 Hz, -Me), 3.69 [1H, q, J = 8 Hz, C(3)H], 6,73 [1H, dd, J = 2 Hz, 8 Hz, C(6)H], 6.75 [1H, d, J = 2 Hz, C(4)H], 6.93 [1H, d, J = 8 Hz, C(7)H]; IR (Nujol): 3332, 1762 cm^{-1}.
8. ^{1}H-NMR ($CDCl_3$) δ: 3.13 (2H, s, CH_2), 6,75 [1H, dd, J = 2 Hz, 8 Hz, C(6)H], 6.78 [1H, d, J = 2 Hz, C(4)H], 6.92 [1H, d, J = 8 Hz, C(7)H].
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