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# Novel Synthesis of Kahweofuran: A Flavour Component of Roasted Coffee

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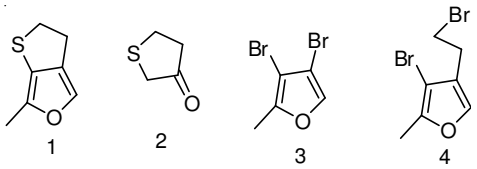
Kahweofuran (**1**), one of the impact flavours of roasted coffee and possesses 6-methyl-2, 3-dihydrothieno[2,3-c]furan structure, was obtained from 4,5-dihydrothiophen-3(2*H*)-one through six steps.

**Key Words: Kahweofuran, Flavour, Palladium-catalyzed inserting reactions.**

Kahweofuran (**1**) was characterized[1] 40 years ago, as one of the impact flavour components of roasted coffee and its structure was determined[2] in 1971 by spectroscopy and synthesis. However, a full evaluation of its aromatic significance is apparently still lacking because it is not easily synthesized.

Four approaches to the carbon-7 framework of **1** have been reported (**Scheme-I**). In order to identify the structure of kahweofuran, Buchi's group[2] reported its synthesis starting from 3-ketotetrahydro thiophene (**2**) by acylation and the Grignard reaction followed by acid treatment. Although this synthesis involve only three steps, the reported acylation reaction lack specificity and thus difficult isomeric separations are required and the overall yield was only 2 %. Gorzynski's group[3] prepared kahweofuran **1** from 3,4-dibromofuran **3**, from which the C-7 framework derivative **4** was obtained through two C-C bond forming reactions based on carbanion chemistry. Although this synthesis was only four steps, these know procedures still afforded low overall yields. To avoid the difficulty of isomeric separation, Brenna's group[4] also prepared kahweofuran **1** from α-methylcinnamaldehyde with dimethyl succinate. Although this synthesis avoided the difficulty of isomeric separation, its synthetic route was too long in fourteen steps. Other synthesis was also unsatisfactory from the viewpoint of efficiency and yield[5]. Thus, more efficient and rapid synthesis of kahweofuran was exactly desired and here we reported the novel synthesis of kahweofuran.

We selected 3-ketotetrahydro thiophene (**2**) as a suitable starting material because it contains the thiophene ring. Ketone **2** was enolized[6] and the enolate was trapped with trifluoroacetic anhydride in dichloromethane at 0 ºC to afford

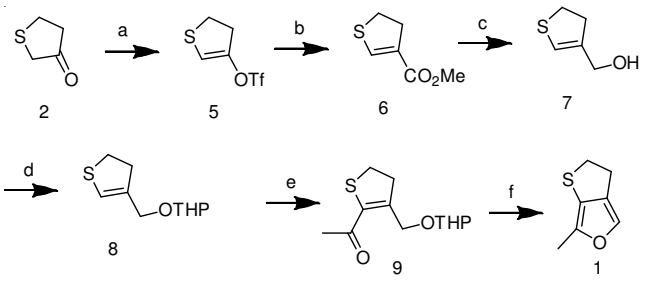



**Scheme-I**

the corresponding ester **5** in 78 % yield as colourless oil, which was inserted with carbon monoxide through palladium-catalyzed process[7] to afford an oil **6** in 86 % yield. Ester **6** was quantitatively reduced with $LiAlH_4$ in THF to corresponding alcohol **7** as colourless oil, whose hydroxyl group was protected with 3,4-dihydro-2*H*-pyran to afford the ether **8** as an colourless oil in 96 % yield[8]. Regioselective generation of and anion at the 2-position[9] of the ether **8** was successful by a chelation-controlled effect with the 3-hydroxymethyl tetrahydropyranyl ether. Although the reaction of the corresponding anion with acetic anhydride gave the desired 2-acetylated compound **9** in 26 % yield, rapid addition of N-methoxy-N-methylacetamide instead of acetyl chloride into the anion solution at -78 ºC afford the desired acetylated compound **9** in 68 % yield. Treatment of compound **9** with a catalytic amount of dilute sulphuric acid in boiling THF to remove the DHP group and meanwhile the corresponding hydroxyketone proceeded ring close to form kahweofuran (**1**) in 27 % overall yield. Based on the spectral data of **9** the structures of compound **1**, **5-9** were proposed as shown in **Scheme-II**.

## Conclusion

In summary, the synthetic sequences of kahweofuran (**1**) described all the reactions involved are regiospecific. Moreover,




**Scheme-II:** Reagents and conditions: (a) 2,6-di-*tert*-butyl-4-methylpyridine, $(CF_3CO)_2O$, DCM, 0 ºC, 19 h, 78 %; (b) CO, $PdAcO_2$, $PPh_3$, DMF, $Et_3N$, MeOH, 60 ºC, 8 h, 86 %; (c) LAH, THF, Reflux, 2 h, 100 %; (d) DHP, PPTS, DCM, 1 h, 96 %; (e) *n*-BuLi, HMPA, $CH_3CON(OMe)Me$, DME, -78 ºC, 6 h, 68 %; (f) 1 N HCl, THF, 80 ºC, 4 h, 62 %

these designed synthetic paths can be considered as a general method to prepare a wide variety of disubstituted kahweofuran derivatives.

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