Atropisomeric and atropdiastereoisomeric 2-substituted 1-aryl-3,5-diphenylpyrroles

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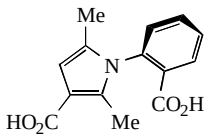
(3,5-Diphenyl-1-*o*-tolyl-1*H*-pyrrol-2-yl)phenylmethanone **3a** and (1-naphthalen-1-yl-3,5-diphenyl-1*H*-pyrrol-2-yl)phenylmethanone **4a** are atropisomeric and their LAH reductions afford mixtures of atropdiastereoisomeric (3,5-diphenyl-1-*o*-tolyl-1*H*-pyrrol-2-yl)-phenylmethanoles **3b**,**c** and (1-naphthalen-1-yl-3,5-diphenyl-1*H*-pyrrol-2-yl)phenylmethanoles **4b**,**c**, respectively.

While the atropisomerism caused by restricted rotation around various C–C bonds in biaryls[1] as well as around C–N bonds in heterobiaryls and related heterocycles[2] is well documented by many examples, the axial chirality of 1-arylpyrrole derivatives has been observed rarely. Thus, racemic 1-(2-carboxyphenyl)-2,5-dimethyl-1*H*-pyrrole-3-carboxylic acid **1** was resolved[3] in the pioneering studies by Adams and coworkers on possible atropisomeric Knorr pyrroles.[3,4] Many years later, 1-aryl-2,5-dimethylpyrrole-3-carbaldehydes **2** (R = Me, CN, OMe and OCH_2Ph)[5] have been proven to exhibit axial chirality. We report that (3,5-diphenyl-1-*o*-tolyl-1*H*-pyrrol-2-yl)phenylmethanone **3a** and (1-naphthalen-1-yl-3,5-diphenyl-1*H*-pyrrol-2-yl)phenyl-methanone **4a**, which can be easily prepared by extended Decker oxidation[6] of corresponding quaternary pyridinium salts,† are also atropisomeric although substituents in their five-membered pyrrole rings may be expected to cause a less hindrance to rotation about the C–N bonds. Indeed, the molecular geometry optimisation for various fixed torsion angles ϕ by the semi-empirical PM3 method[7] predicts the corresponding rotation barriers to be 22.3–27.2 kcal mol^{-1} suggesting possible detection of appropriate atropisomers. Hence, ^{1}H NMR spectra of ketones **3a** and **4a** have been investigated both in the absence and in the presence of the chiral shift reagent Eu(hfc)$_3$ which caused a typical 1:1 splitting of certain proton signals indicating the racemic character of both of the substrates in C_6D_6 solutions. For example, two separated 4-H proton and methyl signals clearly indicate this behaviour.‡

Similarly, as in a series of axially chiral imidazo[1,2-*a*]pyridinoic ketones,[8] and one 3-chlorobenzoyl derivative of polysubstituted 4-(thien-2-yl)-4*H*-1,2,4-triazoles,[9] the atroposelective reductions of compounds **3a** and **4a** to corresponding secondary alcohols also gave atropdiastereoisomeric products§ due to a restricted rotation around C(sp^2)–N(sp^2) bonds. Thus, LAH with **3a** in diethyl ether at –30 to –25 °C afforded a 7:3 mixture of two (3,5-diphenyl-1-*o*-tolyl-1*H*-pyrrol-2-yl)phenylmethanols **3b**,**c** while the same procedure with **4a** led analogously to



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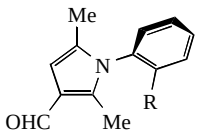

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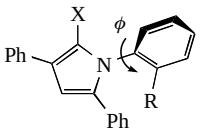

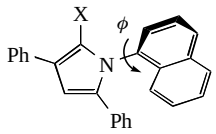

3a X = PhCO, R = Me
3b,**c** X = PhC*H(OH), R = Me
3d X = PhCO, R = H

4a X = PhCO
4b,**c** X = PhC*H(OH)

atropdiastereoisomeric (1-naphthalen-1-yl-3,5-diphenyl-1*H*-pyrrol-2-yl)phenylmethanols **4b**,**c** in the ratio 8:7.¶ Pure major atropdiastereoisomers **3b** and **4b** can be separated from the mixtures with their minor counterparts **3c** and **4c** using preparative TLC and/or crystallisation. The atropdiastereoisomers **3b**,**c** and **4b**,**c** seem to be quite stable at room and somewhat elevated temperatures both in the solid state and in various solutions. As

† Details of the preparative procedures will be published elsewhere. IR spectra were taken on 'Nicolet 704' FTIR spectrometer; NMR spectra were recorded on Varian Gemini 300, Bruker AMX 400 and DRX 500 Avance instruments at 298 K.

For **3a**: mp 162–163 °C, yield 83%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.69 (s, 3H, *o*-Me), 6.66 (s, 1H, 4-H), 7.00–7.38 (m, 17H, aromatic), 7.60 (d, 2H, *o*-5-Ph). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.39 (*o*-Me), 111.47 (4-CH), 126.76 (CH), 127.09 (CH), 128.21 (CH), 128.27 (2CH), 128.51 (CH), 128.84 (2CH), 129.04 (2CH), 129.16 (2CH), 129.98 (2CH), 130.21 (CH), 130.65 (CH), 131.16 (CH), 132.35 (CH), 132.55 (CH), 133.65 (C), 135.96 (2C), 136.91 (C), 138.94 (C), 139.17 (C), 140.10 (C), 188.33 (CO). IR ($CHCl_3$, ν_{max}/cm^{-1}): 1629 (C=O).

For **4a**: mp 156–158 °C, yield 93%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.76 (s, H, 4-H), 7.84 (m, 22H, aromatic). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 111.73 (4-CH), 123.37 (CH), 125.57 (CH), 126.92 (CH), 127.22 (CH), 127.82 (CH), 128.09 (CH), 128.20 (2CH), 128.28 (CH), 128.59 (2CH), 128.73 (2CH), 128.90 (CH), 129.05 (2CH), 129.49 (CH), 130.06 (2CH), 130.55 (2CH), 131.98 (C), 132.20 (C), 132.49 (CH), 134.46 (C), 135.95 (2C), 136.46 (C), 139.13 (C), 141.47 (C), 188.37 (CO). IR ($CHCl_3$, ν_{max}/cm^{-1}): 1629 (C=O).

‡ ^{1}H NMR δ [400 MHz, C_6D_6, Eu(hfc)$_3$ 1:10 molar ratio] for **3a**: 2.05 (s, 3H, *o*-Me, first enantiomer), 2.06 (s, 3H, *o*-Me, second enantiomer), 7.04 (s, 1H, 4-H, first enantiomer), 7.06 (s, 1H, 4-H, second enantiomer); for **4a**: 6.90 (s, 1H, 4-H, first enantiomer), 6.92 (s, 1H, 4-H, second enantiomer).

§ All reactions were monitored by HPLC using an Ecom LCP 4000 pump with an UV-VIS detector on Macherey Nagel C-18 guard and common C-18 Nagel columns, eluent MeOH–H_2O 4:1. Preparative TLC was performed on 20×20 cm plates of Aldrich TLC high purity grade silica gel (15 g) with a gypsum binder and a fluorescent indicator; eluent PE–DCM 5:1. All products gave satisfactory elemental analyses.

¶ Atropdiastereoisomeric mixture of **3b** and **3c**: HPLC (MeOH–H_2O 7:3, two peaks 111.6 and 121.5 min), mp 129–130 °C, yield 89%. ^{1}H NMR (300 MHz, [$^2H_6$]DMSO) δ: 1.14 (s, 3H, *o*-Me), 1.82 (s, 3H, *o*-Me), 5.70 (s, 1H, H-6 ?), 5.93 (d, OH-6 and H-6 ?), 6.59 (s, 1H, 4-H), 6.70–7.78 (m, aromatic). IR (KBr, ν_{max}/cm^{-1}): 3526 (OH).

Major atropdiastereoisomer **3b**: HPLC (MeOH–H_2O 7:3, one peak 111.6 min); mp 133–137 °C (diethyl ether–heptane). ^{1}H NMR (300 MHz, [$^2H_6$]DMSO) δ: 1.14 (s, 3H, Me-7′), 5.93 (m, 2H, OH-6 and H-6), 6.57 (s, 1H, H-4), 6.70–7.76 (m, 19H, aromatic). ^{13}C NMR (75.4 MHz, [$^2H_6$]DMSO) δ: 16.88 (Me, C-7′), 65.91 (CH, C-6), 109.07 (CH, C-4), 124.53 (C), 125.10 (2CH), 125.62 (2CH), 125.95 (CH), 126.03 (CH), 126.40 (CH), 127.03 (2CH), 127.20 (2CH), 128.17 (2CH), 128.42 (2CH), 128.80 (2CH), 129.90 (CH), 131.31 (CH), 132.90 (C), 133.35 (C), 134.43 (C), 136.37 (2C), 137.59 (C), 142.85 (C).

Atropdiastereoisomeric mixture of **4b** and **4c**: HPLC (MeOH–H_2O 4:1 or 7:3, a single broad peak 26.3 or 160.9 min, respectively), mp 165–171 °C, yield 94%. ^{1}H NMR (300 MHz, [$^2H_6$]DMSO) 5.73 (d, 1H, OH-6), 5.86 (dd, 2H, H-6 and H′-6), 5.93 (d, 1H, OH-6), 6.69 (s, 1H, H-4), 6.74 (s, 1H, H-4), 6.44–7.96 (m, 22H, aromatic). IR (ν_{max}/cm^{-1}): 3545 (OH).

Major atropdiastereoisomer **4b**: HPLC (MeOH–H_2O 7:3, one peak 160.2 min), mp 174–178 °C. ^{1}H NMR (300 MHz, [$^2H_6$]DMSO) δ: 5.86 (d, 1H, H-6, *J* 3.8 Hz), 5.93 (d, 1H, OH-6, *J* 3.8 Hz), 6.69 (s, 1H, H-4), 6.44–7.96 (m, 22H, aromatic). ^{13}C NMR (75.4 MHz, [$^2H_6$]DMSO) δ: 65.88 (CH, C-6), 109.39 (CH, C-4), 123.18 (CH), 124.70 (CH), 124.77 (CH), 124.96 (CH), 125.75 (CH), 126.12 (CH), 126.19 (CH), 126.44 (CH), 126.54 (CH), 127.17 (CH), 127.44 (CH), 128.03 (CH), 128.44 (CH), 128.86 (CH), 129.05 (CH), 130.78 (C), 132.97 (C), 133.13 (C), 134.92 (C), 135.23 (C), 135.63 (C), 136.32 (C), 142.17 (C). IR (ν_{max}/cm^{-1}): 3545.

expected, the presence of the methyl group in the molecules of **3a**–**c** should be a necessary condition for the axial chirality behaviour. In fact, the formerly reported[10] 1-phenyl derivative **3d** is not atropisomeric under the same conditions. Quantum-chemical calculations and experiments with other **3a**-like ketones as well as an extended study on the stereochemistry of **3b**- and **3c**-like alcohols are in progress.

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