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Unusual reduction of a lactone carbonyl in a Bu_3SnCl and $Na(CN)BH_3$ mediated radical cyclization of 3-(*o*-bromophenoxymethyl)coumarins

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Abstract—3-Chloromethyl coumarin was treated with different substituted 2-bromophenols in the presence of anhydrous potassium carbonate in refluxing acetone to afford a number of 3-(2-bromophenoxymethyl)coumarins **3a**–**f** in 80–95% yield. These were then refluxed with tributyltin chloride and sodium cyanoborohydride in benzene under nitrogen, in the presence of a catalytic amount of azobisisobutyronitrile (AIBN) for 7–10 h to give spiro[chroman-3,3′-(2′*H*)-benzofurans] **4a**–**f** in 60–75% yields.

Construction of both carbocycles as well as heterocycles by free radical cyclization onto a suitably placed unsaturated bond has emerged as an extremely useful synthetic strategy in organic synthesis.[1] Free radical cyclizations leading to the synthesis of oxygen heterocycles, mainly spiro heterocyclic compounds, employing a radical cyclization strategy continues to be of increasing interest. Several methodologies based on free radical cyclization for the construction of five- and six-membered oxygen heterocycles are available.[2] In contrast, only a few examples dealing with the synthesis of spiro oxygen heterocycles have been described.[3]

Cyclic α,β-unsaturated lactones may serve as a radical acceptor to facilitate cyclization.[4] In the course of our study on the application of radical cyclization for the synthesis of heterocyclic compounds we recently reported the formation of a six-membered pyran ring in the case of a substrate containing a 4-hydroxycoumarin[5] and a 4-hydroxyquinoline-2-one.[6] As demonstrated by Zhang,[4] in the case of an aryl radical attached at the β-carbon of an α,β-unsaturated lactone system, intramolecular free radical Michael-type addition facilitates the spirocyclization process. Stabilization of the intermediate radical by the carbonyl group controls this regioselectivity.[4] However, in the case of an aryl radical tethered (via an ether linkage) to the α-carbon of an α,β-unsaturated lactone system, both 5-*exo* and 6-*endo* cyclization can occur.[7] It is well known that a 5-hexenyl radical cyclizes preferentially to the cyclopentylmethyl radical via 5-*exo* cyclization and not to the more stable cyclohexyl radical via 6-*endo* cyclization.[8] The regiochemical outcome of a radical cyclization can be altered by the attachment of a radical stabilizing group to the acceptor double bond.[7,9a,9b] Many examples of a 6-*endo* cyclization involving a strongly activating carbonyl group have been reported.[7,9a] In view of this we became interested in undertaking a study on the radical cyclizations of 3-(2-bromophenoxymethyl)benzopyran-2-ones where these very criteria are present.

We selected 3-chloromethyl coumarin as our starting material to synthesize the cyclization precursors **3a**–**f**. Compounds **3a**–**f**[10] were readily prepared by the reaction of various *o*-bromophenols with 3-chloromethyl coumarin in refluxing acetone in the presence of anhydrous potassium carbonate for 5–8 h (Scheme 1).

Ether **3a** was refluxed in degassed benzene under nitrogen with Bu_3SnCl and $Na(CN)BH_3$ in the presence of a catalytic amount of AIBN for 7 h to afford the cyclic product, spiro[5′-methylchroman-3,3′-(2′*H*)-benzofuran] **4a**[11] in 75% yield. Compound **4a** was characterized by elemental analysis and spectroscopic data. The IR spectrum of **4a** clearly indicated the absence of a carbonyl

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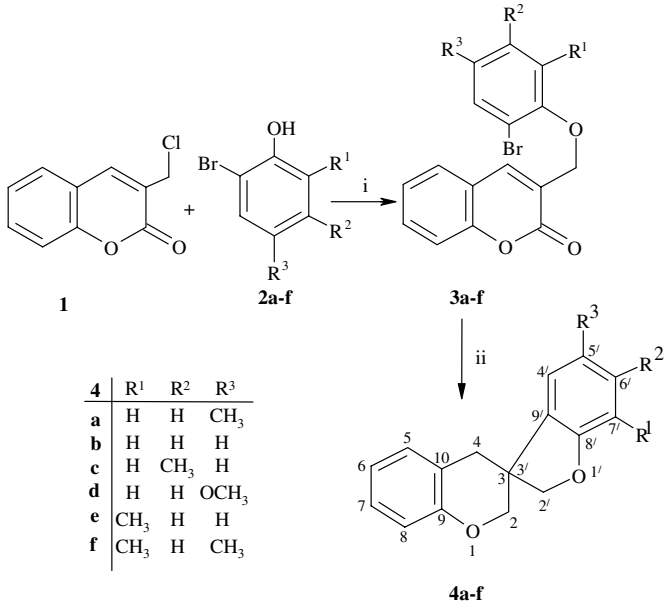

4	R^1	R^2	R^3
a	H	H	CH_3
b	H	H	H
c	H	CH_3	H
d	H	H	OCH_3
e	CH_3	H	H
f	CH_3	H	CH_3

Scheme 1. Reagents and conditions: (i) K_2CO_3, acetone, reflux, 5–8 h; (ii) Bu_3SnCl, $Na(CN)BH_3$, AIBN, benzene, N_2, reflux, 7 h.

group in the molecule, whereas the cyclization precursor **3a** had a carbonyl group stretching at 1706 cm^{-1}. The high field (300 MHz) ^1H NMR spectrum of **4a** had a singlet at δ 2.23 due to the $-CH_3$ group and doublets at δ 3.57 ($J = 11$ Hz), 3.65 ($J = 11$ Hz), 4.20 ($J = 9$ Hz) and 4.49 ($J = 9$ Hz) for each of the four $-OCH_2$ protons. Two benzylic protons appeared as doublets at δ 2.98 ($J = 14$ Hz) and 3.91 ($J = 14$ Hz). The ^{13}C chemical shifts values of compound **4a** and multiplicities were assigned from the DEPT experiment. The DEPT spectrum obtained showed nine protonated carbons, one $-CH_3$ and three $-CH_2$'s. Final confirmation of the deoxygenation of the lactone carbonyl group was obtained from the mass spectrum, which showed the molecular ion at *m*/*z* 252 (M^+). To test the generality of the reaction, compounds **3b–f** were similarly treated to afford **4b–f** in 60–75% yields (Scheme 1).

The formation of the spiro furan ring in compounds **4a–f** from **3a–f** can be explained by 5-*exo*-*trig* radical cyclization of the initially generated aryl radical onto the double bond of the coumarin moiety. Although both 5-*exo* and 6-*endo* cyclization are possible, in spite of our efforts, by varying the reaction conditions, we could not generate the 6-*endo*-*trig* cyclized product or the corresponding lactone of compound **4**. The reason for the formation of the 5-*exo* cyclization product only is not clear. The stability of the intermediate benzylic radical may facilitate the formation of the spiro benzofuran ring.

Deoxygenation of a carbonyl group giving the corresponding saturated hydrocarbon is a frequently encountered process in organic syntheses.[12] The conversion of a lactone carbonyl into a cyclic ether by employing certain Lewis acid–hydride complexes is well established in the literature.[13] In such reactions, the in situ generated diborane in the presence of the Lewis acid presumably facilitates the deoxygenation reaction through the formation of an oxonium ion intermediate.[14] Although $Na(CN)BH_3$ in the presence of a Lewis acid can deoxygenate carbonyl groups,[12a] the reaction fails with lactones.

Compound **3a** on treatment with Bu_3SnH in the presence of a catalytic amount of AIBN in refluxing benzene under nitrogen furnished only the debrominated product. No deoxygenated compound **4a** or the corresponding lactone was obtained. This excludes the possibility of a radical pathway for the deoxygenation with simultaneous cyclization and signifies that $Na(CN)BH_3$ plays an important role in the deoxygenation reaction. Next, the compounds **3a–f** were treated with Bu_3SnCl and $Na(CN)BH_3$ in the absence of AIBN in refluxing benzene under nitrogen, however, no reaction was observed. We also treated simple coumarin itself and 3-phenoxymethylcoumarin with Bu_3SnCl and $Na(CN)BH_3$ in the presence of, and in the absence of AIBN in refluxing benzene, but here too no deoxygenation of the lactone carbonyl was observed. These observations clearly indicate that the deoxygenation process does not proceed via the oxonium ion intermediate pathway. Also tri-*n*-butyltin chloride and $Na(CN)BH_3$ could not have effected deoxygenation without the involvement of a radical intermediate.

In conclusion, $^nBu_3SnH$-mediated radical cyclization has been applied for the synthesis of spiro heterocycles. A novel deoxygenation of a lactone carbonyl group was observed. All the reactions were clean with moderate to good yields. Further work to establish the mechanism of the deoxygenation step is in progress and a full account will be reported later. This is the first instance where deoxygenation of a lactone carbonyl has occurred in a Bu_3SnCl and $Na(CN)BH_3$ mediated radical cyclization reaction.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.07.102.

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10. General procedure for the preparation of 3-(2-bromophenoxymethyl)coumarins (**3a**–**f**): To a solution of 3-chloromethylcoumarin **1** (410 mg, 21 mmol) in dry acetone (100 mL), 2-bromophenol **2a**–**f** (365 mg, 21 mmol) and anhydrous potassium carbonate (2 g) were added and the reaction mixture was refluxed for 5–8 h. The reaction mixture was cooled, filtered and the solvent was removed. The residual mass was extracted with $CHCl_3$ (3×25 mL). The organic layer was washed with 5% Na_2CO_3 solution (3×10 mL), then with water (3×20 mL) and finally with brine (10 mL). After removal of the solvent the residue was subjected to column chromatography over silica gel. Elution of the column with petroleum ether–ethyl acetate (20:1) afforded compounds **3a**–**f**. All the compounds were recrystallized from chloroform–petroleum ether.
Compound **3a**: Yield 85%; white solid; mp 172 °C; IR (KBr): $\gamma_{max} = 2920$, 1706, 1175, 754 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta_H = 2.29$ (s, 3H, CH_3), 5.04 (s, 2H, OCH_2), 6.88–7.31(m, 4H, ArH), 7.51–7.73 (m, 3H, ArH), 8.08 (s, 1H, =CH). MS: $m/z = 344$, 346 (M^+); UV (EtOH): $\lambda_{max} = 230$, 278, 311 nm; Anal. Calcd for $C_{17}H_{13}O_3Br$: C, 59.13; H, 3.76. Found: C, 59.38; H, 3.92 %.
11. General procedure for the preparation of spiro[5′-methylchroman-3,3′-[2′*H*]-benzofurans] (**4a**–**f**): A suspension of the coumarins **3a**–**f** (250 mg, 0.75 mmol), $^nBu_3SnCl$ (0.10 mL, 0.368 mmol), $Na(CN)BH_3$ (250 mg, 3.98 mmol) and AIBN (10 mg) in degassed benzene (10 mL) were refluxed for 7–10 h under N_2. The solvent was removed under reduced pressure and to the residue water (10 mL) was added and the mixture was extracted with $CHCl_3$ (3×10 mL). The combined organic extract was washed with 1% aqueous NH_4OH (2×15 mL) and brine (10 mL) and dried (Na_2SO_4). Evaporation of the solvent furnished a crude material, which was stirred with a saturated solution of potassium fluoride (10 mL) for 24 h. It was then extracted with $CHCl_3$ (3×20 mL) and washed several times with water and dried (Na_2SO_4). After removal of the solvent the residue was subjected to column chromatography over silica gel. The column was eluted with petroleum ether–ethyl acetate (9:1) to give the cyclized products **4a**–**f**. Compound **4a**: Yield 72%; viscous liquid; IR (KBr): $\gamma_{max} = 2924$, 1457, 1247, 1180 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta_H = 2.23$ (s, 3H, CH_3), 2.98 (d, $J = 14$ Hz, 1H, ArCH), 3.15 (d, $J = 14$ Hz, 1H, ArCH), 3.57 (d, $J = 11$ Hz, 1H, OCH), 3.65 (d, $J = 11$ Hz, 1H, OCH), 4.20 (d, $J = 9$ Hz, 1H, OCH), 4.49 (d, $J = 9$ Hz, 1H, OCH), 6.71–6.90 (m, 4H, ArH), 7.10–7.24 (m, 3H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta_C = 157.6$ (C-8′), 154.9 (C-9), 132.8 (C-7′), 131.0 (C-9′), 129.6 (C-5′), 129.3 (C-6′), 128.4 (C-5), 125.4 (C-4′), 122.9 (C-10), 120.4 (C-6), 116.1 (C-8), 109.47 (C-7′), 79.6 (C-2′), 65.9 (C-2), 51.5 (C-3), 34.6 (C-4) and 20.7 (CH_3); MS: $m/z = 252$ (M^+); UV (EtOH): λ_{max} 218, 231, 282 nm; Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.95; H, 6.34. Found: C, 81.18; H, 6.52%.
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