Synthesis of 7-trifluoromethyl- and 7-trichloromethylnorkhellins

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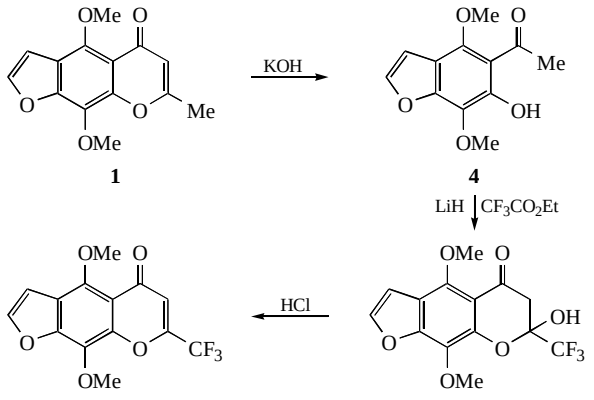
The title compounds were prepared by the condensation of khellinone with ethyl trifluoroacetate and trichloroacetonitrile.

The natural furochromone khellin (4,9-dimethoxy-7-methyl-5*H*-furo[3,2-*g*][1]benzopyran-5-one) **1** obtained from the fruits and seeds of *Ammi visnaga L* is a well-known medicinal substance.[1] It exhibits a high antiatherosclerotic activity[2] and is a constituent of various medicinal preparations.[3]

As an extension of previous studies[4–10] concerning 2-polyhaloalkylchromones, we replaced a Me group at the 7-position of khellin **1** by CF_3 and CCl_3 groups and prepared 7-trifluoromethyl- and 7-trichloromethylnorkhellins **2** and **3**. These latter are of considerable interest as highly reactive building blocks for the synthesis of new khellin derivatives.

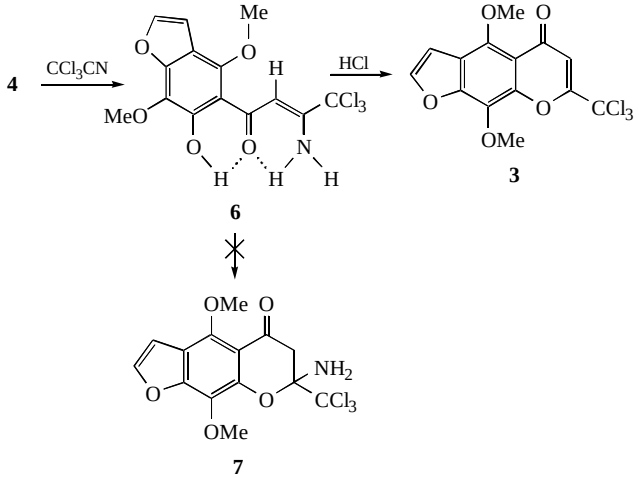
It is well known[11] that condensation products of 2-hydroxyacetophenones with ethyl trifluoroacetate exist only in a cyclic semiketal form in both a crystalline state and in solution. We found that the Claisen condensation of khellinone (5-acetyl-6-hydroxy-4,7-dimethoxybenzo[*b*]furan) **4**, which was obtained by the alkaline hydrolysis of **1**,[12] with ethyl trifluoroacetate in the presence of LiH in THF afforded furochromone **5**, which is a cyclic form of the corresponding -diketone. Previously,[13] 7-hydroxydihydrokhellin, a nonfluorinated analogue of compound **5**, was synthesised by the treatment of khellinone with *tert*-butyl lithioacetate in toluene at 100 °C. The boiling of furochromanone **5** in ethanol or acetic acid with a catalytic amount of hydrochloric acid afforded 7-trifluoromethylnorkhellin **2** in 80% yield.†



Scheme 1

Note that the ^{1}H NMR spectrum of compound **5** in [$^2H_6$]DMSO exhibits the signal due to the OH proton as a doublet at δ 8.72 ppm with J 1.6 Hz because of the spin–spin interaction with the downfield proton of the CH_2 group. This fact is indicative of their *trans*-diaxial arrangement at which the W-conformation becomes possible.[14] In a $CDCl_3$ solution, the hydroxyl proton gives a singlet at 5.03 ppm. Moreover, on going from $CDCl_3$ to [$^2H_6$]DMSO, the doublets of the furan protons H(2) and H(3) become downfield shifted by 0.47 and 0.32 ppm, respectively. This is probably a result of solvation effects, which are responsible for deshielding these protons.[15]

In contrast to ethyl trifluoroacetate, condensation with the participation of ethyl trichloroacetate is often accompanied by side reactions resulting in the degradation to chloroform[16] and dichlorocarbene.[17] In this connection, to synthesise 7-trichloromethylnorkhelline **3**, we used the reaction of khellinone **4** with trichloroacetonitrile in the presence of *N*-methylanilinomagnesium bromide. This reaction afforded aminoenone **6** in 37% yield. The treatment of **6** with concentrated HCl at room temperature gave 7-trichloromethylnorkhelline **3** in 87% yield.‡



Scheme 2

It was found[5] that the condensation of 2-hydroxy-4,6-dimethylacetophenone with trichloroacetonitrile resulted in 2-amino-5,7-dimethyl-2-trichloromethylchroman-4-one. Thus, it might be expected that an analogous reaction with khellinone **4**, which

† *4,9-Dimethoxy-7-trifluoromethyl-5*H*-furo[3,2-*g*][1]benzopyran-5-one* **2**: yield 80%, mp 164–165 °C (acetic acid). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 4.08 [s, 3H, MeO(9)], 4.21 [s, 3H, MeO(4)], 6.60 (s, 1H, =CH), 7.05 [d, 1H, H(3), J 2.4 Hz], 7.68 [d, 1H, H(2), J 2.4 Hz]. IR (Vaseline oil, ν/cm^{-1}): 3150 (=CH), 1670, 1655 (C=O), 1610 (C=C, arom.), 1550 (furan ring). Found (%): C, 53.60; H, 2.81. Calc. for $C_{14}H_9F_3O_5$ (%): C, 53.52; H, 2.89.

*7-Hydroxy-4,9-dimethoxy-7-trifluoromethylfuro[3,2-*g*]chroman-5-one* **5**: yield 63%, mp 177–178 °C (EtOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.07 (AB system, δ 0.14, 2H, CH_2, J_{AB} 16.4 Hz), 4.03 (s, 3H, MeO), 4.05 (s, 3H, MeO), 5.03 (s, 1H, OH), 6.88 [d, 1H, H(3), J 2.3 Hz], 7.50 [d, 1H, H(2), J 2.3 Hz]. ^{1}H NMR (250 MHz, [$^2H_6$]DMSO) δ: 2.77 [d, 1H, C*H*H, J_{AB} 16.0 Hz], 3.31 [d, 1H, CH*H*, J_{AB} 16.0 Hz], 3.94 (s, 3H, MeO), 3.98 (s, 3H, MeO), 7.20 [d, 1H, H(3), J 2.3 Hz], 7.97 [d, 1H, H(2), J 2.3 Hz], 8.72 (d, 1H, OH, J 1.6 Hz). IR (Vaseline oil, ν/cm^{-1}): 3360 (OH), 3150 (=CH), 1660 (C=O), 1600 (arom.), 1550 (furan ring). Found (%): C, 50.54; H, 3.38. Calc. for $C_{14}H_{11}F_3O_6$ (%): C, 50.61; H, 3.34.

‡ *4,9-Dimethoxy-7-trichloromethyl-5*H*-furo[3,2-*g*][1]benzopyran-5-one* **3**: yield 87%, mp 172–173 °C (EtOH). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 4.10 [s, 3H, MeO(9)], 4.22 [s, 3H, MeO(4)], 6.86 (s, 1H, =CH), 7.05 [d, 1H, H(3), J 2.3 Hz], 7.67 [d, 1H, H(2), J 2.3 Hz]. IR (Vaseline oil, ν/cm^{-1}): 3120 (=CH), 1655 (C=O), 1640, 1620, 1605 (sh) (C=C, arom.), 1550 (furan ring). Found (%): C, 46.05; H, 2.55. Calc. for $C_{14}H_9Cl_3O_5$ (%): C, 46.25; H, 2.50.

6-Hydroxy-4,7-dimethoxy-5-[3-amino-4,4,4-trichlorobut-2(Z)-enoyl]-benzo[b]furan **6**: yield 37%, mp 125–126 °C (benzene). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 4.00 [s, 3H, MeO(7)], 4.07 [s, 3H, MeO(4)], 6.83 [d, 1H, H(3), J 2.3 Hz], 7.28 (t, 1H, =CH, J 1.0 Hz), 7.48 [d, 1H, H(2), J 2.3 Hz], 7.83 (br. s, 2H, NH_2), 12.85 (s, 1H, OH). ^{1}H NMR (250 MHz, [$^2H_6$]DMSO) δ: 3.90 [s, 3H, MeO(7)], 3.97 [s, 3H, MeO(4)], 6.62 (s, 1H, =CH), 7.11 [d, 1H, H(3), J 2.2 Hz], 7.87 [d, 1H, H(2), J 2.2 Hz], 8.97 (br. s, 2H, NH_2), 11.48 (s, 1H, OH). IR (Vaseline oil, ν/cm^{-1}): 3420, 3270 (NH_2), 3150 (w, =CH), 1605, 1515 (C=O, C=C, NH_2). Found (%): C, 44.10; H, 3.38; N, 3.50. Calc. for $C_{14}H_{12}Cl_3NO_5$ (%): C, 44.18; H, 3.18; N, 3.64.

bears an *ortho*-MeO group with respect to the carbonyl group, will also give furochromanone **7**. However, we found that the product of this reaction is not prone to ring–chain tautomerism and exists only as open-chain aminoenone **6** in both a crystalline state and $CDCl_3$ or [$^2H_6$]DMSO solutions. Cyclic chromanone form **7** was not detected in these solvents; this is probably due to the fact that the steric hindrance with a methoxy group is lower than that with a methyl group,[18] and the methoxy group does not prevent the appearance of a planar conformation stabilised by intramolecular hydrogen bonds.

The ^1H NMR spectra of aminoenone **6** measured in [$^2H_6$]DMSO and $CDCl_3$ solutions exhibited a signal due to the vinyl proton. On going from [$^2H_6$]DMSO to $CDCl_3$, this signal was downfield shifted by 0.66 ppm. It is likely that the molecule of compound **6** has a near-planar di-s-*cis* conformation in a $CDCl_3$ solution because of two intramolecular hydrogen bonds. In this case, the vinyl proton is close to oxygen of the methoxy group and more strongly deshielded than that in a [$^2H_6$]DMSO solution, where the coplanarity is broken because of the rupture of intramolecular hydrogen bonds. In a $CDCl_3$ solution, the vinyl proton manifests itself as a triplet with J 1.0 Hz because of the spin–spin interaction with protons of the NH_2 group; this is a characteristic feature of ^1H NMR spectra of -amino- -trichloromethylvinyl ketones.[19]

In summary, note that the modification of natural compounds by the replacement of a methyl group with a trihalomethyl group is of considerable interest because electron-acceptor CF_3 and CCl_3 groups affect the electron-density distribution in the molecule and hence the reactivity towards nucleophilic agents. Previously,[20] similar studies were performed in the series of retinoids, steroids, purines and pyrimidines. However, there is no data concerning the target-oriented synthesis of halogenated analogues of natural 2-methylchromones, except for the synthesis of 7-chloromethyl- and 7-iodomethylnorvisnagin,[21,22] 2- and 3-fluorokhellin[23] and 7-iodomethylnorkhellin.[24] This work is the first successful attempt to synthesise trihalomethylfurochromones, highly reactive and promising synthons for the preparation of various heterocyclic systems, which can exhibit biological activity.

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