RING-EXPANSION OF 2-METHYLBENZO[*b*]FURAN TO 3-HYDROXYCHROMEN-4-ONE: A POTENTIAL APPROACH TO A FLAVONOL SKELETON

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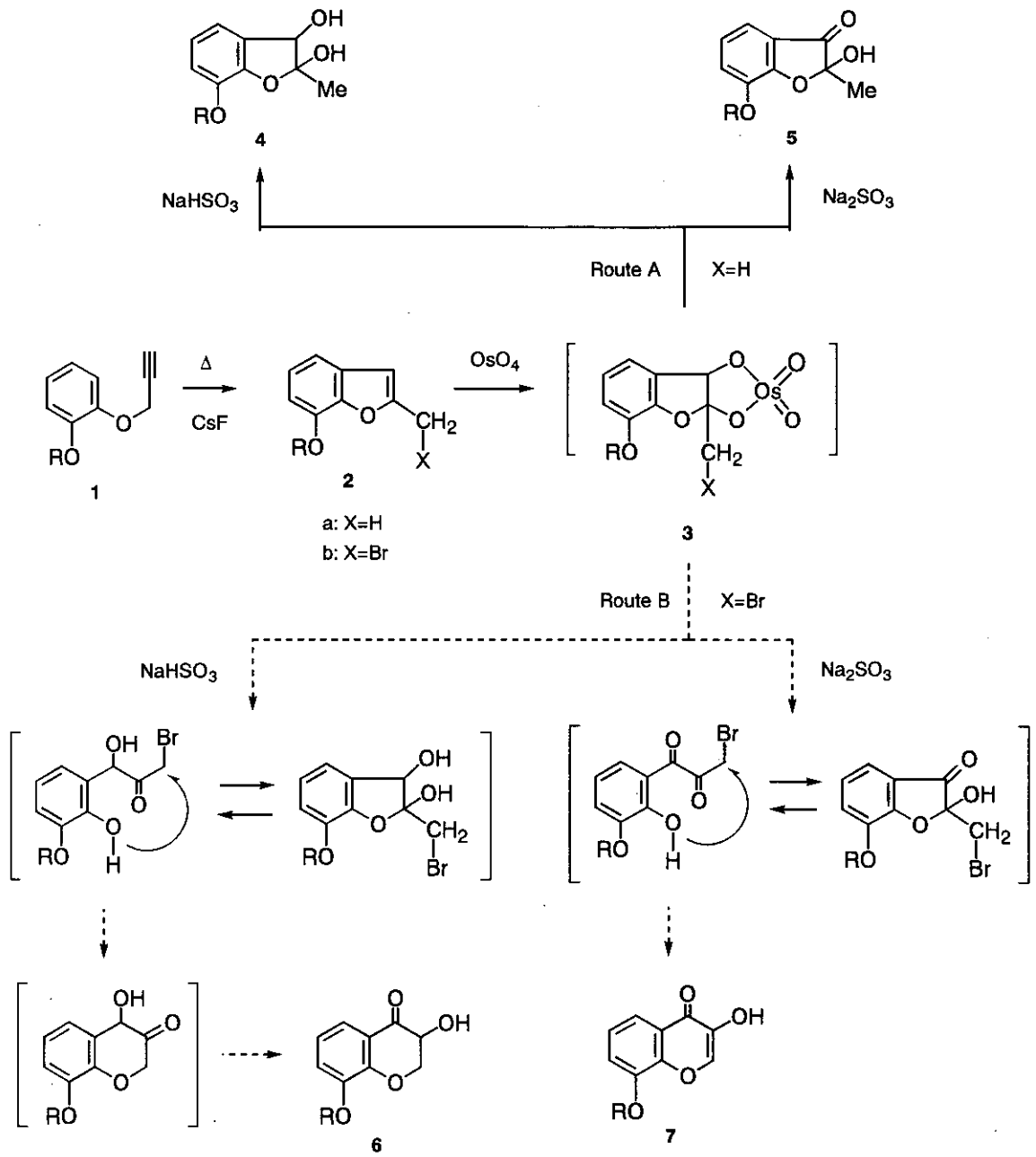
Abstract - A 2-methylbenzo[*b*]furan, prepared by the CsF-mediated Claisen rearrangement of a phenyl propargyl ether, could be smoothly transformed into a 3-hydroxychromen-4-one, a potential flavonol skeleton, by three successive treatment with NBS, OsO_4, and Na_2SO_3.

In the preceeding paper[1] we described the effective formation of 7-alkoxy-2-methylbenzo[*b*]furans (**2**) in the Claisen rearrangement of *o*-alkoxyphenyl propargyl ethers (**1**) in the presence of cesium fluoride (CsF) (the CsF-mediated Claisen rearrangement) dependent upon the *o*-alkoxy substituent effect. We next attempted manipulation of the formed furan ring of a 7-alkoxy-2-methylbenzo[*b*]furan as other synthetic utility than as a masked salicylaldehyde.[2] We had reported that the reductive hydrolysis of an intermediate osmate ester (**3a**) in the oxidation of a 2-methylbenzo[*b*]furan (**2a**) with osmium tetroxide (OsO_4) by sodium hydrogensulfite ($NaHSO_3$) gave a 2,3-dihydroxydihydrofuran derivative (**4**), while treatment with sodium sulfite (Na_2SO_3) in place of $NaHSO_3$ afforded a further oxidized 2-hydroxy-3-oxo derivative (**5**)[3] (Route A in Scheme 1). Thus, when a possible intermediate osmate complex (**3b**), derived from a 2-bromomethylbenzo[*b*]furan (**2b**), is subjected to reductive hydrolysis with $NaHSO_3$, a 3-hydroxychroman-4-one (**6**) could be formed through ring-opening and ring-closure, while a 3-hydroxychromen-4-one (**7**) would be obtained in reductive hydrolysis with Na_2SO_3 as shown in Route B in Scheme 1.

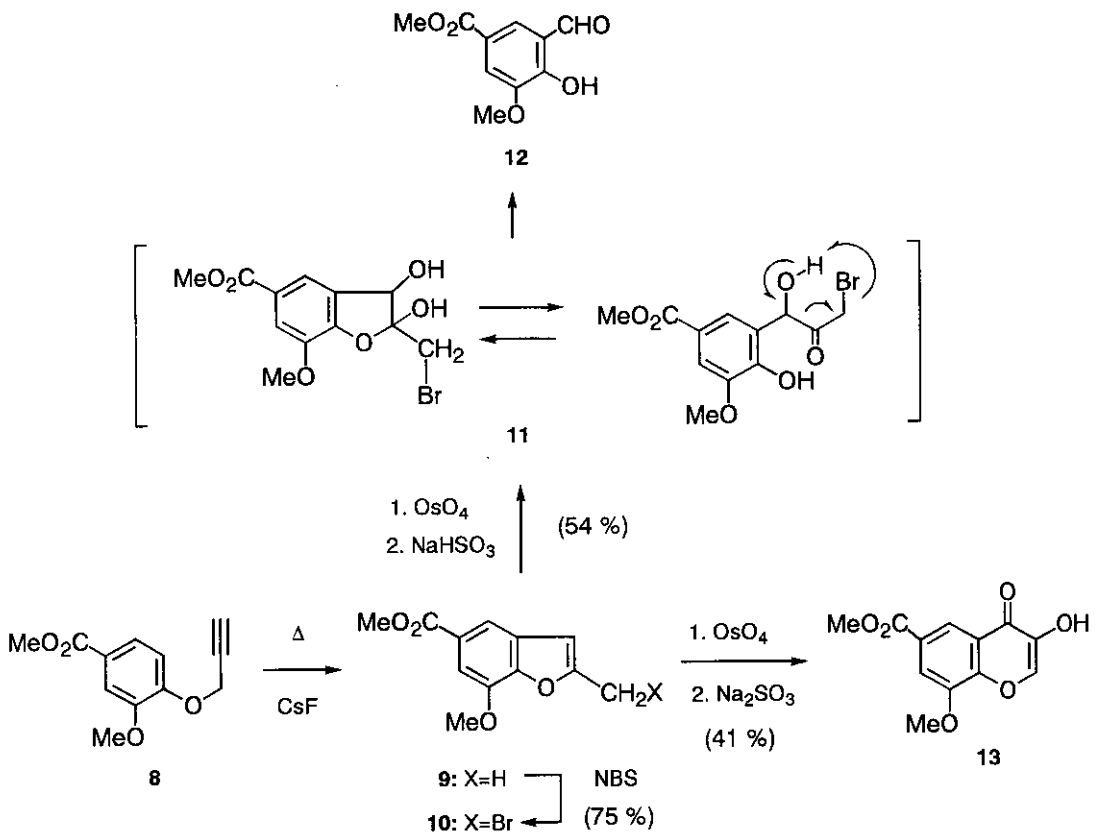
In this paper we present the ring expansion of 7-methoxy-5-methoxycarbonyl-2-methylbenzo[*b*]furan (**9**), derived from the propargyl ether (**8**) of methyl vanillate through the CsF-mediated Claisen rearrangement,[1] into a 3-hydroxychromen-4-one (**13**) by three successive reactions of allylic bromination with *N*-bromosuccinimide (NBS), oxidation with OsO_4, and reductive hydrolysis with Na_2SO_3.

The starting 2-bromomethyl derivative (**10**) was easily prepared in 75% yield by treatment of the 2-methylbenzofuran (**9**) with NBS. However, OsO_4 oxidation of **10** followed by reductive hydrolysis with $NaHSO_3$ resulted in giving a salicylaldehyde (**12**) in 54 % yield, but not a 3-hydroxychroman-4-one like **6**. The formation of **12** suggested the elimination of both ketene and hydrogen bromide units from a supposed bromomethyl hydroxybenzyl ketone intermediate (**11**) during the reaction. On the other hand the intended 3-hydroxychromen-4-one (**13**) was obtained as a sole product in 41 % yield, when treated with Na_2SO_3 instead of $NaHSO_3$ (Scheme 2). Its structure was confirmed by spectral data (see **EXPERIMENTAL**).



Scheme 1

Thus, it was found that bromination followed by OsO_4-Na_2SO_3 treatment could convert a 2-methylbenzofuran into a 3-hydroxychromen-4-one. Application of this new ring expansion reaction to a benzofuran derivative with a benzyl group at the 2 position might lead to the construction of a 3-hydroxy-2-phenylchromen-4-one, a key skeleton of natural flavonols.



Scheme 2

EXPERIMENTAL

All melting points were measured on a micro melting-point hot stage (Yanagimoto) and are uncorrected. IR spectra were recorded on a JASCO IR-700 spectrophotometer. NMR spectra were recorded in $CDCl_3$ with a JEOL JNM-GSX500A spectrometer with tetramethylsilane (TMS) as an internal reference. EIMS and HRFABMS were measured with a Hitachi M-60 spectrometer using a direct inlet system and a JOEL JMS-HX110 spectrometer, respectively. For column chromatography alumina (Brockmann) was used, while for TLC silica gel 60 F254 (Art. 5715, Merck) was used.

2-Bromomethyl-7-methoxy-5-methoxycarbonylbenzo[*b*]furan (10) A mixture of 7-methoxy-5-methoxycarbonyl-2-methylbenzo[*b*]furan (**9**)[1] (0.200 g, 0.91 mmol), NBS (0.210 g, 1.18 mmol), and benzoyl peroxide (0.048 g, 19.82 μmol) in benzene (2 mL) was stirred for 45 min under reflux. After removal of precipitates by filtration, the filtrate was evaporated. Column chromatography of the residue gave **10** as a colorless needles (0.206 g, 76%), mp 132-137 °C, which were recrystallized from ether. *Anal.*

Calcd for $C_{12}H_{11}O_4Br$: C, 48.18; H, 3.71. Found: C, 48.08; H, 3.59. IR ν_{max} ($CHCl_3$): 1714 cm^{-1}. ^1H NMR (500 MHz) δ: 3.94 (3H, s, OMe), 4.06 (3H, s, OMe), 4.60 (2H, s, CH_2Br), 6.82 (1H, s, 3-H), 7.53 (1H, d, *J*=1.1 Hz, 6-H), 7.91 (1H, d, *J* =1.1 Hz, 4-H).

Methyl 3-Formyl-4-hydroxy-5-methoxybenzoate (12) A mixture of **10** (0.050 g, 0.167 mmol) and OsO_4 (0.054 g, 0.212 mmol) in pyridine (1 mL) was stirred at rt for 3 h. After addition of a solution of $NaHSO_3$ (0.076 g, 0.735 mmol) in H_2O (1.14 mL) and pyridine (0.76 mL), the mixture was stirred at 50 °C for 1.5 h, poured into H_2O, and extracted with ethyl acetate. The ethyl acetate solution was washed with sat. $CuSO_4$ and brine, dried over $MgSO_4$, and evaporated. Purification of the crude product by preparative TLC (benzene : ethyl acetate=5 : 1) gave colorless prisms (0.019 g, 54%), mp 133-136 °C. EIMS *m/z*: 210 (M^+, 100 %). IR ν_{max} (KBr): 1726 cm^{-1}. ^1H NMR (500 MHz) δ: 3.94 (3H, s, OMe), 3.98 (3H, s, OMe), 7.75 (1H, fine splitting, 6-H), 7.98 (1H, fine splitting, 2-H), 9.96 (1H, s, CHO), 11.55 (1H, s, OH).

3-Hydroxy-8-methoxy-6-methoxycarbonylbenzo[*b*]pyran-4(2*H*)-one (13) A mixture of **10** (0.050 g, 0.167 mmol) and OsO_4 (0.060 g, 0.236 mmol) in ether (0.8 mL) and pyridine (0.02 mL) was stirred at rt for 20 h. After addition of a solution of Na_2SO_3 (0.211 g, 1.672 mmol) in H_2O (2 mL) and EtOH (1 mL) the mixture was stirred at rt for 20 h. The insoluble materials were removed by filtration and washed with H_2O and then EtOH. The filtrate was extracted with ethyl acetate. The ethyl acetate solution was washed with sat. $CuSO_4$ and brine, dried over $MgSO_4$, and evaporated. Purification of the crude product by preparative TLC (benzene : ethyl acetate=4 : 1) gave pale yellow prisms (0.017 g, 41 %), mp 243-244 °C, which were recrystallized from $CHCl_3$-MeOH. *Anal.* Calcd for $C_{12}H_{10}O_6 \cdot CHCl_3$: C, 42.24; H, 3.00. Found: C, 42.42; H, 2.78. HRFABMS *m/z*: 251.0558 (Calcd for $C_{12}H_{11}O_6$: 251.0555). EIMS *m/z*: 250 (M^+, 100 %). IR ν_{max} (KBr): 3326, 1712, 1634 cm^{-1}. ^1H NMR (500 MHz) δ: 3.98 (3H, s, OMe), 4.07 (3H, s, OMe), 6.14 (1H, s, OH, exchangeable), 7.79 (1H, fine splitting, 7-H), 8.08 (1H, s, 2-H), 8.85 (1H, fine splitting, 5-H). ^{13}C NMR (125 MHz) δ: 52.61 (OMe), 56.66 (OMe), 113.40 (CH), 119.09 (CH), 122.26 (C), 126.56 (C), 138.25 (CH), 142.20 (C), 149.20 (C), 149.31 (C), 165.89 (CO), 172.97 (CO).

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