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Synthesis, resolution and structure of axially chiral atropisomeric *N*-arylimides

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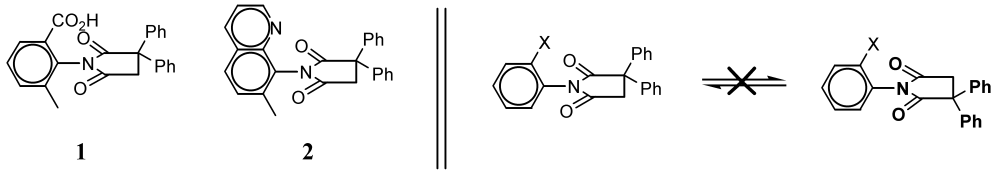
Abstract

Reported is the synthesis and structures of a new series of axially chiral molecules based on restricted rotation. The *ortho*-substituted *N*-arylimides have enantiomeric atropisomers that are stable and separable at room temperature. The compounds are notable for their ease of synthesis as well as positioning of functionality (a carboxylic acid and an amine) in a highly asymmetric configuration. © 2000 Published by Elsevier Science Ltd.

Keywords: atropisomers; resolution; X-ray crystal structures.

Molecules with axial chirality are among the most proficient in effecting enantioselective differentiation. The most common examples are the chiral biphenyls and binaphthyls that are ubiquitous components in asymmetric catalysts, resolving agents and chiral auxiliaries.[1] Despite their utility, the synthesis of new chiral biaryls remains challenging due to the difficulties in forming the C_{aryl}–C_{aryl} bond.[2] Therefore, we have set out to develop the synthesis of a new class of axially chiral molecules that retain the enantioselective properties of the biaryls but have greater accessibility and variability in their structures. Our efforts have focused on *ortho*-substituted chiral arylimides in which restricted rotation leads to the formation of two stable enantiomeric atropisomers. The *ortho*-aryl substituent is easily varied and creates a highly asymmetric environment as exemplified by carboxylic acid **1** and quinoline **2**.



1 **2**

Restricted rotation in *N*-arylimides has long been recognized,[3] however, only recently has the utility of the resulting atropisomers been demonstrated. These have included applications in

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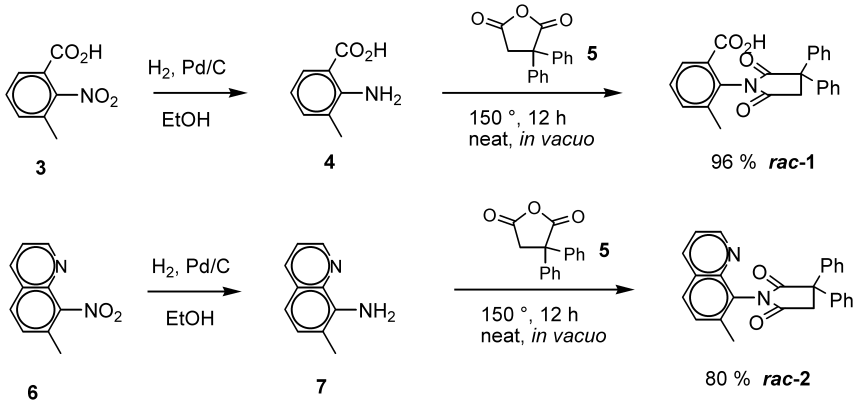
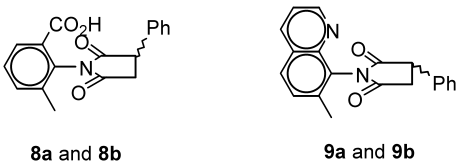
molecular recognition,[4] stereoselective reactions,[5] and as enzyme mimics.[6] For the most part, these applications have centered on the chemistry of the imide portions of the molecules, in particular as dieneophiles or electrophiles.[5,6] Our strategy is to focus instead on the *ortho*-substituent on the aryl ring as a handle for applications as resolving agents, transition metal catalysts, and NMR shift reagents.[7]

The most attractive attribute of the new chiral compounds is the ease with which they can be synthesized. The central C_{aryl}–N_{imide} bond is efficiently formed by simply heating an *ortho*-substituted aniline with a cyclic anhydride neat in vacuo at 150°C.[5a,8] To generate enantiomeric atropisomers an unsymmetrical anhydride is required in which there are two different types of carbonyls. Diphenyl succinic anhydride **5** was selected because the phenyl groups project out of the plane of the imide ring and block one face of the *ortho*-substituent.[9] Molecular modeling suggested that a single *ortho*-substituent would be insufficient to inhibit rotation about the C_{aryl}–N_{imide} bond at ambient temperatures.[10] Therefore, a second *ortho*-substituent (–Me) was inserted as a blocking group. The resulting anilines **4** and **7** were readily synthesized from their corresponding nitro arenes (Scheme 1). Condensations with succinic anhydride **5** cleanly yielded the desired aryl imides **1** and **2**.



Scheme 1.

The rotational barriers for **1** and **2** were determined indirectly by study of their monophenyl analogs **8** and **9**. Restricted rotation was immediately evident by the observation of two diastereomeric rotamers (phenyl up and phenyl down) that were stable and separable at room temperature. Equilibration experiments revealed a rotational barrier for carboxylic acid **8** of 28.0 kcal/mol ($t_{1/2}$ = 40 h at 60°C).[11] The quinoline succinimide **9** was considerably more stable with a barrier of 33.2 kcal/mol ($t_{1/2}$ = 190 h at 106°C). Molecular modeling gave the same ordering of rotational barriers; however, the absolute magnitudes were ~12% lower at 25 and 29 kcal/mol, respectively.[12]



The three-dimensional structures of the axially chiral acid and amines **1** and **2** were established by X-ray crystallography (see Fig. 1).[13] The crystals containing both enantiomers were obtained by recrystallization of the racemates. The molecular structures are almost identical to those calculated by molecular modeling. The cyclic imide and aryl planes are nearly perpendicular (85.4° for **1** and 71.9° for **2**), placing the carboxylic acid and quinoline amine in the desired chirally enshrouded environment. Approach from one face of the functionality is hindered by the steric bulk of the 3,3-diphenyl groups.

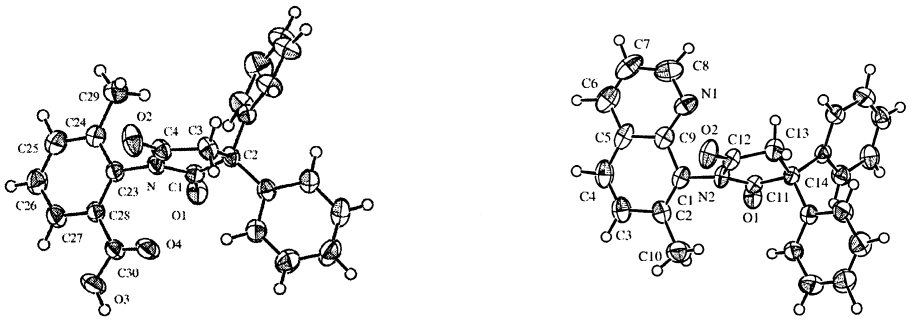
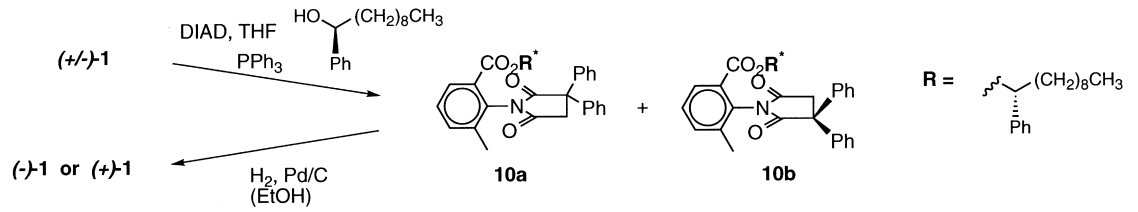


Figure 1.

Resolution of the enantiomeric conformations was achieved in the case of the acid **1** by esterification with (*S*)-1-phenyldecanol (Scheme 2). The reaction of the highly hindered acid **1** was done under Mitsunobu conditions that proceeds with absolute inversion of stereochemistry.[14] The resulting diastereomeric esters were separable by flash chromatography. Subsequent removal of the chiral auxiliary under mild hydrogenolysis conditions afforded the partially resolved acids **10a** and **10b** (ee $>95\%$). Complete resolution was achieved by recrystallization of the partially resolved acids in acetone to yield pure crystals of the predominant enantiomer.[15] The quinoline arylimide **2** has not been resolved in large scale. However, analytical chiral chromatography (Covalent Pirkle HPLC column) clearly shows the presence of both isomers.[16]



We are currently exploring applications that utilize the chiral environments in carboxylic acid **1** and quinoline **2**. For example, carboxylic acid **1** is an excellent NMR shift reagent for α-methylbenzyl amine. We have also synthesized axially chiral *N*-arylimides with higher rotational barriers. For example, replacement of the *ortho*-methyl substituent with a *t*-butyl group lead to extremely stable atropisomers ($\Delta E_a > 35$ kcal/mol).

References

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10. The barriers of rotation were calculated using MM2 as implemented in the software program MacroModel v5.5 (Mohamadi, F.; Richards, N. G. J.; Cuida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440–467). The rotational barrier varied greatly with the step angle of the dihedral driver. Accurate values were attained only for small step angles $< 1^\circ$. Larger step angles would jump over the barrier and predict considerably smaller rotational barriers.
11. Calculated from the Arrhenius equation assuming an ideal value of $A = 2.08 \times 10^{10}$.
12. The discrepancy may be due to the severe distortions in the transition state that lead to significant ΔS contributions to the observed rotational barrier that are not accounted for in the molecular modeling forcefields.
13. Crystal data for acid **1**: space group = $P2_1/c$, $a = 7.6765(7)$ Å, $b = 19.431(3)$ Å, $c = 13.378(1)$ Å, $\alpha = 90.00(0)^\circ$, $\beta = 97.879(8)^\circ$, $\gamma = 90.00(0)^\circ$, $Z = 4$, 2920 reflections, $R = 0.034$. Crystal data for amine **2**: space group = $P2_1/n$, $a = 8.667(2)$ Å, $b = 9.316(3)$ Å, $c = 24.669(4)$ Å, $\alpha = 90.00(0)^\circ$, $\beta = 93.48(2)^\circ$, $\gamma = 90.00(0)^\circ$, $Z = 4$, 3402 reflections, $R = 0.04395$. Crystallographic data for the structural analysis has been deposited with the Cambridge Crystallographic Data Center, CCDC No. CCDC 139122 for **1** and CCDC 139123 for **2**. Copies of this information may be obtained free of charge. www:http://www.ccdc.cam.ac.uk.
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15. Characterization data for (+)-**1** and (–)-**1**: ^{1}H NMR (300 MHz, acetone-d_6) δ 8.04 (d, 1H, $J = 6.43$ Hz), 7.5–7.2 (m, 12H), 3.74 (d, 1H, $J = 18.19$ Hz), 3.45 (d, 1H, $J = 18.24$ Hz), 1.90 (s, 3H); IR (KBr) 3056, 1781, 1714, 1591, 1474, 1442 cm^{-1}; found (HRMS, FAB) m/z 385.1308; calcd for $C_{24}H_{19}NO_4$: 385.1314; mp 225–228°C, $[\alpha]_D^{25} = -26.0$ (c 1.350, 1:1 CH_2Cl_2/MeOH).
16. Compound (+/–)-**2** ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.67 (dd, 1H, $J = 1.65$ Hz and 4.23 Hz), δ 8.11 (d, 1H, $J = 1.63$ Hz), 7.80 (d, 1H, $J = 8.46$ Hz), 7.54–7.24 (m, 12H), 3.86 (d, 1H, $J = 19.4$ Hz); 3.74 (d, 1H, $J = 18.28$ Hz), 2.23 (s, 3H); found (HRMS, FAB): m/z 392.1521; calcd for $C_{26}H_{20}N_2O_2$: 392.1525. IR 3059, 2924, 2924, 1714, 1398, 1208 cm^{-1}. Mp 194°C.