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Rapid synthesis of kahweofuran and its derivatives, the coffee aroma components

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Abstract—Kahweofuran, as an impact flavor component of roasted coffee and possesses the 6-methyl-2,3-dihydrothieno[2,3-*c*]furan structure, was rapidly synthesized from 2-acetyl-3-hydroxymethylthiophene by the formal reductive cyclization using the Wilkinson's catalyst. Similarly, the syntheses of the 4-methyl, 6-ethyl and 4,6-dimethyl derivatives were also achieved in favorable yields.

Kahweofuran **1** was isolated[1] in 1967 from roasted coffee as an impact flavor component, and its structure was determined[2] in 1971 by spectroscopy and synthesis. The 6-ethyl and 4,6-dimethyl derivatives, **2** and **3**, were also isolated as flavor components from roasted coffee. The 4-methyl derivative **4**, the regioisomer of kahweofuran, is an ideal component and its flavor character is very interesting. However, full evaluations of their significance in aroma research are apparently still lacking, because they have not been easily synthesized (Fig. 1).

In order to identify the structure of kahweofuran, Buchi's group[2] reported its synthesis starting from 3-keto tetrahydrothiophene through the key intermediate **5** by acylation and the Grignard reaction followed by acid treatment. Although this synthesis was only three steps, the regioselectivity of the acylation was not admitted and the overall yield was only 2%. There have been two other papers on the synthesis of kahweofuran. Rewicki's group reported the synthesis starting from 3,4-dibromofuran through the 2-methyl-3-bromo-4-(2-bromoethyl) furan **6** by the regioselective lithiation of the furan ring followed by the thiophene ring formation. The overall yield of this synthesis was 15%.[3] In order to avoid the difficulty of separation from regioisomers, Fuganti's group[4] prepared compound **7** by the Stobbe condensation of α-methylcinnamaldehyde with dimethyl succinate, and carried out a series of reactions involving the transformation of the carboxyl group to a sulfur group and then formation of the tetrahydrothiophene ring by an intramolecular Michael addition to obtain the key intermediate **8**, which was treated with dilute sulfuric acid to provide kahweofuran (**1**) in 14 steps (Fig. 2).

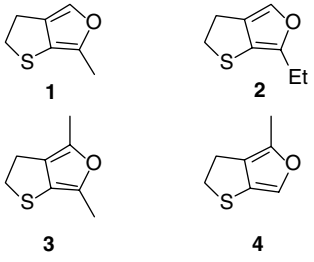

Figure 1. Structures of kahweofuran and its derivatives.

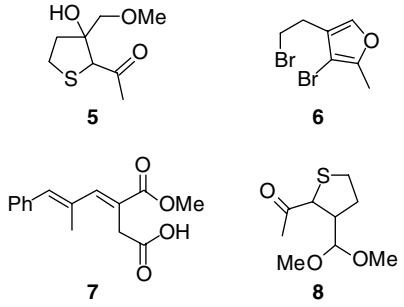

Figure 2. The key intermediates of the previous synthesis.

Keywords: Kahweofuran; Reductive cyclization.
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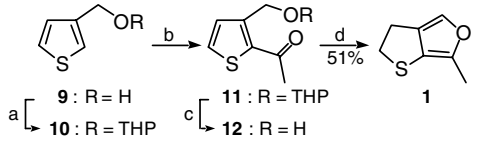
Thus, a more efficient and rapid synthesis of kahweofuran is desired, and we now report the highly efficient and rapid synthesis of kahweofuran and its derivatives.

After a detailed survey of the previous results, we chose thiophene-3-methanol (**9**) as the starting material, which was first protected with 3,4-dihydro-2*H*-pyran[5] to afford the corresponding ether **10**. Regioselective generation of an anion at the 2-position[6] of compound **10** was successful by a chelation-controlled effect with the 3-hydroxymethyl tetrahydropyranyl ether. Although the reaction of the corresponding anion with acetyl chloride gave the desired 2-acetylated compound **11** in 41% yield along with the 4-acetylated compound as a by-product in 11% yield, the rapid addition of acetic anhydride instead of acetyl chloride into the anion solution at −78 °C produced the desired compound **11** in 68% yield. The treatment of **11** with camphorsulfonic acid in MeOH afforded the corresponding alcohol **12** in 86% yield, which is present as a hydroxyketone structure.[7] Our attempts to partially or completely reduce the thiophene ring of **12** were unsuccessful by usual methods. The thiophene ring was not affected by dissolving metals in various solvents as well as hydrogenation with palladium on carbon[8] and platinum dioxide. Quite fortunately, however, by using Wilkinson's catalyst under a hydrogen atmosphere in benzene at 100 °C, kahweofuran was directly obtained from hydroxyketone **12** by the formal reductive cyclization in 51% isolated yield (Scheme 1). Thus, we succeeded in the highly efficient and rapid synthesis of kahweofuran.

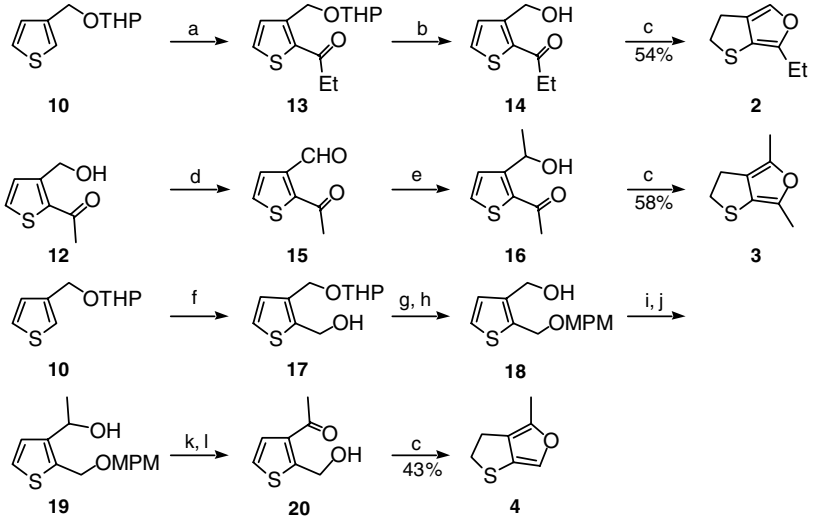


Scheme 1. Reagents and conditions: (a) 3,4-dihydro-2*H*-pyrane, pyridinium *p*-toluenesulfonate, CH_2Cl_2, rt, 100%; (b) *n*-BuLi, Ac_2O, −78 °C, 68%; (c) (±)-camphor-10-sulfonic acid, MeOH, rt, 86%; (d) $Rh(PPh_3)_3Cl$, H_2, benzene in a sealed tube, 100 °C, 51%.

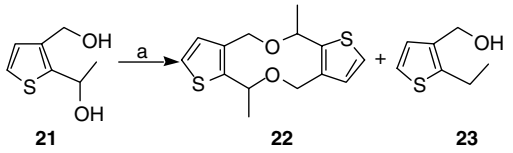
In order to explore the generality of this reductive cyclization with the Wilkinson's catalyst, a series of analogues of the hydroxyketone **12** were synthesized, and attempted the formal reductive cyclization.

Based on the synthesis of compound **12**, the corresponding hydroxyketone derivatives **14**, **16**, and **20** were synthesized as shown in Scheme 2. Hydroxyketone **14** was prepared using propionic anhydride instead of acetic anhydride. Compound **16** was prepared from **12** by MnO_2 oxidation[9] of the primary alcohol and then the Grignard reaction of the resulting aldehyde.[10] Meanwhile, compound **20** was synthesized from **10** as follows. Ether **10** was reacted with paraformaldehyde[11] to afford alcohol **17** in 99% yield, which was protected by a 4-methoxybenzyl group.[12] After removal of the THP group of **17** with an acid treatment in 80% yield, the obtained alcohol **18** was oxidized with manganese dioxide followed by the reaction with methyl magnesium bromide to provide **19** in 64% yield in two steps. Compound **20** was obtained by the oxidation of **19** with chromium trioxide–pyridine complex[13] and then removal of the MPM group of the resulting ketone with DDQ[14] in 70% yield. Thus, we obtained four kinds of thiophene derivatives **12**, **14**, **16**, and **20**, containing the hydroxyketone substituents.

We then examined the formal reductive cyclization of the obtained hydroxyketone derivatives using Wilkinson's catalyst.[15] The corresponding 6-ethyl, 4,6-dimethyl and 4-methyl derivatives[3] of kahweofuran were successfully obtained in 54%, 58%, and 43% yields, respectively.



Scheme 2. Reagents and conditions: (a) *n*-BuLi, propionic anhydride, −78 °C, 65%; (b) (±)-camphor-10-sulfonic acid, MeOH, rt, 88%; (c) $Rh(PPh_3)_3Cl$, H_2, benzene in a sealed tube, 100 °C; (d) MnO_2, CH_2Cl_2, rt, 99%; (e) CH_3MgBr, THF, −78 °C, 56%; (f) *n*-BuLi, $(CH_2O)_n$, −78 °C, 99%; (g) *p*-$MeOC_6H_4CH_2Cl$, NaH, THF, 84%; (h) (±)-camphor-10-sulfonic acid, MeOH, rt, 80%; (i) MnO_2, CH_2Cl_2, rt, 90%; (j) CH_3MgBr, THF, −78 °C, 71%; (k) CrO_3, pyridine, CH_2Cl_2, rt, 78%; (l) DDQ, H_2O/CH_2Cl_2 (1:1), rt, 90%.



Scheme 3. Reagents and conditions: (a) $Rh(PPh_3)_3Cl$, H_2, benzene, 100 °C, **22**: 47%, **23**: 49%.

Thus, the rapid and efficient syntheses of the kahweofuran derivatives were achieved.

On the other hand, the treatment of the THP derivative derived from **12** with the Wilkinson's catalyst under the same reaction conditions gave a complex mixture. The treatment of the dihydroxy compound **21**, which was quantitatively prepared by the LAH reduction[16] of compound **12**, using the Wilkinson's catalyst under the same reaction conditions gave dimer **22** and reduced compound **23** in 47% and 49% yields, respectively (Scheme 3). Obviously, both the hydroxy and ketone groups of the substituents at the 2- and 3-positions in the thiophene ring are necessary for the successful furan ring formation. It is quite interesting that this formal reductive cyclization produces furan derivatives and not thiophene derivatives.

In conclusion, we achieved the highly efficient and novel synthesis of kahweofuran and its derivatives by the formal reductive cyclization using the Wilkinson's catalyst. This synthetic method can be used to prepare a wide variety of substituted kahweofuran derivatives.

Acknowledgements

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7. NMR date of compound **12** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, $J = 4.8$ Hz, 1H), 7.13 (d, $J = 4.8$ Hz, 1H), 4.74 (d, $J = 5.6$ Hz, 2H), 4.24 (t, $J = 5.6$ Hz, OH, 1H), 2.58 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 192.43, 149.98, 136.57, 130.91, 130.51, 59.98, 29.09.
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15. Typical procedure: To a solution of **14** (312 mg, 2 mmol) in benzene (10 ml) was added tris(triphenylphosphine) rhodium(I) chloride (92 mg, 0.1 mmol). The reaction mixture was stirred at 100 °C under a 1 MPa hydrogen atmosphere for 24 h. The reaction mixture was then concentrated. The obtained residue was separated by chromatography on silica gel (pentane/ether 100:1) to obtain **1** (142 mg, 51%) as a colorless oil. Since the desired molecules 1–4 are very volatile, their isolated yields tend to be lower than the TLC aspects.
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