Regioselective synthesis of [4b, 12c-cis]-Δ^6a,12b-4b,5,12c,13-tetrahydropyranono-[2,3-c : 4,5-c']bis[1]benzopyran-7-one

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Hitherto unreported [4b, 12c-cis]-Δ^6a,12b-4b,5,12c,13-tetrahydropyranono-[2,3-c : 4,5-c']bis[1]benzopyran-7-one 2a-f have been regioselectively synthesized in 65-75% yields from 1-aryloxymethylpyrano-[2,3-c] [1]benzopyran-5(3H)-ones 1a-f by heating in N,N-diethylaniline via tandem cyclization involving [3,3] sigmatropic rearrangement followed by enolisation and an internal [1,6] Michael addition of the phenolic moiety to the diene-lactone moiety.

The Claisen rearrangement² has been proved to be an excellent method for the C-C bond formation and also for the construction of heterocyclic ring in fused heterocycles. In continuation of our work on the sigmatropic rearrangements of allylic and propynyl ethers of coumarin³ we have recently reported³ the regioselective synthesis of a series of 1-aryloxymethylpyrano-[2,3-c] [1]benzopyran-5(3H)-ones 1. It occurred to us that a further investigation on the rearrangement of 1 which still possess an allyl aryl ether moiety would be interesting mechanistically as well as we expected to obtain polyheterocycles from the reaction. Here we report the results.

Results and Discussion

The starting materials for this study viz. 1-aryloxymethylpyrano-[2,3-c] [1]benzopyran-5(3H)-ones 1a-f were synthesized according to earlier published procedure.²

Compound 1a³ (m.p. 154°C, yield 85 %) was refluxed in N,N-diethylaniline for 8 hr to give a crystalline solid, m.p. 224°C, yield 75 % (C_{20}H_{16}O_{5} from elemental analysis), m/z 336 (M^+). It showed λ_{max} 303 (log ε 2.86) and 218 (2.74) nm; ν_{max} (KBr) 3000, 1760 (>C = O), 1490 and 1210 cm⁻¹; ^1H-NMR signals (CDCl₃, 500 MHz) at δ 3.40 (dt, H_6), J=11.2, 5.0 Hz), 3.65 (dt, H_6, J=11.2, 5.0 Hz), 3.82 (s, 3H, OCH₃), 4.00 (t, H_3 or H_6, J=11.2 Hz), 4.25 (t, H_1 or H_3, J=11.2 Hz), 4.66-4.72 (m, H_5 and H_4), 6.73 (d, 1H, J=2.8 Hz, C_{2′}-H), 6.83 (dd, 1H, J=8.9, 2.8 Hz,C_{5′}-H), 6.88 (d, 1H, J=8.9 Hz, C_{1′}-H), 7.36-7.41 (m, 2H, C_{6′}-H and C_{12}-H) 7.44-7.48 (m, 1H, C_{10}-H), 7.69 (d, 1H, J=8 Hz, C_{11}-H) and ^13C-NMR signals (CDCl₃, 200 MHz) at δ 29.73 (C_{12}), 31.49 (C_{6a}), 55.78 (OCH₃), 65.70 (C_{11}), 68.18 (C_{3}), 81.07 (C_{6b}), 114.34 (C_{2}), 115.15 (C_{4}), 117.14 (C_{9}), 118.04 (C_{1}), 119.02 (C_{12a}), 120.62 (C_{12b}), 122.01 (C_{11}), 124.93 (C_{12}), 128.78 (C_{10}), 139.98 (C_{6a}), 148.78 (C_{14}), 149.32 (C_{8a}), 154.08 (C_{5}) and 156.50 (C_{3}, >C = O). Its DEPT spectrum showed twelve protonated carbons, two aliphatic -CH and seven aromatic -CH. Assignments of protons were made from 2D, HETCOR and NOE experiment. NOE results are as follows : H_b and H_f are very close in space and shows 8% NOE. These data indicate pyranopyran structure 2a with cis-ring junction stereochemistry rather than furanopyran 3. Encouraged by the results other substrates 1b-f were also treated similarly to give [6, 6] pyranopyrans 2b-f in 65-75% yields (Scheme I).

The pyranopyran (6, 6) ring junction stereochemistry is found to be cis from NMR studies and also from molecular mechanics calculations. The cis-isomer of 2 (Figure 1, calculated total steric energy 36.57 Kcals/mole) is found to be more stable than the trans-isomer of 2 (Figure 2, calculated total steric energy 40.59 Kcals/mole) by ~ 4 Kcals/mole.

The formation of the product 2 from 1 may be easily explained by the [3,3] sigmatropic rearrangement of 1 to 4 followed by enolisation to give 5. The phenol 5 in N,N-diethylaniline base may then add to the diene-lactone moiety by a [1, 6] Michael addition to give finally the product 2 Another pathway via 1,6-internal Michael type addition of

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¹Dedicated to Prof. U. R. Ghatak on his 70th birthday
N,N-DEA to give 8 followed by a Friedel-Crafts cyclization which is irreversible may also be considered (Scheme II).

The present result seems to be quite unusual as it is markedly different from earlier reports in this area. Similar rearrangement studies have been reported on a number of analogous system viz., 4-aryloxymethyl-D-chromene 9 is reported to give the benzofuro [3,2-c] benzopyran 10, 7-chromenylmethoxy-4-methylcoumarin 11 gave mainly the angularly fused furopyran system 12 and 7-chromenylmethoxy flavones 13 also gave exclusively the angularly fused furopyran 14 whereas 4-aryloxymethylpyran[3,2-c]coumarins 15 gave only the phenolic products whereas 1-aryloxymethyl-3H-pyrano[2,3-c]quinolin-5(6H)-ones 17 afforded only 1-2a

Therefore, the result reported here is interesting and noteworthy. It is relevant to mention here that recently there is flurry of activity on the synthesis of pyrano-pyran 9• To our knowledge this is the first report on the formation of fused pyranopyran [6,6] ring from the [3,3] sigmatropic rearrangement and subsequent cyclisation from an allyl aryl ether derivative. Coumarin 10 and its derivatives are important because of their biological activity and this has made their synthesis of interest. These pyranopyran derivatives have the potential to be useful as drugs. The methodology described here is simple and facile.

Experimental Section

Compounds 1a-f (0.20 g) were refluxed in freshly distilled N,N-diethylaniline (2 mL) for 8 hr. The reaction mixture was cooled, poured into ice-cold dil. HCl and left overnight. It was then extracted with chloroform (3 × 25 mL). The chloroform extract was washed with dil. (1:1) HCl solution, water (2 × 25 mL) and dried (Na2SO4). Removal of solvent gave a viscous mass which was subjected to column chromatography over silica-gel (60-120 mesh). The products 2a-f were obtained as crystalline solids when the column was eluted with benzene.

Compound 2a. Yield 75 %; m.p. 224°C; UV (EtOH): 218 (log ε 2.74) and 303 (log ε 2.86) nm; IR(KBr): 3000, 1760 (C=O), 1490 and 1210 cm⁻¹; ¹H-NMR (500 MHz; CDCl₃/TMS): δH 3.40 (dt, J = 11.2, 5 Hz), 3.65 (dt, J = 11.2, 5 Hz), 4.00 (t, J = 11.2, 5 Hz), 4.25 (t, J = 11.2 Hz)
J = 11.2 Hz), 4.66-4.72 (m, $H_2$ and $H_4$), 6.73 (d, 1H, $J = 2.8$ Hz, $C_2-H$), 6.83 (dd, 1H, $J = 8.9$, 2.8 Hz, $C_3-H$), 6.88 (d, 1H, $J = 8.9$ Hz, $C_1-H$), 7.36-7.41 (m, 2H, $C_2$ and $C_12-H$) 7.44-7.48 (m, 1H, $C_10-H$) and 7.69 (d, 1H, $J = 8$ Hz, $C_{11}-H$); $^{13}$C-NMR (200 MHz, CDCl$_3$): $\delta$ 29.73 ($C_{12c}$), 31.49 ($C_{2a}$), 55.78 (OCH$_3$), 65.70 ($C_{13}$), 68.18 ($C_2$), 81.07 ($C_{4a}$), 114.38 ($C_7$), 115.15 ($C_4$), 117.14 ($C_9$), 118.04 ($C_{10}$), 119.02 ($C_{12a}$), 120.62 ($C_{12b}$), 122.01 ($C_{11}$), 124.93 ($C_{12}$), 128.78 ($C_{10}$), 139.98 ($C_{3a}$), 148.78 ($C_{14a}$), 149.32 ($C_{6a}$), 154.08 ($C_3$) and 156.50 ($C_7$, >C=O); m/z 336 (M$^+$). Anal. Found: C, 68.09; H, 4.89. C$_{20}$H$_{16}$O$_5$. Calcd. for: C, 67.80; H, 5.16 %. 

Scheme II

Scheme III
**Compound 2b.** Yield 75%; m.p. 208°C; UV (EtOH): 315 (log ε 4.92), 285 (log ε 3.87) and 250 (log ε 4.45) nm; IR (KBr): 1750 (C=O), 1505 and 1260 cm⁻¹; ¹H-NMR (250 MHz, CDCl₃/TMS): δ₈ 3.37-3.49 (m, 1H), 3.58-3.70 (m, 1H), 4.03 (t, 1H, J = 11.7 Hz), 4.24 (t, 1H, J = 11.9 Hz), 4.61-4.77 (m, 2H), 6.90-7.07 (m, 2H), 7.13-7.50 (m, 5H) and 7.80 (dd, 1H, J = 8, 1.7 Hz); m/z 306 (M⁺). Anal. Found: C, 66.73; H, 4.03. C₂₉H₁₈O₄. Calcd. for: C, 66.96; H, 3.82 %.

**Compound 2d.** Yield 70%; m.p. 186°C; UV (EtOH): 314 (log ε 4.87), 292 (log ε 3.79) and 244 (log ε 4.53) nm; IR (KBr): 1750 (C=O), 1500 and 1295 cm⁻¹; ¹H-NMR (100 MHz, CDCl₃/TMS): δ₈ 3.26-3.70 (m, 2H), 3.98 (t, 1H, J = 11.5 Hz), 4.20 (t, 1H, J = 12 Hz) 4.52-4.92 (m, 2H), 6.88 (d, 1H, J = 8 Hz), 7.16-7.56 (m, 5H) and 7.64 (dd, 1H, J = 8, 1.7 Hz); m/z 342, 340 (M⁺). Anal. Found: C, 67.16; H, 4.01. C₁₉H₁₃ClO₄. Calcd. for C, 67.42; H, 3.82 %.

**Compound 2e.** Yield 75%; m.p. 238°C; UV (EtOH): 215 (log ε 2.97) and 309 (log ε 3.17) nm; IR (KBr): 1720 (C=O), 1500 and 1170 cm⁻¹; ¹H-NMR (100 MHz, CDCl₃/TMS): δ₈ 3.36-3.80 (m, 2H), 4.08 (t, 1H, J = 11.8 Hz), 4.20 (t, 1H, J = 12 Hz) 4.52-4.92 (m, 2H), 6.88 (d, 1H, J = 8 Hz), 7.16-7.56 (m, 5H) and 7.64 (dd, 1H, J = 8, 1.7 Hz); m/z 342, 340 (M⁺). Anal. Found: C, 67.10; H, 4.03. C₁₉H₁₃ClO₄. Calcd. for: C, 66.96; H, 3.82 %.

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References


