Synthesis of 2,3-Dihydro-6-methylthieno[2,3-*c*]furan (Kahweofuran), a Coffee Aroma Component, from an Acyclic Precursor

J. Chem. Research (S), 1998, 74–75
J. Chem. Research (M), 1998, 0551–0563

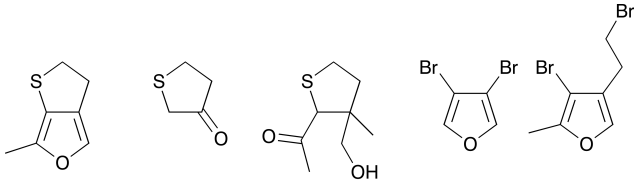
Elisabetta Brenna,[a] Claudio Fuganti,*[a] Stefano Serra[a] and Andrea Dulio[b]

[a]*Dipartimento di Chimica del Politecnico, Centro CNR per la Chimica delle Sostanze Organiche Naturali, Via Mancinelli 7, Milano I-20131, Italy*
[b]*Perfetti s.p.a, Via XXV Aprile, 7/9, Lainate (MI) I-20020, Italy*

Kahweofuran **1**, one of the impact flavours of roasted coffee, was obtained from the acyclic unsaturated ester **8**, produced in a Stobbe condensation of α-methylcinnamaldehyde with dimethyl succinate, through the key intermediate tetrahydrothiophene **14** and the C-7 derivatives **20** or **24**, respectively.

2,3-Dihydro-6-methylthieno[2,3-*c*]furan **1** was characterised thirty years ago[1] as one of the impact flavour components of roasted coffee. However, a full evaluation of its aromatic significance is apparently still lacking because it is not easily synthesised.

Two approaches to the C-7 framework of **1** have been reported. The first one[2] uses the commercially available 4,5-dihydrothiophen-3(2*H*)-one (**2**) and involves a Claisen condensation with ethyl acetate and a Grignard reaction with methoxymethylmagnesium chloride in order to prepare the key intermediate **3** from which **1** is obtained upon acid treatment. The reported reactions lack specificity and thus difficult isomeric separations are required. Alternatively,[6] **1** is accessible from 3,4-dibromofuran **4**, from which the C-7 derivative **5** is obtained through two C—C bond forming reactions based on carbanion chemistry. These know procedures either afford low overall yields from expensive precursors or require the extensive use of organometallic reagents at low temperature. Thus, a more direct access to kahweofuran **1** seemed desirable and here we report the results of our studies.



1 **2** **3** **4** **5**

We selected substrate **8**, obtained by a Stobbe condensation[7] of α-methylcinnamaldehyde with dimethyl succinate, as a suitable starting material because it contains the entire carbon framework (see brackets in structural formula **8**) and all the functionalities required to obtain product **1**, Scheme A. Indeed, reduction of the free carboxyl moiety of **8** to carbinol **10**, *via* $NaBH_4$ reduction[8] of the mixed anhydride **9**, followed by exchange of the oxygen and the sulfur functionality under Violante conditions,[9] afforded compound **12**. This latter underwent ring closure to tetrahydrothiophene **14** quantitatively on treatment with NaOMe in methanol.

The product **14** was most likely derived from an intramolecular Michael addition of the intermediate sulfur nucleophile **13** onto the α,β-unsaturated ester moiety,[10] and was found to be a 2:1 mixture of two diastereoisomers on the basis of NMR spectra.

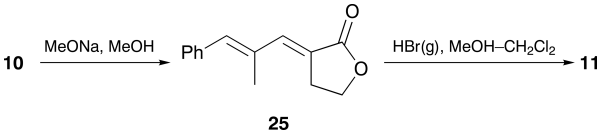
*To receive any correspondence.

Tetrahydrothiophene **14** was quantitatively reduced with $LiAlH_4$ in Et_2O to **15**, whose hydroxy group was protected by conversion into the benzoate ester **16**. Indeed, reaction with ozonized oxygen at −78 °C in methylene chloride, followed by Ph_3P treatment, transformed **16** into a mixture of benzaldehyde and sulfoxide **17**. This latter was reduced to the sulfide **18** on reaction with PCl_3 at −50 °C in DMF. Treatment of the ester **18** with catalytic NaOMe in methanol afforded carbinol **19**. Finally, Swern oxidation[11] of **19** provided the 1,4-dicarbonyl compound **20** which cyclized to kahweofuran **1** upon treatment with boiling dilute sulfuric acid.[12]

Alternatively, product **1** was obtained from **15** through a sequence involving Swern oxidation to the aldehyde **21**, whose carbonyl moiety was protected by conversion into the acetal **22**. Ozonolysis, Ph_3P treatment and PCl_3 reduction of the intermediate sulfoxide **23** gave the ketoacetal **24**, similarly providing kahweofuran **1** on acid treatment.

Both these synthetic paths, using tetrahydrothiophenes **20** and **24** as direct precursors of kahweofuran, are characterised by the common key intermediate **14**, whose preparation involved a troublesome Violante reaction on substrate **10**. Two different solutions were devised. The acetate ester **12** was obtained from **10** *via* the corresponding bromo derivative **11**, accessible upon treatment with *N*-bromosuccinimide and Ph_3P in methylene chloride, followed by displacement with potassium thiocetate in dimethylformamide.

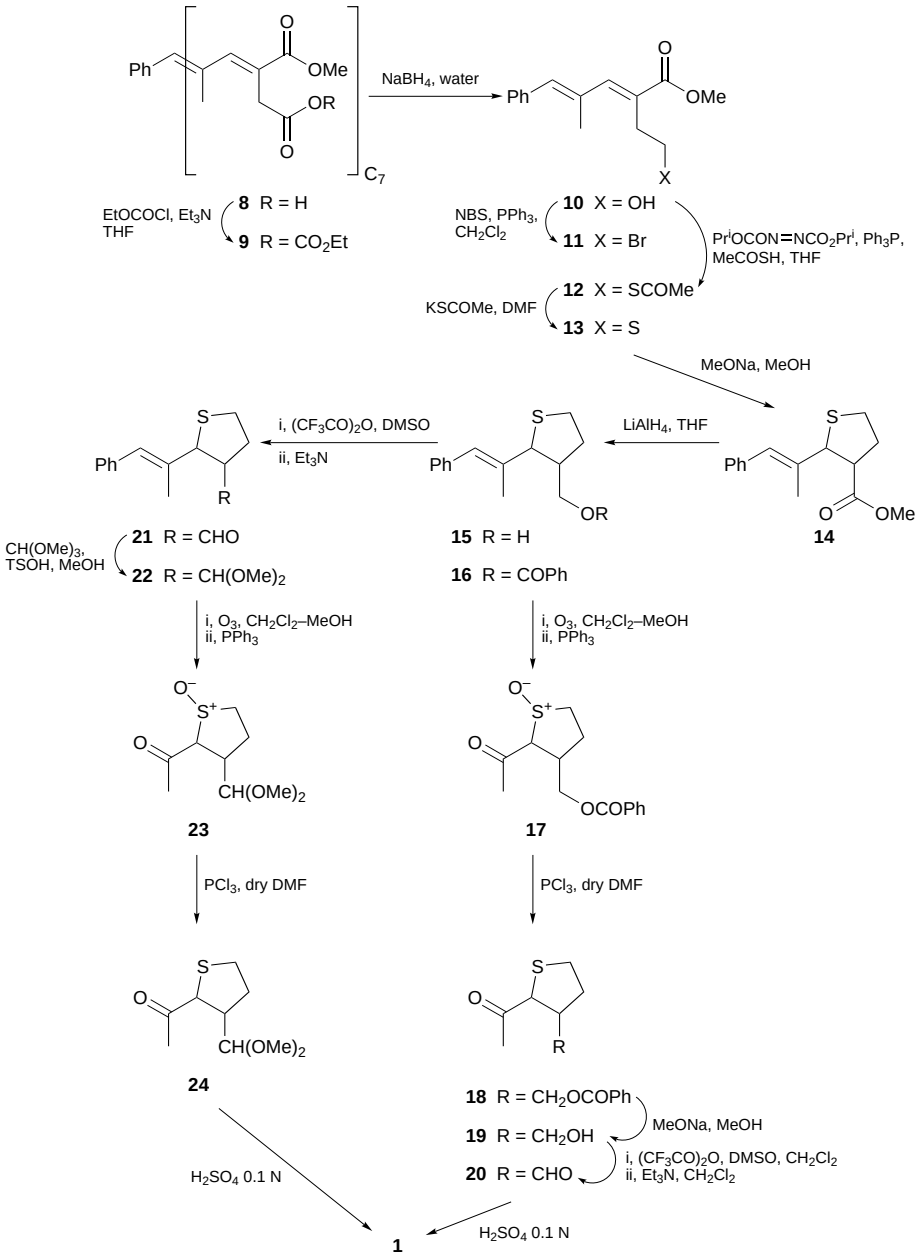
The second alternative took advantage of lactone **25**, which was obtained in quantitative yield by ring closure of the hydroxy ester **10** promoted by sodium methylate in methanol, Scheme 3. Subsequent treatment of lactone **25** with gaseous hydrogen bromide in methanol–methylene chloride solution afforded the bromo derivative **11** *via* an unusual acidic cleavage of the lactone ring.[13]



25

Scheme 3

In the synthetic sequences described all the reactions involved are regiospecific and no expensive precursors or dangerous organometallic reagents are used. Moreover, these designed synthetic paths can be considered as a general method to prepare a wide variety of 2,3-disubstituted tetrahydrothiophenes. These latter derivatives are suitable precursors of bicylic systems showing a heterocyclic ring condensed on the tetrahydrothiophene moiety.



Scheme A

Techniques used: ^{1}H NMR, IR, GC-MS

Schemes: 3

References: 13

Received, 28th August 1997; Accepted, 28th October 1997
Paper E/7/06334B

References cited in this synopsis

1 M. Stoll, M. Winther, F. Gautschi, I. Flament and B. Willhalm, *Helv. Chim. Acta*, 1967, **50**, 628.
2 G. Büchi, P. Degen, F. Gautschi and B. Willhalm, *J. Org. Chem.*, 1971, **36**, 199.
6 M. Gorzynski and D. Rewicki, *Liebigs Ann. Chem.*, 1986, 625.
7 F. Fichter and S. Hirsch, *Chem. Ber.*, 1901, **34**, 2188.
8 K. Ishizumi, K. Koga and S-I. Yamada, *Chem. Pharm. Bull.*, 1968, **16**, 492.
9 R. P. Violante, *Tetrahedron Lett.*, 1981, **22**, 3119.
10 J. L. Szabo and E. T. Stiller, *J. Am. Chem. Soc.*, 1948, **70**, 3667.
11 K. Omura, A. K. Sharma and D. Swern, *J. Org. Chem.*, 1976, **41**, 957.
12 C. Botteghi, L. Lardicci and R. Menicagli, *J. Org. Chem.*, 1973, **38**, 2361.
13 D. S. Noyce and J. H. Canfield, *J. Am. Chem. Soc.*, 1954, **76**, 3630.