Asymmetric Induction Mediated by an N–N Chiral Axis

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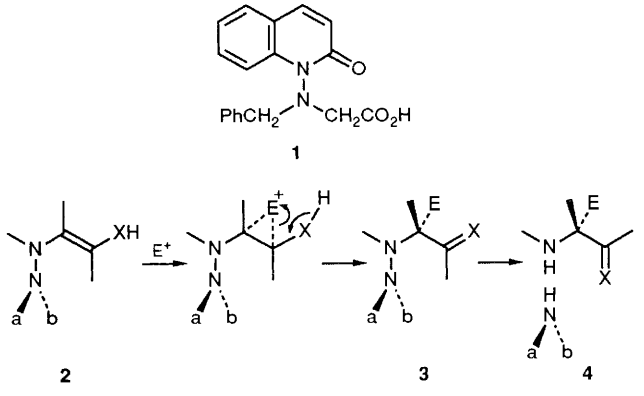
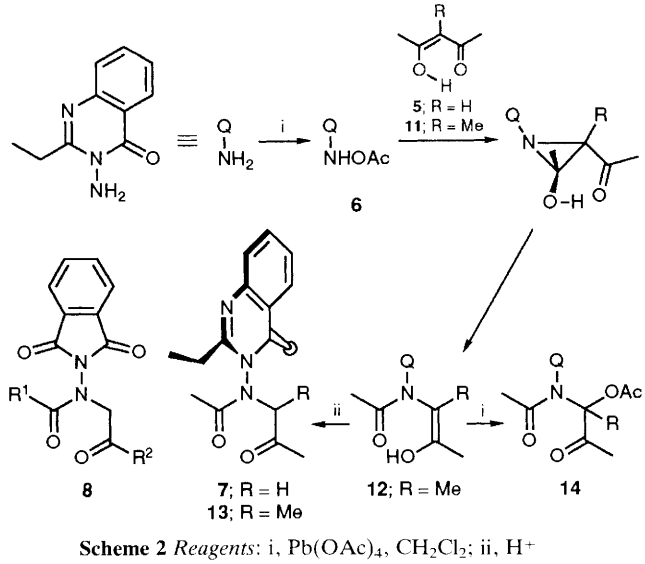
Reaction of 3-methylpentane-2,4-dione **11** with *N*-acetoxyaminoquinazolinone **6** gives an isolable enol **12**, which is chiral by virtue of the high barrier to rotation around its N–N bond; protonation of the double bond occurs in glacial acetic acid to give a single diastereoisomer of keto-amide **13**.

Over the past decade, enantiopure 1,1′-binaphthyl-derivatives have been extensively used as chiral auxiliaries in stereoselective synthesis.[1] In principle, σ-bonds linking a variety of other appropriately substituted atoms could function as chiral axes as does the 1,1′-bond in the above binaphthyls:[2] we have shown that the barrier to rotation around the N–N bond in **1** is sufficient for this molecule to sustain optical activity.[3]

The possibility of using an N–N bond as a chiral element to bring about asymmetric induction in addition to a prochiral double bond (Scheme 1) was attractive for two reasons: (*i*) the prochiral double bond could be located adjacent to the chiral axis as in **2** thus maximising the differential effects of a and b on the accessibility of its two diastereofaces and (*ii*) starting with **2** in enantiopure form, cleavage of the N–N bond in a single diastereoisomer of the product **3** should deliver a functionalised amine **4** in enantiopure form (chiral 1,1′-binaphthyl systems are seldom used as sources of chiral naphthalenes not least because of the difficulty in selectively cleaving the 1,1′-bond).



Scheme 1



Scheme 2 *Reagents*: i, $Pb(OAc)_4$, CH_2Cl_2; ii, H^+

We elected to study *N*,*N*′-dicarbonyl-substituted hydrazines to test the feasibility of the reactions in Scheme 1 since (*i*) sp^2-hybridised nitrogens are known to augment the barrier to N–N bond rotation[4] and (*ii*) this substitution is also known to facilitate reductive fission of the N–N′ bond.[5]

Aziridination of pentane-2,4-dione **5** with the *N*-acetoxyaminoquinazolinone **6**[6] results in the keto-amide **7** (15%)† (Scheme 2).‡

This route to keto-amide **7** is analogous to that suggested by Foucaud *et al.* who oxidised *N*-aminophthalimide with lead tetraacetate in the presence of a variety of enolic β-diketones and obtained the corresponding *N*-phthalimidoketo-amides **8**.[7]

Because of its low enol content, ethyl acetoacetate does not react with **6** under the conditions successful for dione **5**. However, the analogous ester-amide **9** has been obtained by the route in Scheme 3 [in which 3-amino-2-isopropylquinazolin-4(3*H*)-one **10** was used].

The symmetry of the phthalimido group in **8** means that the N–N bond in this compound is not a chiral axis. However, the effects of N–N chiral axes in both **7** and **9** are evident from their NMR spectra: both pairs of protons in the methylene groups in **7** and the methylene and isopropyl-methyl protons in **9** are diastereotopic.§ Thus rotation around the N–N bonds in these compounds is slow on the NMR time-scale and most probably on the real time-scale (see below).

Aziridination of 3-methylpentane-2,4-dione **11** (Scheme 2) gave a crystalline compound (66%) m.p. 114 °C (decomp.) to which we assign the enol structure **12**.¶ In the NMR spectrum of this compound the methylene protons of the ethyl group are also diastereotopic: the sharp singlet for the enol proton at δ 9.8 suggests that this proton is not hydrogen bonded.‖

† The major product is 2-ethylquinazolin-4(3*H*)one **16**.

‡ Satisfactory analytical and spectroscopic data were obtained for all new compounds.

§ ^{1}H NMR for **7** (300 MHz) NC*HH* at δ 3.76 and 4.98 (2 × d, *J* 17.3 Hz); MeC*HH* at 3.05 (dq, *J* 7.3 and 17.5 Hz). For **9** (300 MHz) δ NC*HH* at 3.59 and 4.98 (2 × d, *J* 16.9 Hz), *Me*CH*Me* at 1.36 and 1.41 (2 × d, *J* 6.6 Hz). For both these compounds, signals from minor amounts of the amide rotamers were visible: for **7** NC*HH* at δ 4.34 and 5.04 (2 × d, *J* 19.7 Hz), MeC*HH* at 2.95 (dq, *J* 7.3 and 17.2 Hz); for **9** NC*HH* at 4.14 and 4.87 (2 × d, *J* 18.7 Hz). The gross difference in chemical shift between the NC*HH* protons in **7** and **9** suggests that in each case a single rotamer around the N–CH_2COMe and NCH_2–COMe bonds is preferred with one of these methylene protons deshielded by the quinazolinone carbonyl oxygen.

¶ Foucaud *et al.*[7] also report the isolation of an analogous enol from oxidation of *N*-aminophthalimide in the presence of 2,2,6,6-tetramethylheptane-3,5-dione: we have repeated the preparation of this compound and find good agreement with its (previously unreported) ^{13}C NMR spectrum and that of **12** where comparisons are appropriate.

‖ For **12**: ^{1}H NMR (300 MHz) δ 9.80 (s, OH), 8.24–7.42 (m, 4 × ArH), 2.80 (dq, *J* 7.3 and 16.8 Hz, MeC*HH*), 2.30 (s, Me), 1.91 (s, Me), 1.83 (s, Me), and 1.38 (t, *J* 7.3 Hz, *Me*CH_2) IR ν_{max}/cm^{-1} (Nujol) 3183m, 1686s and 1661s.

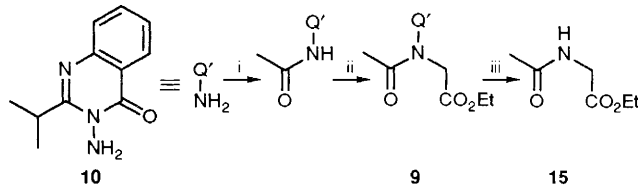
On stirring in glacial acetic acid overnight or on heating briefly under reflux in ethanol, enol **12** is converted into a single diastereoisomer of the keto-amide **13a** [m.p. 162–163 °C. ^{1}H NMR spectrum includes signals at (300 MHz) 4.45 (q, *J* 7.2 Hz, MeC*H*), 2.80 (ABX_3, CH_2Me), 2.39 (s, Me), 1.74 (s, Me), 1.43 (t, *J* 7.2 Hz, CH_2*Me*) and 1.33 (d, *J* 7.2 Hz, CH*Me*)]. After setting aside for three days in acetonitrile this keto-amide **13a** is converted into a diastereoisomer **13b** [m.p. 127–129 °C; ^{1}H NMR spectrum included signals at (300 MHz) δ 4.88 (q, *J* 7.4 Hz, MeC*H*), 3.20 (ABX_3, CH_2Me), 2.38 (s, Me), 1.89 (s, Me), 1.42 (t, *J* 7.4 Hz, CH_2*Me*) and 0.97 (d, *J* 7.4 Hz, CH*Me*)]. Conversion of enol **12** into a mixture (3 : 1) of **13a** and **13b** was effected by briefly heating in glacial acid under reflux.

It appears, therefore, that protonation of enol **12** in cold acetic acid is taking place with complete asymmetric induction under the influence of the N–N chiral axis giving **13a** (*cf.* Scheme 1).**

Enol **12** also reacts with lead tetraacetate to give the α-acetoxylated ketone **14** m.p. 120–120.5 °C in 95% yield (Scheme 2). We assume that this reaction is also completely diastereoselective *i.e.* that **14** is capable of existing in two diastereoisomeric forms.††

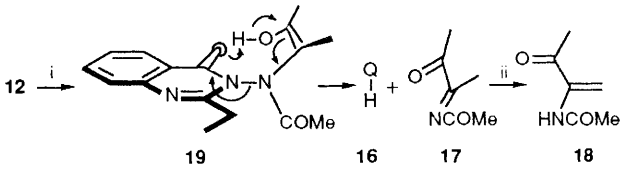
We have confirmed that these *N*,*N*-dicarbonyl-substituted compounds are well-suited for reductive fission by conversion of the ester-amide **9** with aluminium amalgam into ethyl *N*-acetylglycinate **15** in 74% yield (Scheme 3). Cleavage of the N–N bond in enantiopure examples is being investigated.

Enol **12** eliminates 2-ethylquinazolinone **16** quantitatively on heating briefly in boiling ethyl acetate (Scheme 4). The *N*-acylimine **17** is stable enough to be isolated but rearranges readily to the tautomer **18**. Interestingly, this elimination of **16** does not proceed *via* the keto-amides **13a/13b** since these compounds are stable on heating under the same conditions. It is conceivable that elimination takes place *via* the eight-membered transition state **19** in which the eight atoms involved are contained in two planes.



10 9 15

Scheme 3 *Reagents*: i, Ac_2O (66%); ii, NaH, tetrahydrofuran, $BrCH_2CO_2Et$ (89%); iii, Na/Hg, EtOAc (74%)



19 16 17 18

Scheme 4 *Reagents and conditions*: i, heat, 77 °C, 1 min, ethyl acetate; ii, H^+

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** It is likely that the barrier to N–N bond rotation in enol **12** is not significantly different from that in **13a/13b** *i.e.* the rate of rotation around the N–N bond in this compound is effectively zero at room temperature.

†† Decomposition of this compound occurs before interconversion of the diastereoisomers on heating briefly at 203 °C.