Studies on the cyclisation of two key allyl phenol intermediates of bromotyrosine based natural products

Uppuluri V Mallavadhani * & K Narasimhan
Forest and Marine Products Division, Regional Research Laboratory (CSIR), Bhubaneswar 751013, India.

Received 2 June 2000; accepted (revised) 27 November 2001

Cyclisation of two key allyl phenol intermediates viz. 2-allyl-6-bromo-4-formyl phenol 1 and 4-acetyl-2-allyl-6-bromo phenol 2 has been studied under a variety of acid catalysts. While mineral and organic acids did not yield any cyclic products, polyphosphoric acid and 70% perchloric acid affected the cyclisation up to 55-70%. Significantly, the cationic montmorillonite clays have been used for the first time and found to affect the regioselective cyclisation and yielded the five membered coumarans in quantitative yields.

The cyclisation of o-allyl phenols to oxygenated cyclic products is a very important step in natural products synthesis. This cyclisation is acid catalysed and yield either a five membered coumaran system (C2 cyclisation) or a six membered chroman system (C3 cyclisation). Most of the acid catalysts induce regioselective cyclisation and favour the former products. However, a reverse selectivity to get C3 cyclisation is also reported in few instances, where the acid catalyst is used along with a peroxide. A variety of acid catalysts such as conc. H2SO4, hydrobromic acid-acetic acid or formic acid, pyridinium hydrochloride, mercuric salts, CF3COOH, Triflic acid, BF3-Etherate, ZnCl2/Decalin, PTS, PPTS, 70% HClO4, Montmorillonite (H+), Montmorillonite (Fe3+), have been reported in literature to affect such cyclisations.

In connection with our developmental programme on the synthesis of bromotyrosine based natural products, we have done detailed studies on the cyclisation of two key allyl phenol intermediates viz. 2-allyl-6-bromo-4-formyl phenol 1 and 4-acetyl-2-allyl-6-bromo phenol 2. A variety of acid catalysts including mineral, organic, Lewis and montmorillonite cationic clays have been tried. Surprisingly, both the substrates resisted cyclisation with almost all the mineral and organic acids tested and did not yield any cyclic product. However, polyphosphoric acid (PPA) and 70% perchloric acid (HClO4) affected the cyclisation up to 55-70%. More significantly, the cationic montmorillonites, which are used for the first time, found to be very efficient and yielded the cyclic products in almost quantitative yields (Chart 1). The cyclic products obtained with both the substrates were identified as five membered coumarans (3 and 4) by spectroscopic analysis (IR and 1H NMR). It is interesting to note that no six membered chroman units were found even in traces.

**Experimental Section**

Melting points were determined on Buchi capillary melting point apparatus and are uncorrected. IR spectra were recorded as KBr pellets on JASCO FTIR-5300 spectrophotometer, 1H NMR spectra on Jeol Fx 90Q at 90MHz using CDCl3 as solvent and TMS as an internal standard. Silica gel G for Thin Layer Chromatography and silica gel 100-200 mesh for column chromatography have been used.
Cyclisation of compound 1 in presence of polyphosphoric acid (PPA): Formation of 7-bromo-5-formyl-2-methyl-2,3-dihydrobenzofuran 3. A mixture of compound 1 (100 mg) and PPA (1 mL, prepared from P₂O₅ - 5 parts and ortho phosphoric acid - 8 parts) was stirred at room temperature for 5 hr. The reaction mixture was treated with ice cold water and extracted with chloroform (3x5 mL). The combined chloroform extract was washed with brine solution (3x5 mL), dried over anhyd. MgSO₄ and evaporated in vacuo. The resulting residue was chromatographed over a column of silica gel (10 g, 100-200 mesh) and eluted with n-hexane and n-hexane-ethyl acetate mixtures. The n-hexane-ethyl acetate (98: 2) column fractions on evaporation followed by recrystallisation from n-hexane gave the title compound 3 as colourless shining flakes (65 mg); m.p. 66-68°C; Rf 0.5 (n-hexane-ethyl acetate, 9: 1); FeCl₃ coloration: Negative; IR (KBr): 2850 (-CHO), 1690 (-HCO), 1579, 1543, 1452, 1361, 1090 (cyclic ether) and 670 cm⁻¹ (C-Br); ¹H NMR (CDCl₃, 90 MHz): δ 1.5 (d, J=6.0 Hz, 3H, -C₂-H₃), 2.8-3.7 (m, 2H, C₃ -CH₂), 5.2 (m, 1H, C₂ -H), 7.7 (d, J=2Hz, 1H, Ar-H), 7.9 (d, J=1.8Hz, 1H, Ar-H), 9.9 (s, 1H, -CHO).

Cyclisation of compound 1 in presence of 70% HClO₄: Formation of compound 3. A mixture of compound 1 (100 mg) and 70% HClO₄ (1 mL) was stirred for 1 hr at room temperature. The reaction mixture was treated with ice cold water and after usual work-up followed by chromatography over a column of silica gel (10 g, 100-200 mesh, n-hexane-ethyl acetate 98: 2) gave the title compound 3 as colourless shining flakes from n-hexane (70 mg).

Cyclisation of compound 1 in presence of montmorillonite: Formation of compound 3. A mixture of compound 1 (100 mg) and montmorillonite (100 mg) in diphenyl ether (5 mL) was heated for 3hr at 185°C. The reaction mixture after usual work-up followed by chromatography over a column of silica gel (10 g, 100-200 mesh, n-hexane-ethyl acetate 98: 2) gave the title compound 3 as colourless shining flakes from n-hexane (95 mg).

Cyclisation of compound 2 in presence of polyphosphoric acid (PPA): Formation of 5-acetyl-7-bromo-2-methyl-2,3-dihydrobenzofuran 4. A mixture of compound 2 (100 mg) and PPA (1 mL, prepared from P₂O₅ - 5 parts and ortho phosphoric acid - 8 parts) was stirred at room temperature for 5 hr. The reaction mixture after usual work-up followed by column chromatography with n-hexane-ethyl acetate (98: 2) yielded the title compound 4 as colourless glassy needles from n-hexane (55 mg); m.p. 68°C; Rf 0.48 (n-hexane-ethyl acetate, 9: 1); FeCl₃ coloration: Negative; IR (KBrs): 1647 (-COCH₃), 1601, 1548, 1475, 1090 (cyclic ether), 902 and 675 cm⁻¹ (C-Br); ¹H NMR (CDCl₃, 90MHz): δ 1.55 (d, J=6.1Hz, 3H, -C₂ -CH₃), 2.55 (s, 3H, -COCH₃), 2.8-3.65 (m, 2H, C₃ -CH₂), 5.15 (m, 1H, C₂ -H), 7.75 (d, J=1.8Hz, 1H, Ar-H), 7.95 (d, J=1.8Hz, Ar-H).

Cyclisation of compound 2 in presence of 70% HClO₄: Formation of compound 4. A mixture of compound 2 (100 mg) and 70% HClO₄ (1 mL) was stirred at room temperature for 1 hr. The reaction mixture after usual work up followed by chromatography over a column of silica gel (10 g, 100-200 mesh, n-hexane-ethyl acetate 98: 2) gave the title compound 4 as colourless shining flakes from n-hexane (68 mg).

Cyclisation of compound 2 in presence of montmorillonite: Formation of compound 4. A mixture of compound 2 (100 mg) and montmorillonite (100 mg) in diphenyl ether (5 mL) was heated for 3hr at 185°C. The reaction mixture after usual work-up followed by chromatography over a column of silica gel (10 g, 100-200 mesh, n-hexane-ethyl acetate 98: 2) gave the title compound 4 as colourless shining flakes from n-hexane (96 mg).

Acknowledgement

We are highly thankful to the Director and Head, Forest and Marine Products Division, Regional Research Laboratory, Bhubaneshwar for their encouragement.

References
2. (a) Hard & Hoffman, J Org Chem, 5, 1940, 212.
   (b) Smith, Chem Revs, 27, 1940, 287.
   (c) Nesmenjow & Sarewitsch, Ber., 68, 1935, 1476.
NOTES