Tetrahedron Letters 52 (2011) 2436–2439

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Attack on fluorinated 2-aryloxazolines by organolithiums: dearomatisation, lithiation or substitution

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ARTICLE INFO

Article history:
Received 24 January 2011
Revised 17 February 2011
Accepted 21 February 2011

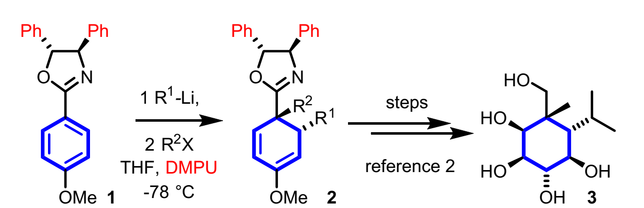
Keywords:
Synthesis
Dearomatisation
Metallation
Oxazoline
Organofluorine chemistry
Carbolithiation

ABSTRACT

Treatment of 4-, 3- or 2-aryl-4,5-diphenyloxazolines with isopropyllithium gives the products of dearomatising addition, fluorine-directed lithiation or nucleophilic aromatic substitution of fluoride depending on substitution pattern and conditions. In the case of the 4-fluoroaryl substrates, fluorinated 1,4-cyclohexadiene may be obtained in good yield.

1. Introduction

In pioneering work on the dearomatisation of naphthyl and pyridyl oxazolines, Meyers[1] showed that the regio- and stereochemical outcomes of nucleophilic attack on the aromatic ring may be controlled by an appropriate chiral oxazoline substituent. Building on Meyers' work, we showed recently[2] that the dearomatisation of *phenyl* rings, previously reported to occur only with the assistance of coordinating metal,[3] is also possible under certain conditions. Dearomatisation of a phenyloxazoline was achieved in good yield only when 2-aryloxazoline (such as **1**) carried the previously unexplored 4,5-*anti*-diphenyl substitution pattern, and when a secondary organolithium nucleophile R^1Li was added in the presence of the deaggregating co-solvent DMPU.[4] Dearomatised products **2** of these reactions were transformed, after a series of functionalisations of the newly revealed diene, into carbasugar analogues such as **3** (Scheme 1).[2,5]



Scheme 1. Synthesis of carbasugars by nucleophilic dearomatisation of a 2-aryl-4,5-diphenyloxazoline.

Introduction of fluorine dramatically changes the physicochemical properties of a molecule.[6] The C–F bond is highly polarised, inducing powerful electrostatic interactions, and substituting OH with F preserves electronegativity whilst removing a hydrogen bond donor/acceptor. Fluorinated drugs often have increased biological activity profiles compared to their non-fluorinated counterparts.[7] The term 'polar hydrophobicity' has been given to the unique properties of C–F bonds which enhance binding to biological receptors.[8]

Widespread interest in the synthesis of fluorinated carbocycles and sugar analogues, notably in the groups of Linclau, O'Hagan and Gouverneur,[9] led us to consider broadening the scope of our dearomatisation methodology to the potential synthesis of fluorinated carbasugars by employing phenyl rings carrying fluorine substituents as substrates for dearomatising attack by organolithiums. A wide range of fluorinated aryl rings are commercially available or are accessible using newly developed fluorination methods,[10] and we hoped the electronegative fluorine would assist nucleophilic attack on the arene. Subsequent diastereoselective transformations of the product fluorodienes would lead to functionalised fluorinated carbocycles.

A series of fluorinated aryloxazolines were made by our one-pot method[11] (Scheme 2). Aminoalcohol **4** was acylated with a fluorobenzoyl chloride and the resulting hydroxyamide **6** was cyclised stereospecifically in the presence of excess triethylamine with methanesulfonyl chloride, to give 2-fluoroaryl-4,5-*anti*-diphenyloxazolines **7**–**10** with reliable inversion of stereochemistry at the oxygen-bearing centre.

Dearomatisation of the fluorinated oxazolines was attempted under the conditions previously optimised for 2-phenyl and

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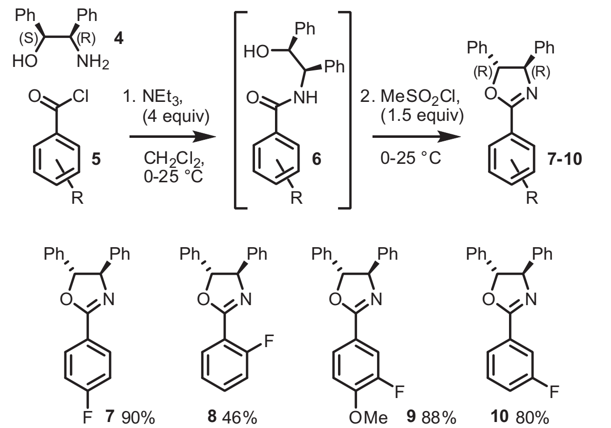
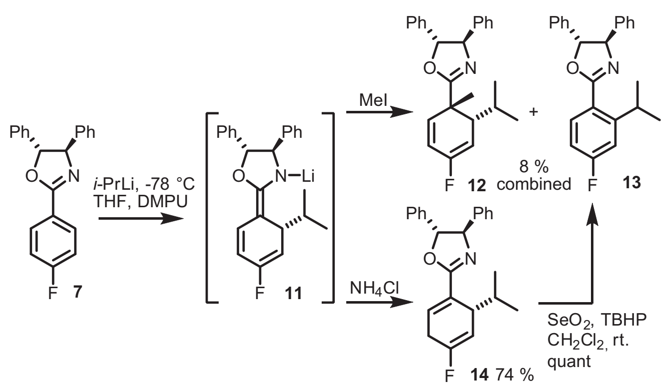
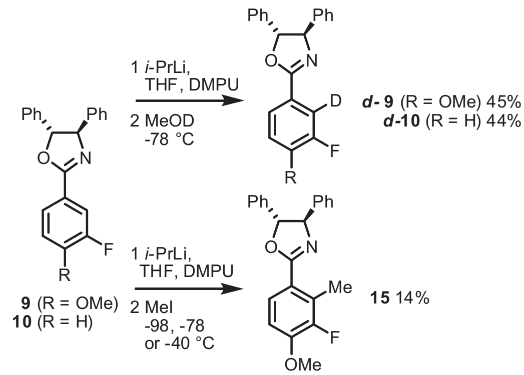
doi:10.1016/j.tetlet.2011.02.091



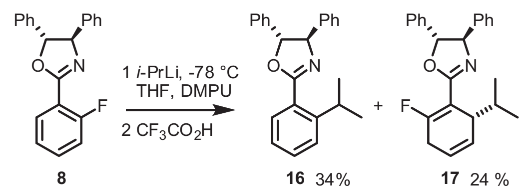
Scheme 2. Fluorinated aryloxazolines as starting materials for dearomatising addition.



Scheme 3. Dearomatisation of a 4-fluoro oxazoline.



Scheme 4. Competing metallation with a 3-fluoro substituent.



Scheme 5. Competing dearomatisation and S_NAr reaction with a 2-fluoro substituent.

2-(methoxyphenyl)oxazolines. Aryl oxazoline **7** was dissolved in THF and DMPU and cooled to −78 °C. Addition of isopropyllithium[2] led to a deep green colour commonly associated with a dearomatised aza-enolate. The colour lasted until the reaction was quenched with methyl iodide (MeI). After workup, the reaction yielded a mixture of inseparable dearomatised **12** (apparently as a single diastereoisomer) and rearomatised compounds **13** (Scheme 3). Similar results were obtained when THF was replaced with cumene or toluene.

We found that rearomatisation of the presumed intermediate azaenolate **11** could be avoided by quenching instead with ammonium chloride. With two equiv *i*-PrLi, in THF and 10 equiv DMPU, a single diastereoisomer of the fluorinated 1,4-cyclohexadiene **14** was formed in 74% yield (Scheme 3). Stereochemistry was tentatively assigned to **14** as shown in Scheme 3 on the basis of related reactions.[2,12] **14** could be rearomatised quantitatively to **13** by treatment with selenium dioxide.[13]

Similar treatment of 3-fluorooxazolines **9** or **10** with isopropyllithium also led to intense, deep colouration—purple in the case of **9** and green in the case of **10**, but on treatment with saturated aqueous ammonium chloride no dearomatised products were evident. Given the well-known metallation-directing power[14] of oxazoline[15] and fluoro[16] substituents, we supposed that competing deprotonation of the 2-position of the ring might be occurring. Quenching the reactions of **9** or **10** with MeOD showed that this was indeed the case: deuteration in the 2-position was indicated in both cases by mass spectroscopy and by disappearance of the 1H doublet at δ 7.78 or 7.75 (Scheme 4). 2-Lithio-**9** was also intercepted by methylation at −78 °C to give **15** in 14% yield, this result remained the same when **9** was treated with isopropyllithium at −98 or −40 °C: no dearomatisation was detected by NMR in the crude products of these reactions.

Under our standard conditions of isopropyllithium in THF/DMPU, 2-fluorophenyloxazoline **8** performed capriciously but gave some intriguing results. Meyers had used 2-fluoro oxazolines to form new C–C bonds by oxazoline-promoted S_NAr displacement of fluoride with an aryl or alkyl organo-metallic reagent.[17] After treatment of **8** with *i*-PrLi and quenching with trifluoroacetic acid, the NMR spectrum of the crude reaction mixture indicated that both substitution and addition had taken place to return **16** and **17** in roughly a 3:2 ratio (Scheme 5).

Attempts to improve the yield of **17** met with little success: the reaction was repeated at −98 °C, with a freshly opened bottle of isopropyllithium, and with different rates of addition of alkyllithium: in all cases no, or very little, **17** could be detected in the crude reaction product, but instead only the product **16** of substitution.

Functionalisation of the fluorodienes **14** and **17** was attempted, but unfortunately without success, in accordance with previous reports.[18]

In summary, extension of oxazoline-promoted diastereoselective nucleophilic dearomatisation[1,2] to fluorinated aryl rings gives results dependent on substitution pattern. A fluoro substituent in the 4-position promotes dearomatisation but only when the reaction is quenched with a proton source. Moving the fluoro substituent to the 3-position cooperatively activates the 2-position towards *ortho*-lithiation, and 2-alkylated products can be obtained. The acidifying effect of the two directing groups is evidently greater than the dearomatisation-promoting power of the oxazoline. With a fluoro-substituent in the 2-position, dearomatisation by attack at the 2- or 6-position is finely balanced: in general the 2-fluoroaryl oxazoline leads to S_NAr substitution of fluoride by alkyllithium, with the product of a capricious dearomatisation (by attack at the 6-position of the ring) observed only when the reaction was performed on a small scale.

2. Experimental

2.1. (4*R*,5*R*)-1-((*R*)-4′-Fluoro-6′-isopropylcyclohexa-1,4-dienyl)-4,5-dihydro-4,5-diphenyloxazole (14)

Oxazoline **7** (0.18 g) was placed in a flame dried round bottomed flask equipped with a stirrer bar, sealed and flushed with N_2, dry THF (10 mL) was added and the oxazoline dissolved. DMPU (0.7 mL, 10 equiv) was added by syringe through the septum and the solution was cooled to −78 °C. Isopropyl lithium solution (2.28 mL, 0.5 M in pentane, 2 equiv) was added to the stirred solution and the reaction turned deep green. After 2 min, saturated aqueous NH_4Cl solution (1 mL) was added to the reaction mixture and the green colour disappeared. The flask was then taken out of the dry ice bath and allowed to reach room temperature before the addition of methanol (1 mL). The reaction mixture was partitioned between ether and saturated aqueous NH_4Cl. The organic layer was then washed four times with water to remove DMPU and dried with $MgSO_4$. The solvent was removed under reduced pressure before purification by flash chromatography (3% EtOAc in petroleum ether) to give compound **14** (0.153 g, 74%) as an opaque oil.

R_f: 0.62 (20% EtOAc in petroleum ether); MS *m*/*z* (ES$^+$) 362.2 (100%, M+H$^+$); HRMS: found 362.1910, M+H$^+$ requires 362.1915; ν_{max} (film)/cm^{-1} 2959 (C–H), 1717 (C=C), 1619 (C=N); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.43–7.10 (m, 10H, Ar), 6.80 (ddd, J^F 7.5, *J* 4.5, 3 Hz, 1H, C6′ CH), 5.24 (ddd, J^F 17.5, *J* 5, 2 Hz, 1H, C6′ CH), 5.14 (d, *J* 7 Hz, 1H, C5 CH), 5.03 (d, *J* 7 Hz, 1H, C4 CH), 3.54–3.49 (m, 1H, C2′ CH), 3.01 (ddd, J^F 23, *J* 6, 3 Hz, 1H, C5′^{a} CH) 2.89 (ddd, J^F 23, *J* 9, 5 Hz, 1H, C5′^{b} CH), 2.43–2.33 (m, 1H, *i*-Pr H), 0.93 (d, *J* 7 Hz, 3H, *i*-Pr Me), 0.71 (d, *J* 7 Hz, 3H, *i*-Pr Me); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.4 (d, J^F 2 Hz), 157.19 (d, J^F 254 Hz), 141.9, 140.6, 131.3 (d, J^F 11 Hz), 2 × 128.9 (d, J^F 11 Hz), 128.5, 128.4, 127.8, 2 × 126.7, 2 × 125.8, 125.7, 100.3 (d, J^F 14 Hz), 88.3, 79.1, 42.3 (d, J^F 6.5 Hz), 31.0, 27.9 (d, J^F 29 Hz), 20.6, 16.3.

2.2. (4*R*,5*R*)-1-(3′-Fluoro-4′-methoxy-2-methylphenyl)-4,5-diphenyl-4,5-dihydrooxazole (15)

Oxazoline **9** (100 mg, 1 equiv) was placed in a flame dried round bottomed flask equipped with a stirrer bar, sealed and flushed with N_2, dry THF (3 mL) was added and the oxazoline dissolved. DMPU (0.34 mL, 10 equiv) was added by syringe through the septum and the solution was cooled to −78 °C. Isopropyllithium solution (0.8 mL, 0.7 M in pentane, 2 equiv) was added to the stirred solution and the reaction turned deep green. After 2 minutes, methyl iodide (0.2 ml, 11.6 equiv) was added to the reaction mixture. The solution became orange/brown. The flask was taken out of the dry ice bath and allowed to reach room temperature. The reaction mixture was partitioned between ether and saturated aqueous NH_4Cl solution. The organic layer was washed four times with water to remove DMPU and dried with $MgSO_4$. The solvent was removed under reduced pressure and purified by flash chromatography (10% EtOAc in petroleum ether) to give compound **15** as an opaque oil (15.3 mg, 14%).

R_f: 0.35 (20%, EtOAc in petroleum ether); MS *m*/*z* (ES$^+$) 362 (100%, M+H$^+$), 384 (90%, M+Na$^+$); HRMS: found 362.1548, M+H$^+$ requires 362.1551; IR ν_{max} (film)/cm^{-1} 1642 (C=N); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.72 (dd, *J* 9.2 Hz, 1H, C6 H), 7.20 (m, 10H, Ar), 6.78 (dd, *J* 8.5, J^F 8.5 1H, C5′ H), 5.24 (d, *J* 7.5 Hz, 1H, C5′), 5.18 (d, *J* 7.5 Hz, 1H, C4′), 3.86 (s, 3H, OMe), 2.58 (d, *J* 3 Hz, 3H, C2 Me); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.6, 149.9, 142.2, 140.6, 129.0, 2 × 128.9, 128.5, 127.8, 127.6, 126.6, 2 × 126.3, 126.2, 2 × 125.8, 120.1, 109.5, 89.2, 88.1, 56.2, 12.85.

2.3. (4*R*,5*R*)-4,5-Dihydro-1-(2′-isopropylphenyl)-4,5-diphenyloxazole 16 and (4*R*,5*R*)-1-((*R*)-2′-Fluoro-6-isopropylcyclohexa-1′,4′-dienyl)-4,5-dihydro-4,5-diphenyloxazole (17)

Oxazoline **8** (50 mg) was placed in a flame dried round bottomed flask equipped with a stirrer bar, sealed and flushed with N_2, dry THF (5 mL) was added and the oxazoline dissolved. DMPU (0.22 mL, 10 equiv) was added and the solution was cooled to −78 °C. Isopropyllithium solution (0.66 mL, 0.45 M in pentane 2 equiv) was added to the stirred solution and the reaction mixture turned deep green. After 2 min, the reaction was quenched with TFA (0.5 mL). The reaction mixture was allowed to warm to room temperature before the addition of methanol (1 mL). The reaction mixture was partitioned between ether and saturated aqueous sodium hydrogen carbonate. The organic layer was then washed four times with water to remove DMPU and dried with $MgSO_4$. The solvent was removed under reduced pressure and purification using preparative HPLC (2% EtOAc in petroleum ether) gave compounds **16** (18 mg, 34%) and **17** (12 mg, 24%) as colourless clear oils.

Compound **16**: R_f 0.5 (20% EtOAc in petroleum ether:); MS *m*/*z* (ES$^+$) 342.2 (100%, M+H$^+$); HRMS: found 342.1860, M+H$^+$ requires 342.1852; ν_{max} (film)/cm^{-1} 3029 (Ar C–H), 1643 (C=N); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.81 (d, *J* 7 Hz, 6H,), 7.30 (m, *J* 7 Hz, 1H, Ar), 5.29 (d, *J* 8 Hz, 1H), 5.21 (d, 1H), 4.00 (sept, *J* 7 Hz, 1H, CH *i*-Pr), 1.23 (d, *J* 7.5 Hz, 6H, both *i*-PrMe); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.9, 148.4, 141.1, 139.4, 130.0, 129.2, 2 × 127.9, 127.8, 127.4, 126.7, 2 × 125.6, 125.4, 125.0, 2 × 124.8, 124.5, 87.3, 78, 28.5, 21.6, 21.3.

Compound **17**: R_f 0.4 (20% EtOAc in petroleum ether); MS *m*/*z* (ES$^+$) 362.2 (100%, M+H$^+$); HRMS: found 362.1926, M+H$^+$ requires 362.1915; ν_{max} (film)/cm^{-1} 2959 (C–H), 1679 (C=N); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35–7.13 (m, 10H, Ar), 5.77–7.64 (m, 2H, C3′ + C4′CH), 5.72 (d, *J* 7.5 Hz, 1H, C5 H), 5.43 (d, *J* 7.5 Hz, 1H, C4 H), 3.51–3.43 (m, 1H, C2′ H), 3.04–2.83 (m, 2H, C5′ CH2), 2.14 (dsept, J^F 7, *J* 3.5 Hz, 1H, *i*-Pr CH), 0.97 (d, *J* 7 Hz, 3H, *i*-Pr Me), 0.79 (d, *J* 7 Hz, 3H, *i*-Pr Me); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.6, 140.2 (d, J^F 144 Hz), 127.8, 2 × 127.7 (d, J^F 8 Hz), 127.3, 126.7, 2 × 125.7, 2 × 124.6, 124.5 (d, J^F 2 Hz), 121.3 (d, J^F 10 Hz), 105.0, 87.3, 77.4, 43.2, 30.2 (d, J^F 14 Hz), 27.7(d, J^F 25 Hz), 19.5, 15.6.

Acknowledgements

We are grateful to the EPSRC and to GlaxoSmithKline for support, and to Dr Diane Coe for many helpful discussions. We acknowledge the EPSRC. National Mass Spectrometry Service Centre, Swansea, for providing mass spectrometric data.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.02.091.

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