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Asymmetric transformation (deracemisation) of an atropisomeric bisheterocyclic amine†

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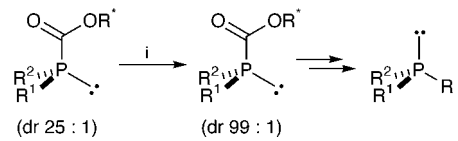
Heating (±)-6,8,14,17-tetrahydro-7*H*-[1,2,5]triazepino[3,2-*b*:7,1-*b*′]diquinazoline-14,17-dione 1 with (+)-CSA gives (−)-1 with >90% ee *via* a crystallisation-induced asymmetric transformation, the first non-racemic example of a C_2 symmetric bisheterocycle which is atropisomeric by virtue of retarded rotation around an N–N bond.

The efficacy of substituted 1,1′-binaphthyls as ligands for metals in catalytic asymmetric reactions has prompted interest in other aspects of atropisomerism: recently hindered aryl amides[2a] and novel binaphthyl ligands and analogues[2b] have been the focus of interest. One system which displays hindered rotation due largely to an electronic rather than steric barrier is the N–N bond of peracylhydrazines.[3] Atkinson *et al.*[4] have shown that the N–N bond in 3-diacylaminoquinazolin-4-ones is a chiral axis when the acyl groups are different and, by analogy, N–N linked biquinazolinones would be expected to display atropisomerism (axial chirality). However, although a range of 3,3′-biquinazoline-4,4′-diones have been prepared,[5] the issue of chirality was not addressed. A stereostable chiral axis in such compounds could lead to the design of novel ligands for metals in catalytic asymmetric reactions. Having verified the presence of chirality it was hoped that, rather than resolution of enantiomers, a deracemisation reaction (asymmetric transformation, AT)[1] could be developed. Vedejs and co-workers have obtained diastereomerically pure materials by AT at the stereogenic but stereolabile heteroatoms of chiral organoboron[6a] and organophosphorus[6b] compounds. Notably, Vedejs and Donde[6b] achieved crystallisation-induced AT at a stereogenic phosphorus utilising an alkoxycarbonylphosphine to both introduce a chiral auxiliary, and lower the barrier to inversion, allowing racemisation at around the melting point (Scheme 1). In the work described here a high barrier to rotation (racemisation) coexists with high crystallinity, and the electronic nature of the barrier is exploited, allowing it to be moderated *via* protonation.

2,2′-Bis(bromomethyl)-3,3′-biquinazoline-4,4′-dione **2** was prepared in two steps from **3**[5] in 58% yield *via* the unstable bisbromoacetate **4** (Scheme 2). The bromomethylene protons of **2** are observed as an AB system [δ 4.43, 4.32 (J 12.0 Hz)] indicating chirality (slow rotation around the N–N bond on the NMR time scale). VT NMR showed line broadening above 60 °C, however even at 135 °C free rotation was not observed around the N–N bond (non-coalescence) which indicates a *minimum* barrier to rotation in the order of 85 kJ mol^{-1}.



Scheme 1 *Conditions*: i, crystalline state, 50 °C, 22 h.

† See ref. 1.

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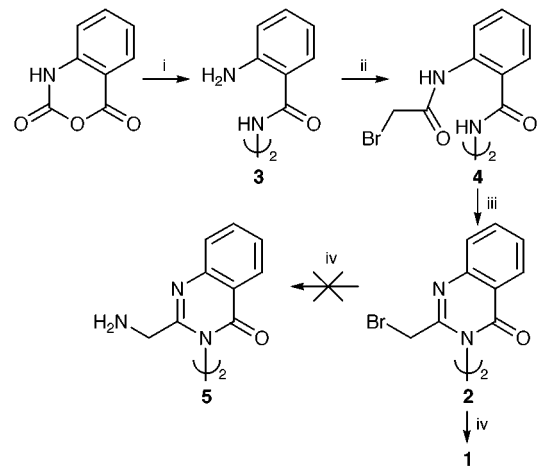
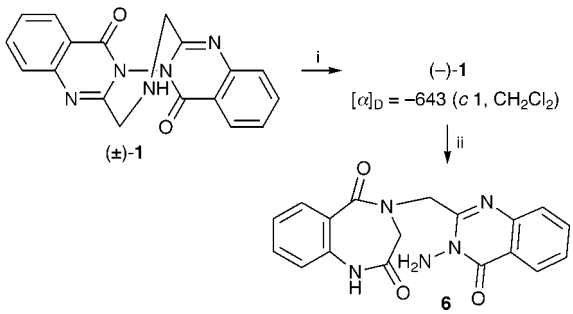
Treatment of a solution of **2** in THF with aqueous NH_3 gave 6,8,14,17-tetrahydro-7*H*-[1,2,5]triazepino[3,2-*b*:7,1-*b*′]diquinazoline-14,17-dione **1** [*m/z* 331 (100%)]§ in 74% yield; none of the anticipated diamine **5** was detected. In amine **1** the diastereotopic protons in each methylene unit [δ 4.00, 3.93 (J 13.2 Hz)] confirmed that rotation around the N–N bond was slow on the NMR time scale; again in VT NMR experiments coalescence was not observed at 135 °C, indicating a minimum barrier to rotation of 85 kJ mol^{-1}. No separation of ^{1}H NMR signals was observed in the presence of acetylmandelic acid[7] or tartaric acid. However, in the presence of 2 equiv. of (+)-CSA, two sets of AB pattens were observed [δ 4.89, 4.75, 4.70 and 4.68 (J 14.4 Hz for all signals)] equating to the two diastereoisomeric salts. To investigate possible AT, a sample of **1** and 2 equiv. of (+)-CSA was suspended in toluene and heated at reflux for 16 h, then evaporated and analysed by ^{1}H NMR. Astonishingly, only one set of diastereotopic protons was observed (δ 4.89, 4.70), along with decomposition products. Base washing gave **1** identical with authentic material which on treatment with CSA displayed only one set of methylene signals, implying that the sample was essentially a single enantiomer. To ascertain whether this phenomenon was due to selective decomposition or AT, optimisation experiments were undertaken in various solvents at a range of temperatures and concentrations. Optimum conditions were heating **1** at reflux with benzene containing (+)-CSA (2 equiv.) for 40 h, which gave an apparent diastereoisomer ratio of >10:1 (judged by NMR) with negligible decomposition. The recovered **1** after base washing accounted for 82% of the starting material, which is incompatible with a selective decomposition of one enantiomer, and had specific rotation $[\alpha]_D$ −643 (c 0.1, CH_2Cl_2) (Scheme 3), raised by a single recrystallisation to −688 (c 0.011, CH_2Cl_2), at which point (+)-CSA as an NMR shift



Scheme 2 *Reagents and conditions*: i, $H_2NNH_2{\cdot}H_2O$ (0.5 equiv.), EtOH, reflux, 16 h, 84%; ii, $BrCH_2COBr$, Et_3N, DMF, 0 °C; iii, TsOH (10 mol%), PhMe, reflux (Dean and Stark), 58% for 2 steps; iv, 35% aq. NH_3 (100 equiv.), THF, 74%.



Scheme 3 *Reagents and conditions*: i, (+)-CSA (2 equiv.), PhH (3.8 ml mol^{-1}), reflux, 40 h; ii, HBr, EtOH–H_2O or $CoSO_4$, EtOH–H_2O.

reagent indicated that the material was enantiopure (> 98% ee).

The use of a paucity of a 'poor' solvent is essential; a *solution* of **1** with 2 equiv. of CSA (1,2-dichloroethane) at 83 °C (*vs.* 80 °C for benzene) for 40 h gave only the racemic material and, on prolonged heating (72 h), decomposition. Two samples of **1** (0.1 mmol) plus 2 equiv. of CSA heated at reflux for 16 h in 10 ml (entirely dissolved) and 1 ml (two phase) of benzene gave diastereoisomer ratios 1 : 1 and 3 : 1, respectively. The use of higher temperatures was detrimental: 2 h at 135 °C led to complete decomposition. These data are indicative of a crystallisation induced AT [see ref. 1(*c*) for a full explanation of the principles involved] rather than the formation of a thermodynamically favourable salt. The racemisation process would appear to be acid catalysed: a solution of (−)-**1** and CSA showed appreciable racemisation (diastereoisomer ratio 4 : 1) after 1 week at room temperature, whereas a solution of the free base showed minimal racemisation after 14 days, and the rate of racemisation of **1** even at 110 °C was slow ($t_{1/2}$ > 24 h at 110 °C). The crystalline material retained its original ee during the same period. It is unlikely that protonation of the secondary amine will assist rotation around the N–N bond, thus it is proposed that protonation of the quinazolinone 1-(imine) nitrogens (hence the requirement for CSA, a strong acid) and the resultant amidinium ion resonance to N-3 reduces the barrier to rotation around the N–N bond. Attempts to grow crystals containing heavy atoms suitable for the determination of absolute configuration with HBr or aqueous $CoSO_4$ led not to the respective salt/complex but to the rearranged hydrolysis product **6** (Scheme 3) as determined by single crystal diffraction.¶ This facile hydrolysis is atypical of biquinazolinones.

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Notes and references

§ All new compounds were fully characterised. *Selected data* for **1**: mp 218.2–220.6 °C (decomp.) (EtOH); δ_H(300 MHz, $CDCl_3$) 8.38 (2H, dd, *J* 8.1, 1.2, 2 × H6), 7.91 (2H, ddd, *J* 8.1, 7.2, 1.5, 2 × H7), 7.81 (2H, dd, *J* 7.5, 1.5, 2 × H9), 7.63 (2H, ddd, *J* 8.1, 7.5, 1.2, 2 × H8), 4.08, 4.02 (4H, 2 × d, *J* 13.5, 2,2′-CH_2), 2.01 (br, NH). For **2**: mp 228.6 °C (EtOAc); δ_H(300 MHz, $CDCl_3$) 8.31 (2H, ddd, *J* 8.1, 1.5, 0.6, 2 × H6), 7.93 (4H, m, 2 × H7 + H8), 7.60 (2H, ddd, *J* 6.9, 1.5, 1.2, 2 × H9), 4.43 (2H, d, *J* 12.0, 2 × H2′), 4.32 (H, d, *J* 12.0, 2 × H2″).

¶ *Crystal data* for **6**: $C_{18}H_{15}N_5O_3$, *M* = 349.35, triclinic, Space group $P\bar{1}$, μ = 0.101 mm^{-1}, *R*1 = 0.2872, *wR*2 = 0.1412, *a* = 4.684(4), *b* = 13.470(5), *c* = 13.786(6) Å, α = 73.144(10), β = 78.90(2), γ = 88.302(10)°, *V* = 816.6(8) $Å^3$, *T* = 293(2) K, *Z* = 2, reflections collected/unique 2307/2201 [*R*(int) = 0.0696]. CCDC 182/1375. See http://www.rsc.org/suppdata/cc/1999/1991/ for crystallographic data in .cif format.

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