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A Stereoselective Intramolecular Retro-Ene Reaction Catalysed by Aluminium Chloride

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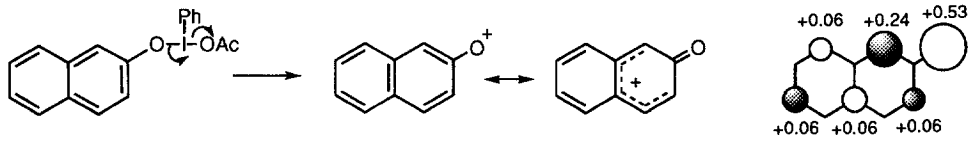
Abstract: Reaction of 5-(2-naphthalenol)-1-pentenes with I(III) reagents results in nucleophilic substitution at C-1 rather than [4+2] intramolecular ionic cycloaddition of the proposed intermediate arenoxenium cations. Treatment of the same precursors with aluminium chloride results in a stereoselective intramolecular cyclisation to spiroketones. Evidence that the mechanism of formation involves a cyclic aluminium intermediate is presented. © 1997 Elsevier Science Ltd.

The ability of hypervalent compounds of iodine and xenon to react first as an electrophile and then as an exceptionally good leaving group (i.e. PhI or Xe) has led us to investigate new reactions of a variety of organic substrates.[1] We now report studies of intramolecular reactions of 2-naphthol derivatives that have led to the discovery of a novel stereoselective cyclisation catalysed by aluminium chloride.

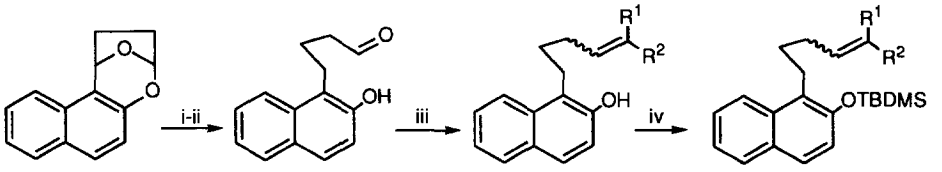


1 2 3 4

The reaction of phenols with hypervalent iodine reagents such as diacetoxyiodobenzene (DAIB) and bis(trifluoroacetoxyiodo)benzene (BFIB) to give cyclohexa-2,5-dienes and related derivatives is well known.[2] The mechanism of this process has not been established but probably occurs by the initial formation of a hypervalent arenoxy intermediate (e.g. **1**): fragmentation with loss of PhI to give an arenoxenium ion (e.g. **2** ↔ **3**) that rapidly reacts with a nucleophile accounts for the observed products. Alternatively, these reactions may occur *via* a concerted mechanism in which a discrete arenoxenium cation is not generated. Although the formation and reactivity of arenoxide ions (ArO^-) and arenoxyl radicals ($ArO\cdot$) are well documented, the chemistry of arenoxenium ions (ArO^+) has received very limited attention.[3]

In addition to reactions with nucleophiles, arenoxenium cations can in principle undergo [4+2] ionic cycloadditions and Woodward and Hoffmann have proposed that a process of this type accounts for the thermal rearrangement of perezone to pipitzol.[4] Similarly, Lewis acid catalysed intermolecular cycloadditions of 2-

methoxy-1,4-benzoquinones have been described by Engler and co-workers.[5] To explore the possibility of trapping arenoxenium ions as intramolecular cycloadducts (i.e. **9**), we have investigated the behaviour of 5-(2-naphthalenol)-1-pentenes **7**. Naphthyl derivatives **7** were chosen for this study to minimise nucleophilic attack at the 3-position of the proposed intermediate cations **3**. Based on the PMO model of the isoelectronic β-naphthylmethyl cation,[6] the LUMO coefficients **4** of the cation should favour cycloaddition.



5 **6** **7a** $R^1=R^2=H$ **8** $R^1=H,R^2=Me$

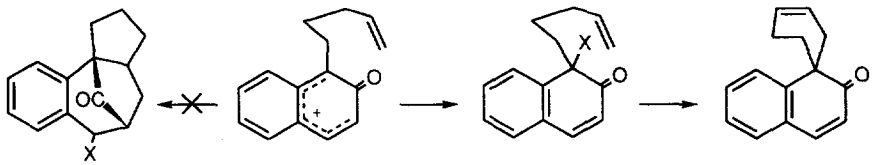
7b $R^1=H,R^2=Me$
7c $R^1=R^2=Me$
7d $R^1=H,R^2=Ph$

Reagents: i, $LiAlH_4$, $AlCl_3$; ii, DMSO, $(COCl)_2$; iii, $R^1R^2CHP^+Ph_3$, $NaNH_2$; iv, TBDMSCl.

Scheme 1

The precursor alkenes **7a-d** were synthesised using the sequence shown in Scheme 1. Reaction of 2-naphthol with 2,5-dimethoxytetrahydrofuran gave 1,4-epoxy-1,2,3,4-tetrahydronaphth[2,1-*b*]oxepin **5**. Complete reduction followed by Swern oxidation of the resulting primary alcohol[7] gave the key aldehyde **6** (90%). Finally, a Wittig reaction using the appropriately substituted ylide gave the alkenes **7a-d** in good yield.[8]

Treatment of compound **7a** with DAIB in CH_2Cl_2 or toluene gave the ether **11a** (57%). Reaction of **7a** with BFIB in CH_2Cl_2 gave the trifluoroacetate **11b** (43%) whereas use of CF_3CH_2OH as solvent resulted in formation of the trifluoroethyl ether **11c** (62%). In all cases the product can be considered to be formed by reaction of a nucleophile at C-1 of the cation **10** (Scheme 2). We observed no evidence to suggest that naphthalenoxyl radicals are generated in any of these reactions. Based on the PMO derived LUMO coefficients and charge distribution **4**, C-1 can be expected to be the most reactive ring atom towards both hard and soft nucleophiles. It is clear that in the presence of nucleophiles intermolecular nucleophilic attack (**10** → **11**) occurs in preference to intramolecular cycloaddition (**10** → **9**). In an attempt to equilibrate a C-1 adduct **11** with an isomeric cycloadduct **9**, the ester **11b** was hydrolysed to the alcohol **11d** (87%). Treatment with mesyl chloride gave the unstable mesyloxy derivative **11e** which upon heating in toluene gave the spiro derivative **12** (16%) as the only isolable product. This result suggests that in the absence of a nucleophile the cation **10** undergoes intramolecular electrophilic addition to the alkene (**10** → **12**).



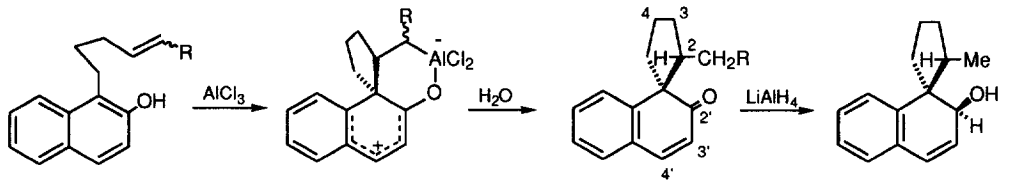
9 **10** **12**

11a X=*O*-2[1-pent-4-enyl]naphthyl
11b X= $OCO.CF_3$
11c X= OCH_2CF_3
11d X=OH
11e X=OSO_2Me

7a

Scheme 2

To avoid reaction of the proposed cation **10** with a nucleophile we investigated the reaction of alkene **7a** with iodosylbenzene-boron trifluoride ($PhI^+OBF_3^-$).[9] This reagent in either CH_2Cl_2 or $CHCl_3$ under reflux gave a new product (20%) that was identified as a mixture of the ketone **14a** and its C-2 epimer (4:1 by ^1H NMR). When $AlCl_3$ was reacted with PhIO in CH_2Cl_2, with the intention of forming the reagent $PhI^+OAlCl_3^-$, and subsequently reacted with the ketone **7a** at room temperature, the product **14a** was again obtained (64%) but none of the C-2 epimer was detected by ^1H NMR. Finally, when the alkene **7a** was treated with $AlCl_3$ in CH_2Cl_2 at room temperature only the diastereoisomer **14a** (86%) was obtained.[10] In a similar manner the alkene **7b** gave the ketone **14b** (87%).



7a R=H
7b R=Me

13a R=H
13b R=Me

14a R=H
14b R=Me

15

Scheme 3

The stereoselectivity of this cyclisation (**7**→**14**) is clearly of some synthetic potential and the steric hindrance of the enone function in **14** provides the opportunity of controlling the formation of additional chiral centres at C-2', C-3' and C-4'. Thus, reduction of compound **14a** with $LiAlH_4$ gave a single product which was identified as the alcohol **15** (74%).[11] The constitution and relative configuration of compound **15** were confirmed by X-ray crystallography.[12] Acid catalysed rearrangement of the alcohol **15** gave 1-methyl and 4-methyltetrahydrophenanthrene which had identical ^1H NMR spectra to those previously reported.[13]

The mechanism of the stereoselective formation of the ketones **14** is of interest. When compound **7a** was deuterated to give the [^{2}HO]naphthol and then treated with $AlCl_3$ none of the deuterium was detected in the product **14a** suggesting that the methyl group is not formed by a simple transfer of the phenolic proton to the alkene. However, when the reaction **7a**→**14a** was worked-up using D_2O partial incorporation of deuterium in the product was detected by mass spectrometry. We interpret these results in terms of the formation of a cyclic aluminium intermediate, e.g. **13a,b**, that controls the stereochemistry of the reaction and which is decomposed to the product upon aqueous work-up (Scheme 3). The proposed formation of the zwitterionic intermediates **13a,b** is also consistent with the deep red coloration of the reaction mixtures.[14] Further support for the formation of cyclic intermediates is provided by the following observation. When the *O*-TBDMS derivative **8** was treated with $AlCl_3$ in CH_2Cl_2 solution a 1:1 mixture of the ketone **14b** and the C-2 epimer was obtained (40%). In this case the bulky *O*-substituent prevents the naphthol oxygen from co-ordinating with the $AlCl_3$ and non-specific Friedel-Craft alkylation leads to an equimolar mixture of both diastereoisomers. It is significant to note that the alkenes **7c** and **7d** did not react with $AlCl_3$ under these conditions and > 90% of the starting material was recovered unchanged. In the case of these alkenes (**7c,d**) Markovnikov addition of the Lewis acid to the double bond presumably leads to tertiary and benzyl cations that cannot cyclise to an arenium ion.

In conclusion we have demonstrated that bifunctional co-ordination of $AlCl_3$ can control the orientation of intramolecular cyclisation of 2-naphthol derivatives. This type of Lewis acid controlled cyclisation may be of general utility and in this context a recently reported proline synthesis catalysed by $ZnBr_2$ is relevant.[15]

Acknowledgements

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8. Compound **7a** (63% yield): m.p. 43-5 °C; υ_{max}(liq.film)/cm^{-1}, 3385 (OH), 1654 (CO) ; δ_H (270 MHz, $CDCl_3$), 7.03-7.92 (6H, m), 5.26-5.97 (1H, m), 5.01-5.14 (3H, m), 3.00-3.06 (2H, m), 2.17-2.25 (2H, m), 1.73-1.83 (2H, m) ; δ_C (68 MHz, $CDCl_3$) 150.5, 138.7, 133.2, 129.4, 128.6, 127.6, 126.3, 126.1, 122.9, 120.2, 117.7, 114.9, 33.7, 28.8, 24.3; *m/z* (%) 212 (M^+)(72), 157 (100), 129 (19), 77 (7), 39 (7).
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10. Alkene **7a** (0.5 g, 2.36 mmol) in dry CH_2Cl_2 (4.0 ml) was slowly added to a well stirred suspension of $AlCl_3$ (0.65 g, 4.87 mmol) in CH_2Cl_2 (20 ml) under dry N_2. Stirring was continued (30 min.) at 20 °C. The mixture was then poured onto crushed ice (20g) and the green mixture extracted with CH_2Cl_2 (3 x 30 ml).The combined extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure to give the crude product as an orange oil (0.46 g, 92%). The product was purified by flash chromatography on silica gel (eluent: petroleum ether (b.p. 40-60 °C)/ EtOAc (10:1)) to give compound **14a** as an oil (86%): υ_{max}(liq.film)/cm^{-1}, 1654 (CO) ; δ_H (270 MHz, $CDCl_3$), 7.05-7.72 (5H,m), 6.09 (1H, d, *J* 10 Hz), 1.72-2.87 (7H, m), 0.75 (3H, d, *J* 7 Hz, CH_3) ; δ_C (68 MHz, $CDCl_3$) 205.2, 144.5, 130.3, 128.7, 127.0, 126.9, 126.8, 126.3, 126.2, 61.8, 56.0, 39.4, 33.2, 25.9, 14.6; *m/z* (%) 212 (M^+)(100), 171 (44), 128 (97), 115 (50), 91 (24), 39 (11); Found: C, 84.76; H, 7.87. $C_{15}H_{16}O$ requires C, 84.87; H, 7.60%.
11. Compound **15**: m.p. 82-3 °C; υ_{max}($CHCl_3$)/cm^{-1}, 3555 (OH) ; δ_H (270 MHz, $CDCl_3$), 7.04-7.28 (4H, m), 6.30 (1H, d, *J* 9 Hz), 6.17 (1H, dd, *J* 9 and 6 Hz), 4.10 (1H, d, *J* 6 Hz), 1.33-2.58 (7H, m), 1.21 (3H, d, *J* 7 Hz) ; δ_C (68 MHz, $CDCl_3$) 142.0, 132.4, 129.8, 129.3, 127.7, 127.3, 126.3, 126.2, 69.5, 53.7, 39.1, 36.7, 34.8, 22.6, 18.9; *m/z* (%) 214 (M^+)(71), 157 (100), 130 (69), 115 (41), 91 (13), 39 (67); Found: C, 84.06; H, 8.61. $C_{15}H_{18}O$ requires C, 84.07; H, 8.46%.
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