Radical-carbanion cyclo-coupling in armed aromatics: overriding steric hindrance to ring closure

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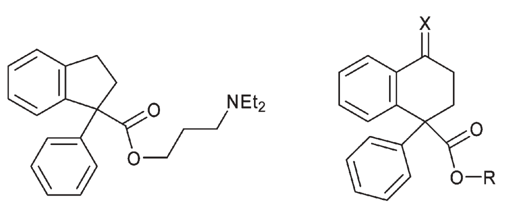
Received (in Cambridge, UK) 6th May 2005, Accepted 12th July 2005
First published as an Advance Article on the web 4th August 2005
DOI: 10.1039/b506391d

ω-(2-Halophenyl)alkyl-2-oxazolines were prepared and reacted *via* base promoted intramolecular coupling of radical with carbanionic centres to yield 1-phenyl-1-oxazolino-indan and -tetralin derivatives containing quaternary C-atoms.

Conventional free radical based ring closures are accomplished by means of intramolecular additions to alkene and related acceptors that favour the 5-*exo* cyclisation mode. A wealth of detail is available in the literature on such cyclizations.[1] Reports of ring closures proceeding by intramolecular radical–carbanion coupling ($S_{RN}1$) are comparatively scant in number.[2,3] Potentially, cyclisation by radical–carbanion coupling is an efficient chain process, applicable for a different range of functionality, with several latent advantages. First, for aryl type radicals, cyclo-coupling with carbanions is expected to be extremely rapid, even when this results in the formation of a *quaternary* centre. Second, it can be anticipated that 6-member ring production by this means should proceed as readily as 5-member ring formation.[2b,2d] Conventional radical cyclizations onto α-substituted alkenes giving *quaternary* centres are comparatively slow[4] and the substituent on the double bond often diverts the regioselectivity to the *endo* mode.[5,6] 6-Member ring formation by 6-*exo* or 6-*endo* processes is also relatively slow and both modes require particular substituent patterns if product mixtures are to be avoided.[4–6]

Anticonvulsant activity has been reported for the benzo-caramiphen analogue **1**.[7] Other aryl-substuted indan derivatives are also precursors for pharmaceuticals.[8] Our initial aim was to develop a new radical-carbanion coupling route to compounds of type **1** containing *quaternary* C-atoms. We also investigated the applicability of similar methodology to preparations of tetralin analogues **2**, containing 6-member rings with *quaternary* C-atoms, which are also precursors to pharmaceuticals.[9]

In 1997 Wolfe and co-workers reported that carbanions derived from 2-oxazolines took part in intermolecular reactions with



1 **2**, X = H_2, CH_2, O

Scheme 1 Biologically active 1-aryl-indan and -tetralin derivatives.

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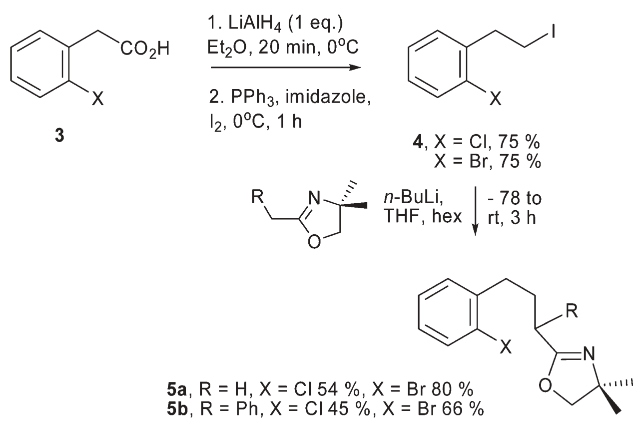
aromatic and heteroaromatic radicals, giving coupled products in moderate to high yields.[10] Reactions were photoassisted and involved the use of KNH_2 in liquid NH_3. 2-Oxazoline units are synthetically useful and may readily be transformed to amides, acids, aldehydes *etc.*[11] Furthermore, suitably functionalised 2-oxazolines are useful as chiral auxiliaries.[12]

2-Haloaryl-2-oxazolines of type **5** were chosen as precursors and prepared from commercially available 2-halophenylacetic acids (**3**) as shown in Scheme 2. In reductions of **3** with $LiAlH_4$ it was necessary to carefully control the amount of metal hydride, and the reaction conditions, in order to avoid dehalogenation of the ring.

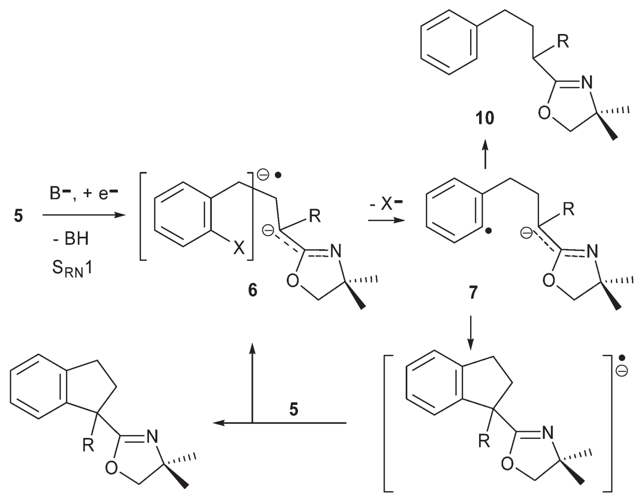
Similarly, during *n*-BuLi mediated alkylation of the 2-oxazolines with phenethyl iodides **4**, solvent polarity was found to be crucial. By using a 3 : 2 mixture of THF : hexane, loss of halogen from the ring was essentially completely suppressed and the 3-(2-haloaryl)-propyl-2-oxazolines **5** were obtained in satisfactory yields.

The planned intramolecular radical–anion coupling process is shown in Scheme 3. Treatment of precursor **5** with base should produce the azaenolate ion present in **6**. An electron is also transferred to **5** in the initiation process giving the aromatic radical anion shown in **6**. Rapid loss of halide from **6** was expected to yield the aryl radical–carbanion-containing intermediate **7**. These events do not necessarily take place in the order described. The subsequent intramolecular reaction was expected to cyclo-couple together the reactive centres in **7** producing indan-type radical anion **8**. SET from **8** to another precursor molecule would then yield functionalised indan **9** and simultaneously propagate the chain (Scheme 3).

Several different sets of conditions for promoting the radical–carbanion coupling reaction were investigated (Table 1). Potassium *tert*-butoxide (pK_a = 19) was probably not a strong



Scheme 2 Preparation of 2-halophenylpropyl-2-oxazolines.



Scheme 3 Chain reaction of 2-haloarylpropyl-2-oxazolines yielding functionalised indanes.

Table 1 Radical–carbanion coupling reactions ($S_{RN}1$) of 3-(2-haloaryl)propyl-2-oxazolines **5**[a]

Precursor	Conditions	Indane **9** (%)	Reduced **10** (%)
5b (X = Br)	*t*-BuOK, Et_3N, DMSO, UV, rt 4h	0	2
5a (X = Cl)	*t*-BuOK, Et_3N, DMSO, UV, rt 3h	0	0
5b (X = Br)	NaH, DMSO, UV, 100°, 4h	66	—
5b (X = Br)	KNH_2, liq. NH_3, UV, −33°, 1h	16	31
5b (X = Br)	LDA (3 eq.), THF, rt, 48h	75	—
5b (X = Br)	LDA (3 eq.), THF, UV, rt, 6h	57[b]	15[b]
5b (X = Br)	LDA (3 eq.), THF, $FeCl_2$, rt, 1h	23	16
5a (X = Br)	LDA (3 eq.), THF, UV, rt, 6h	58[b]	—

[a] Yields (mol%) determined by NMR except as indicated otherwise. In most reactions a small amount (<8%) of 2-halostyrene accompanied the reported products. [b] Isolated yields.

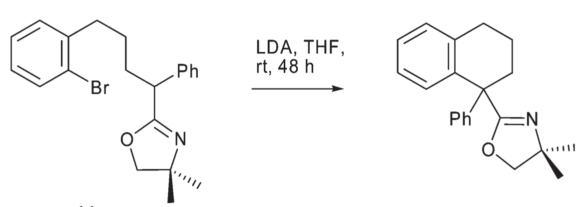
enough base to deprotonate the oxazolines ($pK_a \sim 20$–25) and no reaction took place, even in the presence of added Et_3N as a PET agent.

DMSO (pK_a = 35) is considered a good solvent for $S_{RN}1$ reactions and therefore use of DMSO with NaH (pK_a = 36) should afford a clean solution of the sulfoxide sodium salt. However, the cyclization was not spontaneous with this system. Results suggested anion formation did not take place except at higher temperatures. However, a satisfactory yield of **9b** was obtained in a reaction at 100 °C with UV irradiation. Promotion of the reaction with alkali metal amides in liquid ammonia using conditions similar to those advocated by Wolfe *et al.*[10] resulted in some indane formation (Table 1) but de-halogenative reduction to **10** accounted for the majority of product. Best results were obtained in reactions promoted by LDA in THF at rt. Three equivalents of LDA were required; less base led to slower reactions with greater amounts of **10**. In the reaction irradiated with UV light, the precursor was all consumed in 6 h and a satisfactory yield of **9b** was obtained, accompanied by some **10b**.[13] The cleanest reaction, giving 75% of **9b** with negligible **10b**, took place without UV irradiation over 48 h. It has been reported that Fe(II) salts significantly enhance the rates of some $S_{RN}1$ reactions.[14] We found however, that for 2-oxazoline precursors, addition of $FeCl_2$ (0.1 to 1 equiv) depressed the yield of **9b** and made work-up more difficult. This may be due to the formation of stable complexes between Fe(II) and the oxazoline. The similar yields of **9a** and **9b**, obtained under matching conditions in the LDA promoted reactions, demonstrated that ring closure to give the *quaternary* centre in **9b** took place just as readily as formation of the *tertiary* centre in **9a**.

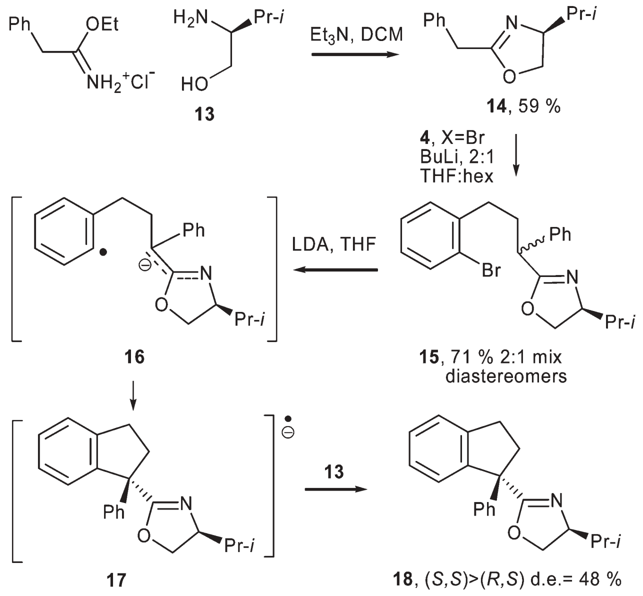
The analogous radical–carbanion coupling reaction to afford a 6-member ring was next examined. 3-(2-Bromophenyl)propionic acid (homologue of **3**) was obtained by treatment of a mixture of 2-bromobenzaldehyde and Meldrum's acid with formic acid and triethylamine,[15] and converted to 4-(2-bromophenyl)butyl-2-oxazoline precursor **11** by an analogous route to that shown in Scheme 1. Treatment of **11** with 3 equivalents of LDA in THF at rt for 48 h gave a 55% yield of tetralin derivative **12**. This yield was comparable to that of **9b** under similar reaction conditions (yield of **12** was 50% in a 6 h reaction illuminated with UV light) and hence our expectation, that 6-member ring closure with generation of a *quaternary* centre would be facile, was fulfilled.

The indan (**9**) and tetralin derivatives (**12**) were obtained as racemates and analogous reactions directed by a chiral 2-oxazoline were next examined to see if stereoselectivity in the ring closure step could be achieved with the oxazoline acting as a chiral auxiliary. (*S*)-Valinol was condensed with ethyl 2-phenylacetimidate hydrochloride **13** to provide (*S*)-4-isopropyl-2-oxazoline **14**. This was alkylated with 2-bromophenethyl iodide **4** (X = Br) to afford the precursor **15** as a 2 : 1 mixture of diastereoisomers at the α-position. Oxazoline **15** was treated with three equivalents of LDA using the best conditions for radical–carbanion coupling developed for **5b**. It was expected that azaenolate **16** would be generated and that the chiral oxazoline would favour production of either the (***S,S***)-indane radical anion **17** or the (***R,S***) diastereomer. A 6 h reaction at rt with UV irradiation gave a 55% yield of the substituted indane diastereoisomer mixture **18** which was readily separable by conventional column chromatography. The d.e. was found to be 18% by comparison of the ^{1}H NMR signals of the two diastereomers. None of the reduced, de-brominated product was detected. The indane yield was lower in a reaction carried out over 48 h without UV irradiation but the d.e. (20%) was virtually unchanged. A reaction carried out at 0 °C without UV irradiation yielded 50% indane **18** with an improved d.e. of 48%. The isopropyl group is a comparatively small substituent so the fact that some stereoselectivity was obtained was encouraging. Work with other chiral oxazolines, designed to improve selectivity is in progress.

The $S_{RN}1$ type chain mechanism of Scheme 3 accounts for product formation, although obviously the illustrated timing of the electron transfer and halide loss steps to give the anion-radical **7** is only tentative. An alternative mechanism involving aryne



Scheme 4 Preparation of a tetralin derivative.



Scheme 5 Preparation of diastereomeric indane derivatives.

formation, followed by intramolecular nucleophilic attack, could be written to account for the products. Wolfe and co-workers studied in detail the mechanisms of related inter- and intramolecular photo-stimulated, base-promoted coupling reactions of nucleophiles with haloarenes.[12e,10] Their evidence that the mechanism proceeds *via* the chain anion–radical coupling process includes the following: (i) the reactions were strongly inhibited when either of the radical traps di-*tert*-butyl nitroxide or *p*-dinitrobenzene was added, (ii) the reactions were extremely sensitive to oxygen (just as ours were), (iii) reaction efficiency increased with photolysis (just as ours did), (iv) most importantly, substrates incapable of affording arynes (because they lacked H-atoms adjacent to the halogen on the aromatic ring) nevertheless gave the coupled product in reactions mediated by LDA (and metal amides in ammonia). We examined the reaction of precursor **5b** with LDA in THF solution, in a quartz capillary tube, directly in the resonant cavity of a 9 GHz EPR spectrometer. In the complete absence of oxygen and on illumination with UV light a strong spectrum was obtained that increased in intensity at lower temperatures. The EPR parameters, *viz*: g = 2.0030, a(1H) = 5.7, a(4H) = 4.2, a(4H) = 1.5 G, were similar to those of the radical anions of models diphenylmethane and indane,[16] and indicate that the spectrum is due to radical-anion **8b**. These observations provide strong evidence in favour of the $S_{RN}1$ mechanism of Scheme 3.

We have established that ω-(2-bromophenyl)alkyl-2-oxazolines readily undergo base-promoted de-brominative-cyclisations that proceed even when *quaternary* centres are formed. In this way 1-phenyl-indane and -tetralin derivatives can be accessed, containing easily manipulated oxazoline moieties, ready for transformation to biologically active compounds. Modest stereoselectivity was realized by incorporating a 4-(*S*)-isopropyl-2-oxazoline unit in the precursor.

The authors thank the EPSRC for financial support and Dr R. A. Aitken for helpful discussions.

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13 To a solution of LDA (2.25 mmol) in THF (3.1 cm^3) at −78 °C was added over 10 min a solution of 2-oxazoline **5b** (X = Br) (279 mg, 0.75 mmol) in THF (1.5 cm^3). After a further 10 min stirring, the yellow solution was allowed to warm to rt over 30 min. THF (4.5 cm^3) was added and the resultant deep red/black solution stirred for 6 h with UV irradiation. After this time a saturated solution of NH_4Cl (7.5 cm^3) was added and the aqueous layer extracted with ether (3 × 4 cm^3). The combined organic layers were washed with water (7.5 cm^3) dried ($MgSO_4$) and evaporated. Purification *via* column chromatography (SiO_2, 9 : 1 hexane : EtOAc) yielded the pure indane **9b** as a clear oil (126 mg, 57%), R_f (SiO_2, 9 : 1 hexanes : EtOAc) 0.35; ν_{max}(film)/cm^{-1} 1649 (C=N); δ_H 1.24 (3H, s, CH_3), 1.40 (3H, s, CH_3), 2.30 (1H, ddd, J = 12.6, 7.7, 5.1, CH_AH_B), 2.82 (1H, ddd, J = 15.6, 7.7, 7.4, $ArCH_CH_D$), 3.00 (1H, ddd, J = 15.6, 7.9, 5.1, $ArCH_CH_D$), 3.18 (1H, ddd, J = 12.6, 7.9, 7.4, CH_AH_B), 3.90 (1H, AB $J \sim 7.9$, CH_EH_FO), 3.97 (1H, AB $J \sim 7.9$, CH_EH_FO), 7.06–7.11 (2H, m, ArH), 7.18–7.31 (6H, m, ArH) and 7.48–7.51 (1H, m, ArH); δ_C 28.0 (CH_3), 28.3 (CH_3), 30.3 (CH_2), 41.3 ($ArCH_2$), 58.2 ($(CH_3)_2C$), 66.8 (PhC), 79.4 (CH_2O), 124.7 (CH_{Ar}), 126.4 (CH_{Ar}), 126.5 (CH_{Ar}), 126.6 (CH_{Ar}), 126.7 (CH_{Ar}), 127.7 (CH_{Ar}), 128.3 (CH_{Ar}), 143.6 (C_q), 144.3 (C_q), 144.8 (C_q) and 167.6 (C=N); m/z (CI) 292 [100%, $(M + H)^+$] [Found: $(MH)^+$ 292.1708. $C_{20}H_{22}ON$ requires 292.1701] and 2-[1,3-diphenylpropyl]-4,4-dimethyl-2-oxazoline **10b**, clear oil, (24 mg, 15%) δ_H 1.25 (3H, s, CH_3), 1.26 (3H, s, CH_3) 2.09–2.18 (1H, m, CH_ACH_B), 2.37–2.44 (1H, m, CH_ACH_B), 2.59 (2H, t, J = 7.7), 3.54 (1H, t, J = 7.7), 3.81 (1H, s, CH_CH_DO), 3.82 (1H, s, CH_CH_DO) and 7.11–7.34 (10H, m, ArH); δ_C 27.0 (CH_3), 28.1 (CH_3), 33.3, 35.2, 44.4, 66.6, 78.6, 125.6, 126.8, 127.6, 128.1, 128.3, 128.4, 139.8, 141.2 and 166.4, plus 2-bromostyrene, clear oil (7%).

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