On the synthesis of vinyl isonitriles

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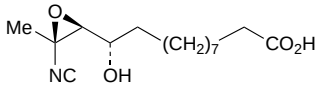
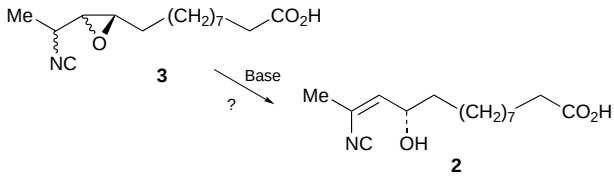
A reversal of the stereochemistry of base mediated isomerisation of some isonitrile epoxides to hydroxy-vinyl isonitriles on changing from lithium diisopropylamide to lithium bis(trimethylsilyl)amide is reported and applied to a synthesis of racemic desepoxyaerocyanidin.

As part of our studies on the synthesis of the epoxy isonitrile antibiotic aerocyanidin **1**[1] we required access to vinyl isonitrile **2**.[2] We considered that base mediated isomerisation of an epoxide of general structure **3** could provide a stereocontrolled access to these systems (Scheme 1). During these studies we noted a pronounced dependence of the stereochemical outcome of the isomerisation on the choice of base.

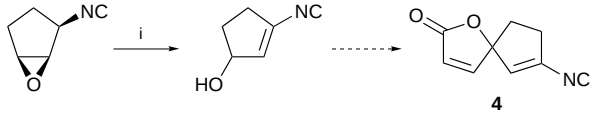


Aerocyanidin **1**

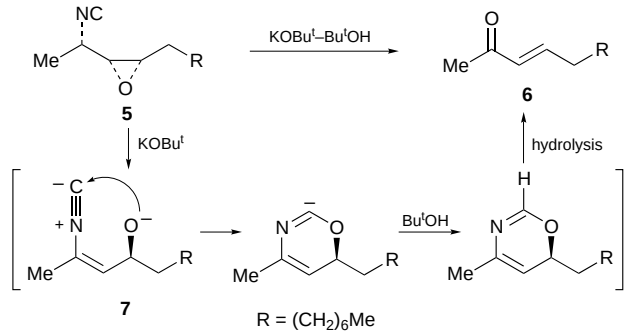


Scheme 1

Following our successful application of this approach to the synthesis of the spirocyclic isonitrile **4**, in which a proton *anti* to the epoxide was removed (Scheme 2),[3] we treated isonitrile epoxide **5** with Bu^{t}OK in Bu^{t}OH but obtained only the α,β-unsaturated ketone **6**. This presumably arises by rearrangement of the initially formed oxyanion **7** as proposed in Scheme 3. This result reflects observations made by Schöllkopf *et al.* regarding the stability of γ-hydroxy isonitriles in saturated acyclic systems.[4] They observed that under basic protic conditions cyclisation to the corresponding 5,6-dihydro-4*H*-1,3-oxazine occurs whereas under basic aprotic conditions the starting material was recovered. Thus we turned to the use of strong bases in an aprotic solvent system. In this context it has been shown that epoxides can be isomerised to allylic alcohols with lithium amide bases *via* a *syn*-elimination process and a cyclic six-membered transition state has been postulated to account for this.[5] Treatment of **8** with LDA in THF at −20 °C gave a 2 : 1 mixture of **9** : **10** with **9** presumably arising *via* a *syn*-β-elimination (Scheme 4).† In an attempt to optimise the selectivity of this process we exchanged the LDA for lithium bis(trimethylsilyl)amide and observed a reversal of stereoselectivity with a **9** : **10** ratio of 1 : 7. To take advantage of this enhanced selectivity we returned to diastereoisomer **5** and found



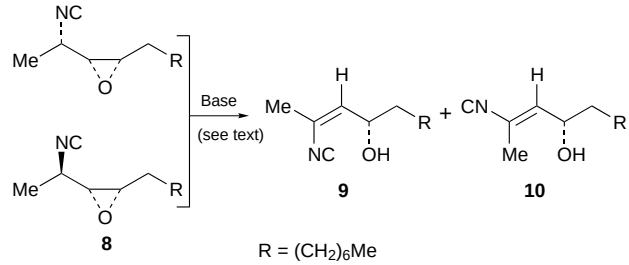
Scheme 2 *Reagents and conditions*: i, KOBu^t, THF, −78 °C, 56%



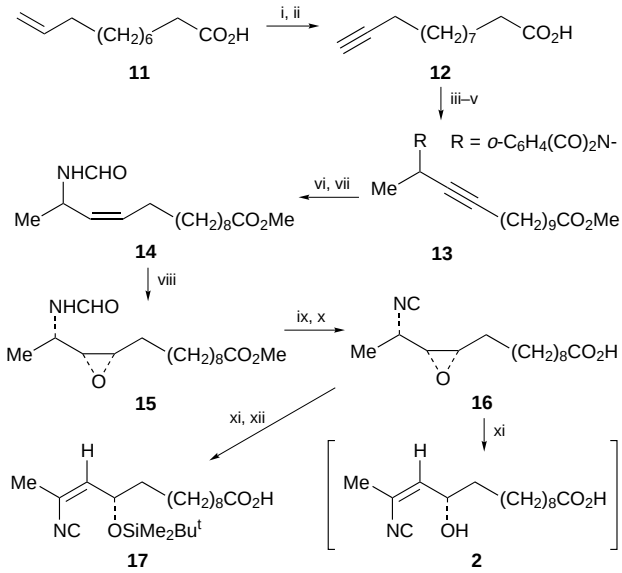
Scheme 3

it to rearrange with a 12 : 1 (**9** : **10**) selectivity and 96% yield. We speculated that this isomerisation proceeded through an *anti*-elimination *via* an open transition state and found that the relative rate of the *anti*-elimination could be increased by the addition of a small quantity of 12-crown-4 which resulted in an increase in selectivity for **9** to 20 : 1. Consistent with this is the observation that while LDA causes rearrangement of **5** with a 1 : 7 (**9** : **10**) ratio addition of 12-crown-4 depresses the ratio to 2 : 3.[6]

With this result in hand we undertook the synthesis of **2** (Scheme 5). Arndt–Eistert homologation of commercially available **11** afforded after bromination and elimination alkyne acid **12** in 66% overall yield. The dilithium anion of **12** was quenched with acetaldehyde and after conversion to the methyl ester introduction of the required amino group was effected under Mitsunobo conditions to give **13** (47% from **12**).[7] Hydrogenation over a Lindlar catalyst afforded the corresponding *Z*-alkene which, after deprotection of the phthalimide with methylamine, was smoothly formylated with acetic formic anhydride in 60% yield for the three steps. Taking advantage of the allylic strain in the *Z*-vinylformamide **14** we used MCPBA to affect a directed epoxidation to yield **15** as a single stereoisomer (79%).[8] Dehydration with trifluoromethanesulfonic anhydride[9] afforded the corresponding isonitrile epoxide (83%) which was saponified with $Ba(OH)_2$ (87%) to afford **16** for the key isomerisation reaction. Treatment of **16** with lithium bis(trimethylsilyl)amide at −15 °C in the presence of a small quantity 12-crown-4 afforded **2** which proved to be an unstable compound decomposing slowly to an α,β-unsaturated ketone corresponding to **6**. Therefore the lithium alkoxide of **2** was protected *in situ* as a *tert*-butyldimethylsilyl ether **17** (57%)



Scheme 4



Scheme 5 *Reagents and conditions*: i, $(COCl)_2$, DMF, CH_2Cl_2; ii, (a) CH_2N_2, Et_2O, Et_3N then Ag_2O, $Na_2S_2O_5$, dioxane, H_2O; (b) Br_2, Et_2O then Na, liq. NH_3, 66% overall; iii, Bu^nLi, THF, −20 °C then MeCHO, THF, −5 °C, 58%; iv, CH_2N_2, Et_2O, 0 °C, 100%; v, phthalimide, Ph_3P, DEAD, THF, 16 h, 81%; vi, H_2, Lindlar's catalyst, quinoline, hexane, EtOAc, 24 h, 90%; vii, $MeNH_2$ (40% aq.) CH_2Cl_2, 16 h then AcOCHO, CH_2Cl_2, 67% (two steps); viii, MCPBA, CH_2Cl_2, 79%; ix, Tf_2O, Pr^i_2NEt, CH_2Cl_2, −78 °C, 83%; x, $Ba(OH)_2$, MeOH then citric acid, 87%; xi, LHMDS, THF, −15 °C; xii, TBSOTf, 57% (for two steps)

to permit full characterisation. The geometry of the double bond was supported by NOE spectroscopy, a 6% enhancement in the intensity of the vinylic proton resonance on irradiation of the vinyl methyl resonance being observed.

In summary we have noted a reversal of the stereochemistry of base mediated isomerisation of a series of isonitrile epoxides to allylic alcohols on switching from LDA to lithium bis-(trimethylsilyl)amide. Using this observation we have prepared racemic desepoxyaerocyanidin **2**.

Footnotes and References

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† Given the established acidity of protons adjacent to isonitriles[10] we cannot preclude the possibility that the isomerisation goes, at least in part, *via* an E_1cb mechanism. In circumstances where a substantial portion of the product derived from this mechanism the differences in stereochemical outcome between the diastereoisomers would require that ring opening of the epoxide is faster than bond rotation.

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