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Dearomatising cyclisation of lithiated allyl phenyl ethers: the role of an oxazoline substituent

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ABSTRACT

Treatment of 3-allyloxyphenyl oxazolines with organolithium bases leads to allyllithiums which undergo dearomatising cyclisation. The resulting dearomatised anions may be quenched with electrophiles to form partially saturated benzopyran derivatives.

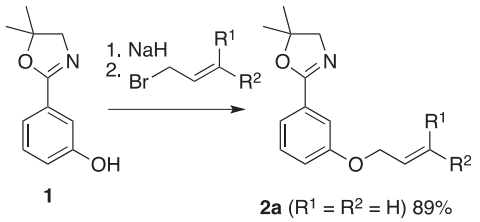
Recent years have seen significant progress in the use of dearomatisation as an efficient synthetic method for the construction of synthetically versatile partially saturated carbocyclic and heterocyclic systems.[1–3] Oxidation of phenols, in particular, has shown particular utility, with the resulting radical cations being trapped by intramolecular nucleophiles to provide spirocyclic products bearing further valuable functionality.[2] Similarly, nucleophilic trapping of pyridinium cations gives spiroheterocyclic systems.[3]

Anionic dearomatisation chemistry[1] relies on the presence of electron-withdrawing substituents to stabilise a forming anion, and seems at first therefore incompatible with phenolic derivatives such as phenyl ethers. However, we reasoned that by combining a nucleophile tethered to a phenyl ether with a second electron withdrawing group, valuable conceptually and practically simple dearomatisations might become possible. The oxazoline group has a successful track-record in the promotion of dearomatisation.[4–6] Meyers used it in conjunction with organometallic nucleophiles to dearomatise pyridyl or phenyl rings, and we showed that under certain conditions and with certain substitution patterns, phenyl oxazolines more generally succumb to dearomatising attack by organolithiums.[5] Alternatively, complexation to stoichiometric Cr has been used to facilitate these reactions.[6]

To explore the possibility of the anionic dearomatisation of phenyl ethers, 3-hydroxyphenyloxazoline **1** was derivatised as the allyl ethers **2a–d** with the aim of forming allyl anions capable of undergoing dearomatising cyclisation (Scheme 1).

Treatment of **2a** with *tert*-BuLi at −78 °C in THF, followed by quench with methyl iodide, gave mixtures of products **4a** and **4b** arising simply from metallation of the allyl group (Scheme 2). However, above −40 °C, dearomatised products were identifiable in the crude reaction mixture, and on warming to 0 °C, a 4:1 mixture of the diastereoisomers of **3a** was isolated in 62% yield. NOE studies identified the relative configuration of the two diastereoisomers. The major product arises from the adoption of the *exo* position by the oxazoline substituent, as noted previously in oxazoline-directed cyclisations.[5]

Under similar conditions, **2b** and **2c** also cyclised, but in low yield, and the cyclisations resulted in inseparable complex mixtures of diastereoisomers. Protonation or oxidation of the intermediate dearomatised anion returned rearomatised benzodihydropyrans **5** in low yield (Scheme 3).



2a ($R^1 = R^2 = H$) 89%
2b ($R^1 = H$; $R^2 = Me$) 87%
2c ($R^1 = Me$; $R^2 = Me$) 89%
2d ($R^1 = H$; $R^2 = Ph$) 25%

Scheme 1. Synthesis of the allyl phenyl ethers **2**.

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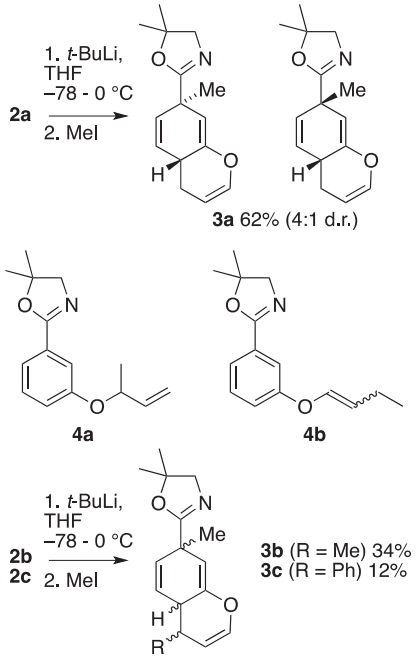
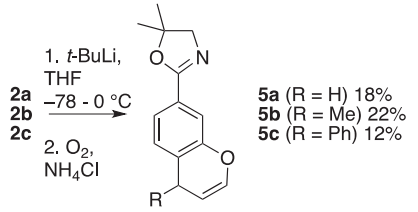


Scheme 2. Dearomatising cyclisations of **2**.



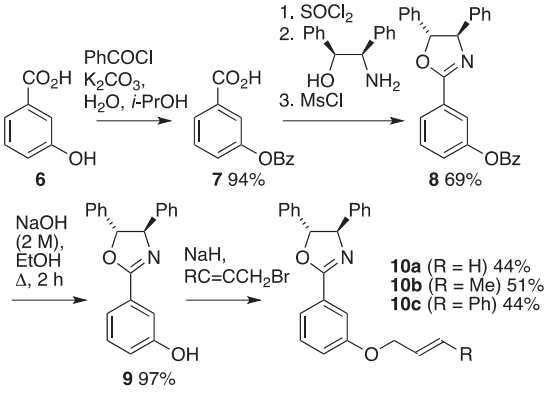
Scheme 3. Rearomatisation in cyclisations of **2**.

Previous work has shown that *trans*-4,5-diphenyl substitution on the oxazoline leads to a more reactive arene, as well as one capable of exhibiting diastereoselectivity.[5] The oxazolines **10a–c** were thus made using our reported method,[7] starting from 3-hydroxybenzoic acid **6**. The phenolic OH was protected as the benzoyl ester in **7**. After formation of the oxazoline **8**, hydrolysis gave **9**, which was alkylated to yield **10a–c** (Scheme 4).

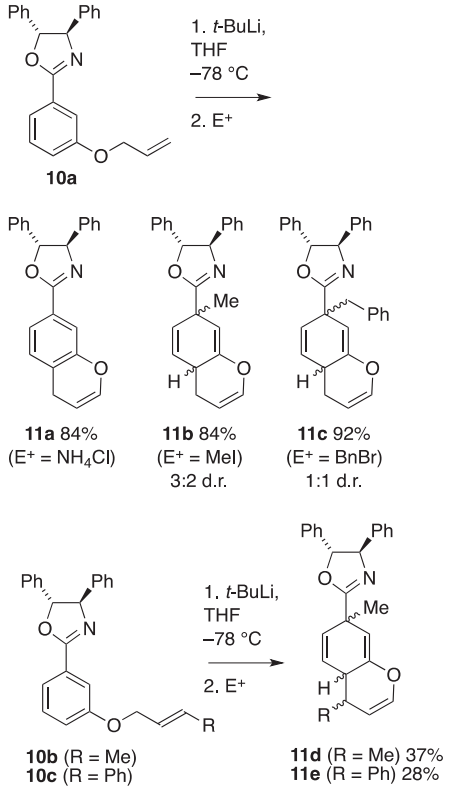
On treatment of **10a** with *tert*-BuLi in THF at −78 °C (no warming was necessary) lithiation and cyclisation proceeded in excellent yield to give dearomatised products **11a–c** on electrophilic quench with ammonium chloride, methyl iodide or benzyl bromide (Scheme 5). However, diastereoselectivity relative to the stereogenic centres of the oxazoline ring was very low. Related crotyl and cinnamyl ethers **10b** and **10c** also cyclised, but in lower yield, and again multiple diastereoisomers were isolated.

Attempts to force cyclisation into the 2-position of the arene ring by using an oxazoline **12** with a blocking group were unsuccessful, and lithiation and methylation gave only the ortholithiation product **13** (Scheme 6).

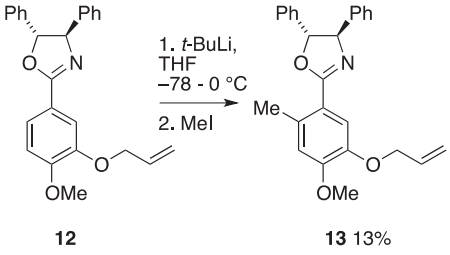
Thus the metallation of allyl phenyl ethers bearing oxazolines on the arene ring leads to dearomatisation, unusually[4,5] into the position *para* to the oxazoline substituent.



Scheme 4. Synthesis of oxazolines **10a–c**.



Scheme 5. Dearomatising cyclisations of **10**.



Scheme 6. Attempted dearomatising cyclisation of **12**.

Experimental

(4*R*,5*R*)-2-(4*a*,7-Dihydro-7-methyl-4*H*-chromen-7-yl)-4,5-diphenyloxazoline **11b**. *Tert*-BuLi (1.13 mmol in pentane) was added dropwise to a stirred solution of oxazoline (200 mg, 0.563 mmol) in dry THF (11 ml) and DMPU (0.44 mL, 3.38 mmol) at −78 °C under a nitrogen atmosphere. After 10 min, MeI (75 μL, 1.13 mmol) was added and the reaction mixture allowed to warm to ambient temperature before addition of an excess methanol. The volume of the reaction mixture was reduced under vacuum, the residue passed through

a silica plug (1:1 EtOAc/petrol) and the solvents were removed before purification by flash chromatography. Cyclised product **11b** (175 mg, 84%) was obtained as 3:2 mixture of diastereoisomers, as a yellow oil. R^f: 0.16 (9:1, petrol/EtOAc); MS *m*/*z* (ES^+) 370 (100%, MH^+), 392 (30%, MNa^+); HRMS: found 370.1800, MH requires 370.1802; IR ν_{max}(film)/cm^{-1} 2918 (w), 1649 (C=N), 1451 (m), 1243, 1078; Data for major diasteroisomer: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.41–7.34 (m, 6H, Ph), 7.33–7.29 (m, 2H, Ph), 7.23–7.18 (m, 2H, Ph), 6.38 (dd, 1H, *J* 6.0, 2.5), 6.00 (d, 1H, *J* 10.0), 5.79 (d, 1H, *J* 10.0), 5.50 (dt, 1H, *J* 16.0, 1.5), 5.23 (dd, 1H, *J* 7.5), 4.99 (d, 1H, *J* 7.5), 4.89 (td, 1H, *J* 6.0, 2.0), 3.10 (m, 1H, H4), 2.28 (dtd, 1H, *J* 16.0, 6.0, 2.5), 2.00 (m, 1H), 1.58 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.3 (C=N), 150.1, 142.1, 141.8, 140.7, 129.1, 129.0, 128.8, 128.7, 128.3, 127.6, 126.5, 126.4, 125.4, 105.3, 101.1, 88.9, 78.4, 40.7, 31.1, 28.2, 26.9.

Acknowledgements

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