Non-photochemical rearrangements of *o*-nitrobenzyl compounds

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Received (in Cambridge, UK) 11th June 1999, Accepted 12th August 1999

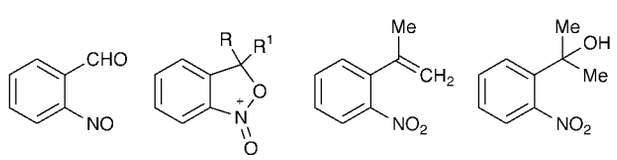
Three rearrangements of 2-nitrobenzyl compounds with increasingly complex structural changes are described. The first is a remarkably facile conversion of 2-nitrobenzyl triflate to 2-nitrosobenzaldehyde. The second is an unexpected formation of 1-acetyl-2,1-benzisoxazolone **7** during attempted preparation of the *tert*-butyl ester of *O*-acetyl 2-nitromandelic acid. The third, found in the reaction of 2-nitrobenzaldehyde cyanohydrin TMS ether **10** with cyclic secondary amines, results in oxidative cyanation of the position alpha to the amino group, giving the novel *N*-arylamino-α-cyanoamines **12a**–**e**.

Introduction

Photochemical rearrangements and fragmentations of *o*-nitrobenzyl compounds have been of interest since the discovery in 1901 of the photochemically-induced internal redox reaction of 2-nitrobenzaldehyde to yield 2-nitrosobenzoic acid.[1] However, *o*-nitrobenzyl compounds also undergo numerous rearrangement and intramolecular condensation reactions under non-photochemical conditions to generate a wide range of products, including various heterocycles. These were reviewed in 1972[2] and new examples continue to appear.[3] Our interest in the chemistry of *o*-nitrobenzyl compounds stems from their use as photolabile derivatives of bioeffectors. These protected compounds enable rapid release of biologically-active compounds at or near their site of action by flash photolysis with near-UV light.[4] During investigations of synthetic routes to new types of such photolabile precursors, we have encountered three different rearrangements of *o*-nitrobenzyl derivatives, with increasingly deep-seated structural changes and these results are reported here.

Results and discussion

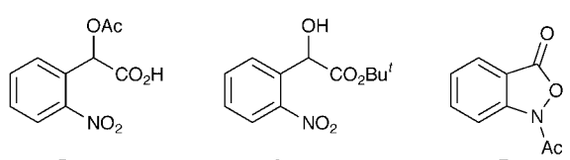
The first rearrangement occurred during an attempt to prepare 2-nitrobenzyl triflate, under conditions similar to those previously used for the synthesis of benzyl triflate itself.[5] Treatment of a mixture of 2-nitrobenzyl alcohol and 2,6-di-*tert*-butylpyridine with triflic anhydride at −30 °C in dichloromethane gave 2-nitrosobenzaldehyde **1**. The same product has recently



1 **2a** R, R^1 = H **3** **4**
2b R = H, R^1 = Me
2c R, R^1 = Me

been identified, together with 2-nitrobenzyl alcohol, from the solvolysis of 2-nitrobenzyl tosylate in aqueous acetonitrile.[6a] In the present case there can be little solvolytic assistance and rearrangement must be driven by the leaving group potential of the triflate anion. The formation of the rearrangement product **1** implies involvement of the cyclic intermediate **2a**, although the alcohol product formed during solvolysis of the tosylate could in principle arise without participation of the nitro group. It is evident from literature data and our own results that **2a** and similar intermediates can produce different products, depending upon the conditions of reaction and work up. For example, under more vigorous conditions (triflic acid at 90 °C) **2a** is converted to 4-amino-3-carboxyphenyl trifluoromethanesulfonate.[6b] 2-Nitrostyrene rearranges *via* intermediate **2b** to give 2-nitrosoacetophenone upon treatment with cold concentrated sulfuric acid[7a] and a comparable rearrangement of 2-cyclopropylnitrobenzene has been observed in triflic acid at low temperature.[7b] 2-Nitro-α-methylstyrene **3** forms stable salts of **2c** upon treatment with hydrogen chloride and $AgBF_4$ or $AgSbF_6$. These salts of **2c** are reported to revert to the starting olefin upon exposure to water or alcohols.[8] We confirmed that the starting olefin is recovered when 2-nitro-α-methylstyrene is treated with concentrated sulfuric acid, followed by aqueous quench. However, when the same reaction mixture was worked up by slow addition to aq. NaOH, ensuring that the aqueous mixture remained alkaline throughout, the tertiary alcohol **4** was obtained instead. Whether the alcohol oxygen of **4** derives from the nitro group or from the solvent is an interesting mechanistic point but we have not investigated this.

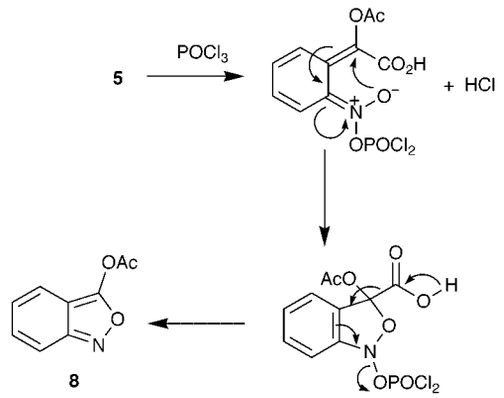
The second rearrangement was encountered during attempted preparation of *tert*-butyl 2-nitromandelate† **6** by



5 **6** **7**

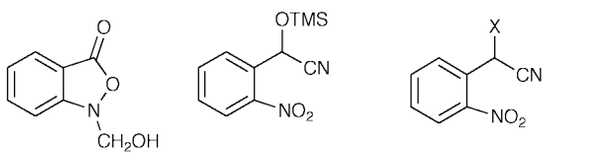
esterification of the acid **5** under conditions (*t*-BuOH–pyridine–$POCl_3$) previously applied to *O*-acetylmandelic acid.[9] Instead of the expected ester we obtained *N*-acetylbenzisoxazolone **7** in 72% yield. The ester **6** was subsequently prepared from **5** under conventional conditions (isobutylene–conc. H_2SO_4) and has also been prepared by esterification of **5** with *tert*-butyl trichloroacetimidate.[10] Formation of **7** from **5** requires both loss of CO_2 and migration of the acetyl group. The former can be rationalised as shown in Scheme 1 but the initial product would be the isomeric *O*-acetate **8**. However comparison with an authentic sample[11] confirmed that the isolated product was indeed **7**. We presume transfer of the acetyl group to the nitrogen to be intermolecular, probably mediated by pyridine present in the reaction mixture. The efficient intermolecular migration of the acetyl group, leading to the more

† IUPAC name for mandelic acid is phenylglycolic acid.



Scheme 1

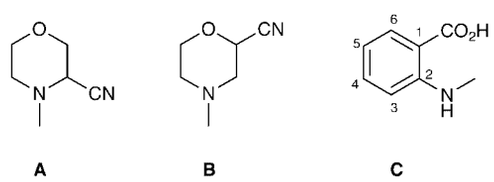
stable benzenoid isomer, has some precedent in this heterocyclic system in the related loss and reattachment of formaldehyde during the formation of **9** from 2-nitrostyrene oxide under acidic catalysis.[12]



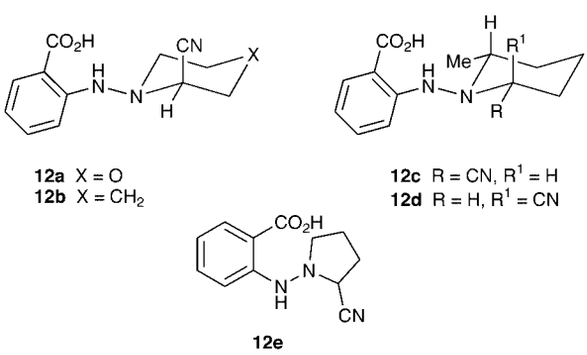
The third and most complex rearrangement was encountered when morpholine was allowed to react with **10**, the cyanohydrin TMS ether of 2-nitrobenzaldehyde, in order to obtain the α-aminonitrile **11a**. The reaction has been described for a range of cyanohydrin TMS ethers of aromatic aldehydes and generally proceeds in excellent yield.[13] In our case, **11a** was formed in modest yield but was accompanied by an additional, highly crystalline product. Elemental analysis and mass spectrometry established the molecular formula as $C_{12}H_{13}N_3O_3$, isomeric with **11a**. The IR spectrum showed the presence of a carbonyl group (1670 cm^{-1}) and this band, together with broad absorption in the range 2500–3300 cm^{-1}, suggested the presence of a carboxylic acid. Characteristic IR absorption bands of a nitro group were absent and the UV spectrum, with a band at 321 nm, was different from the typical spectrum (λ_{max} ~260 nm) of a 2-nitrobenzyl compound. The ^1H NMR spectrum in methanol-d_4 showed signals for 11 protons, while 13 protons were observed in DMSO-d_6. The two additional signals at 8.67 and 12.90 ppm were therefore from exchangeable protons and the broad signal at δ 12.90 was consistent with a carboxylic acid. Spectral dispersion was much better in DMSO-d_6 than in methanol-d_4 and all further spectra for the structure determination were run in the former solvent. Initial groups of spin systems were identified from 1-dimensional ^1H and ^{13}C NMR spectra, a 2-dimensional ^1H–^{13}C HSQC spectrum and several 1-dimensional DPFGSE-TOCSY spectra. Full details of chemical shifts and spectroscopic acquisition parameters are given in the Experimental section. Only those signals relevant to the structural determination are discussed here.

The presence of an *ortho*-disubstituted aromatic ring was expected from the structure of the starting material and was readily confirmed from the spectra. A ^{13}C resonance at δ 169.3 was consistent with the carboxy group already inferred. A further resonance at δ 116.4 from a carbon not directly bonded to hydrogen was assigned to a cyano group[14] and a weak band in the IR spectrum at 2230 cm^{-1} supports this. The ^1H NMR spectrum in the range 2.9–4.3 ppm showed signals for seven protons that were correlated in the HSQC spectrum with four carbons in the range 51.7–67.3 ppm and assigned as one methine and three methylene groups. 1-Dimensional DPFGSE-TOCSY spectra with increasing mixing times were measured from the methine signal at 4.29 ppm. Magnetisation was transferred from this proton to an adjacent methylene group with signals at 3.85 and 3.98 ppm but no further transfer was observed. A second set of DPFGSE-TOCSY spectra were recorded from the proton at 3.67 ppm and showed coupling to one geminal proton and to an adjacent pair of methylene protons. Again, there was no further transfer of magnetisation and thus two structural fragments must be present, CHX–CH_2 and CH_2–CH_2, each isolated from other protons. Since one starting material was morpholine, the data could reasonably be accommodated if one of the hydrogens on the original morpholine ring had been replaced by another substituent.

Further structural details were deduced from long range proton–carbon couplings, obtained from a 2-dimensional ^1H–^{13}C HMBC spectrum. The carbon of the cyano group identified above showed 2- and 3-bond couplings respectively to the methine and methylene protons of the CHX–CH_2 unit and this part of the molecule was provisionally assigned as substructure **A** or **B**. Other structural fragments already identified



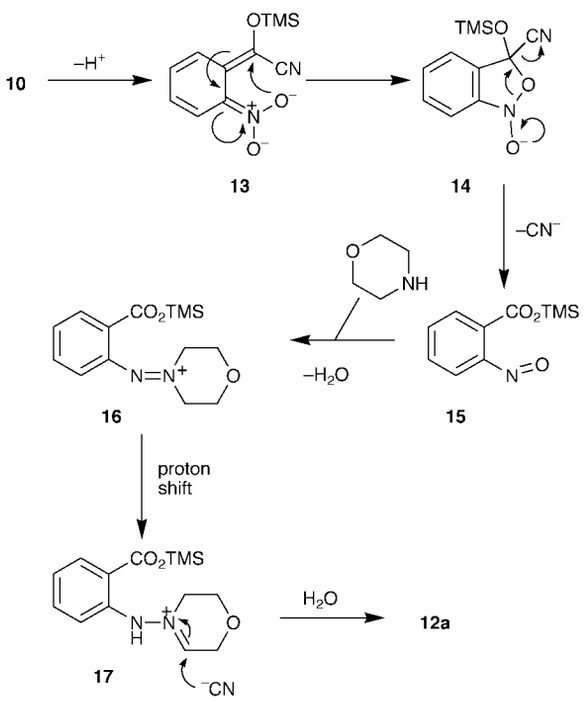
were the *ortho*-disubstituted aromatic ring and a carboxylic acid group, leaving only a nitrogen and hydrogen atom for which to account. In the HMBC spectrum, the exchangeable proton at δ 8.67 was coupled to the carbons at 111.1, 113.3 and 149.1 ppm, of which the first and third were the substituted carbons of the aromatic ring. The most likely formulation was therefore with the "missing" atoms as a secondary amino substituent *ortho* to the carboxy group, giving substructure **C**. The carbon at 111.1 ppm corresponds to C-3 of this substructure. Chemical shift data[15] for anthranilic acid in DMSO-d_6 support the proposed substructure, with the 149.1 ppm signal being from C-2. These partial structures can be connected to give a full structure **12a** or its isomer with the cyano group adjacent to



the oxygen of the morpholine ring. Assignment of **12a** as the correct structure was indicated by the ^{13}C chemical shifts in the morpholine ring, consistent with two methylene groups adjacent to oxygen (66.3 and 67.3 ppm). Final confirmation was given by the HMBC spectrum, in which important features were couplings from the exchangeable N–H proton to the methine carbon of the morpholine and to one of the methylene carbons (51.7 ppm) of the intact CH_2–CH_2 system in the morpholine ring. The ^{13}C chemical shift of this carbon is consistent with it being adjacent to the morpholine nitrogen atom. The lack of long range coupling to either of the other

methylene carbons indicates that they are distant from the N–H proton and by implication that the substituent on the morpholine must be adjacent to the nitrogen, as shown in **12a**. The vicinal coupling constants of 2.5 and 2.8 Hz for the methine proton show that the cyano group is axial and a final set of DPFGSE-NOE spectra were compatible with the deduced structure. Further discussion of the preferred conformation of these compounds is given below.

A mechanism to account for formation of **12a** is shown in Scheme 2, in which the reaction is initiated by base-catalysed



Scheme 2

deprotonation at the benzylic position. Unusually high acidity of the benzylic proton of **10** is expected from the combined effects of the α-cyano and *o*-nitro groups and leads to formation of the intermediate **13**, shown as the resonance-stabilised *aci*-nitro anion. Related *aci*-nitro anions generated photochemically from 2-nitrobenzyl compounds are known to convert to bicyclic species analogous to **14**, leading ultimately to transfer of one of the oxygens of the original nitro group to the benzylic carbon.[16] Numerous similar transformations are known among non-photochemical rearrangements of 2-nitrobenzyl compounds.[2,3] Expulsion of cyanide from **14** to generate the nitroso compound **15** appears to be necessary in order to generate free cyanide ion for its eventual incorporation into the morpholine ring (see below), and is analogous to the reversibility of cyanohydrin formation. Activation of the α-position of the morpholine ring can be realised by initial condensation of the released nitroso compound **15** with morpholine to give diazenium ion **16**, which then undergoes a prototropic shift to form the hydrazonium salt **17**. Electrophilic addition of the cyanide ion to the sp^2 iminium carbon of **17** then forms the final product, with an assumption that the TMS ester generated in the course of the rearrangement undergoes hydrolysis during aqueous work up.

There is some precedent for these proposals, firstly in the numerous oxidative conversions of secondary and tertiary amines to α-cyanoamines. Examples for secondary amines include oxidation by phenylseleninic acid or its anhydride,[17a] alkaline persulfate[17b] or hydrogen peroxide–sodium tungstate.[17c] The last of these reactions proceeds *via* an intermediate nitrone and leads to *N*-hydroxy-α-cyanoamines. Conditions reported for tertiary amines include DDQ,[17d] chlorine dioxide,[17e] anodic oxidation[17f] and the Polonovski reaction of the derived *N*-oxides.[17g] Thus the nitroso group of the putative intermediate **15** can be regarded as yet another oxidant. Reactions of aliphatic amines with aromatic nitroso compounds, as is required in the present case, have been investigated by several groups with variable results. However it is clear that, under mild conditions, primary amines undergo simple condensation to afford phenylazoalkanes.[18] Corresponding data for secondary amines are almost non-existent, but oxidation of dimethyl- and diethylamines to the corresponding imines has been proposed as an initial step upon treatment with nitrosobenzene, although a specific mechanism was not discussed.[18] It is possible that the reaction observed in our case is promoted by the potential for conjugation of the aromatic amino group with the adjacent carbonyl group. This effect could be expected to favour the prototropic rearrangement **16**→**17** and to stabilise **17** until its capture by cyanide.

We have examined the reactivity of a few other secondary amines in this reaction. Piperidine gave analogous "normal" and rearrangement products **11b** and **12b** respectively. 2-Methylpiperidine was also used to determine the regiochemistry of iminium ion formation, *i.e.* whether the intermediate analogous to **17** (Scheme 2) would be formed towards or away from the 2-methyl substituent. In previous oxidative cyanations of 2-methylpiperidine, products of either regiochemistry have been reported. Phenylseleninic acid gave 2-cyano-6-methylpiperidine[17a] of undefined stereochemistry (*cf.* results below), while H_2O_2–tungstate oxidation gave 1-hydroxy-2-cyano-2-methylpiperidine.[17c] From our reaction with 2-methylpiperidine we isolated three products, of which the "normal" product **11c** was obtained in very low yield as a mixture of diastereoisomers (85:15). The polar material contained two principal components that were separated in approximately equal yields by chromatography and identified as the 2-cyano-6-methyl epimers **12c** and **12d**. Identification was straightforward from the NMR spectra, that showed a methyl doublet for each, with a methine proton as a triplet (J ~3 Hz) for the *trans*-compound **12d** (CN axial) and a doublet of doublets (J 12.0 and 2.7 Hz) for the *cis*-compound **12c** (CN equatorial). The formation of the two epimers in approximately equal proportions was surprising and evidently represents a kinetic product ratio. Exposure of either epimer to further treatment with 2-methylpiperidine in boiling methanol established an equilibrium of approx. 4:1 in favour of the axial epimer **12d**.

Stereoelectronic effects strongly favour the axial conformation in 2-cyanopiperidine but ring inversion, which implies an equatorial conformation, is rapid at room temperature.[19] The energy barrier to interconversion must be somewhat larger in the present series of compounds. For NMR spectra at ambient temperature, the morpholine derivative **12a** shows no conformational interchange, since the spectrum has sharp lines with well-defined coupling constants consistent with a non-inverting chair conformation. In the piperidine compound **12b**, all the lines of the alicyclic protons are broad, consistent with the ring being in intermediate exchange. By contrast the line shapes of the aromatic protons are comparable to those for compound **12a**. Finally, the two methyl-substituted compounds **12c** and **12d** show sharp lines consistent with a non-exchanging system, but this is expected since ring inversion would put the methyl substituent into an axial conformation. The barrier to ring inversion in all these compounds is expected to be greater than for simple 2-cyanopiperidines because of the *N*-amino substituent. Conformational inversion requires a threefold process of ring and nitrogen inversion and N–N bond rotation. Conformational barriers in hydrazines are well known, although whether nitrogen inversion or N–N bond rotation has the larger barrier, varies with different structures.[20] Typical values of $\Delta G^{\ddagger}$ for conformational interconversion of acyclic hydrazines[20] are in the range 8–10 kcal mol^{-1} and 8.8 kcal mol^{-1} has been reported[21] for 1-amino-2,2,6,6-tetramethylpiperidine. The

principal barrier was attributed to ring inversion in the latter case. Significantly larger barriers have been reported in particular cases: 14.2 kcal mol^{-1} in *N,N′*-dibenzyl-*N,N′*-diphenylhydrazine[22] and 16.6 kcal mol^{-1} in *N,N*-dibenzyl-*N′*-(2,4-dinitrophenyl)hydrazine.[23] In the latter compound, the *o*-nitro group is structurally similar to the *o*-carboxy group in **12a**–**d** and has comparable ability to hydrogen bond with the adjacent N–H group. Whether or not this potential for H-bonding is significant, it is reasonable to infer that **12a**–**d** should have a high barrier to conformational inversion. The broadened line shapes in the ^{1}H NMR spectrum of the piperidine derivative **12b** are surprising, since morpholine and piperidine rings have almost identical inversion barriers.[24] However, given the likely size of the barrier, small structural variations could plausibly result in significant changes to the inversion rate. Further analysis of the conformational properties of these compounds is beyond the scope of the present study.

Lastly, we investigated the reaction of **10** with pyrrolidine, which was much more reactive than the 6-membered ring amines and under the original conditions the reaction gave no recognisable material. With milder conditions the starting material **10** was transformed to yield a mixture of the rearrangement product **12e** together with the "normal" product **11d** and some 2-nitromandelonitrile derived from desilylation of **10**. Unlike the other aminonitriles **11a**–**c**, the pyrrolidine compound **11d** was somewhat unstable in methanol solution, but we have not investigated this reactivity. By contrast, pyrrolidine has been reported to react with the cyanohydrin TMS ether derived from 3-nitrobenzaldehylde to give the 3-nitro isomer of **11d** in 95% yield.[13] An extensive survey of the reactions of amines with **10** is beyond the scope of the present work but the variations of reactivity and product distribution seen among the present examples suggest that further investigation would be worthwhile. Although yields of the rearranged products reported here are only moderate, there was no attempt at optimisation.

In conclusion, the products **12a**–**12e** derive from a new rearrangement of 2-nitrobenzyl compounds. Hydrolysis of their nitrile groups would generate novel cyclic α-hydrazino acids that could be of interest as analogues of natural α-amino acids. The mechanism proposed in Scheme 2 also implies that preformed nitrosoarenes may react with secondary amines in the presence of a suitable cyanide donor to generate related *N*-arylamino-2-cyanoamines and a wider range of structural diversity could thereby become accessible. Finally, the three rearrangement reactions reported here further illustrate the propensity of suitably-oriented nitro groups to participate unexpectedly in otherwise-straightforward reactions.

Experimental

General

Analyses were performed by MEDAC Ltd, Egham, Surrey. NMR spectra were determined on JEOL FX90Q, Bruker AM400 or Varian Unity 600 spectrometers with tetramethylsilane as internal standard for solutions in deuteriochloroform, unless otherwise specified. *J* Values are given in Hz. High resolution FAB mass spectra were obtained on a VG ZAB-SE instrument. Flash chromatography was performed on Merck 9385 silica gel. Light petroleum describes the fraction boiling between 40–60 °C. Organic extracts were dried over Na_2SO_4 and evaporated under reduced pressure.

Reaction of 2-nitrobenzyl alcohol with triflic anhydride

A solution of 2-nitrobenzyl alcohol (460 mg, 3 mmol) and 2,6-di-*tert*-butylpyridine (0.75 ml, 3.3 mmol) in dry CH_2Cl_2 (15 ml) was added over 15 min to a stirred solution of triflic anhydride (0.50 ml) in dry CH_2Cl_2 (7.5 ml) at −30 °C. After 30 min at −30 °C, the solution was quenched with aq. $NaHCO_3$ and extracted with Et_2O. The organic extract was washed with water and brine, dried and evaporated. The residue was flash chromatographed [$CHCl_3$–light petroleum (1:1)] to give 2-nitrosobenzaldehyde **1** (180 mg, 44%), mp 107–109 °C (decomp.) from $CHCl_3$–light petroleum (lit.[25] 110–111 °C).

2-(2-Nitrophenyl)propan-2-ol 4

2-(2-Nitrophenyl)propene **3**[26] (1.43 g, 8.77 mmol) was cooled to −10 °C and conc. H_2SO_4 (6.8 g) was added dropwise with stirring over 10 min. The mixture was stirred at 0 °C for 1 h, then added dropwise with stirring to ice-cold 2 M aq. NaOH (106 ml). The aqueous mixture was extracted with $CHCl_3$, washed with water, dried and evaporated and the residue was flash chromatographed [EtOAc–light petroleum (17:83)] to give the alcohol **4** (0.74 g, 47%), mp 79–81 °C (lit.[27] 85–87 °C); ν_{max}/cm^{-1} 3245, 1525, 1375; δ_H (400 MHz) 7.33–7.51 (4 H, m, Ar-H), 2.31 (1 H, s, OH, exchanged with D_2O) and 1.70 (6 H, s, CH_3).

O-Acetyl 2-nitromandelic acid 5

Crude 2-nitromandelonitrile [prepared from 2-nitrobenzaldehyde (20 g)[28]] was suspended in conc. HCl (50 ml) and heated under reflux for 3 h. The solution was stirred at room temp. overnight, diluted with brine and extracted with EtOAc. The combined organic phases were dried and evaporated to give a brown solid which was thoroughly washed with ether and dried to give 2-nitromandelic acid (20.38 g, 78%), mp 136–138 °C (lit.[28] 137–138 °C). This material (19.72 g, 100 mmol) was suspended in acetyl chloride (150 ml) and stirred at room temp. for 16 h. The resulting solution was concentrated under reduced pressure and the residue was dissolved in water and washed with EtOAc. The combined organic phases were washed with brine, dried and evaporated, then re-evaporated from toluene. Trituration with Et_2O–light petroleum and recrystallisation from $CHCl_3$–light petroleum gave the acetate **5** (20.39 g, 85%), mp 101–102 °C (lit.[28] 102–103 °C).

tert-Butyl 2-nitromandelate 6

A solution of *O*-acetyl 2-nitromandelic acid **5** (7.17 g, 30 mmol) in Et_2O (25 ml) contained in a heavy-walled vessel was treated with conc. sulfuric acid (0.6 ml), cooled to −78 °C and isobutylene (15 ml) was added. The vessel was sealed, removed from the cold bath and kept at room temp. for 24 h, then cooled to −15 °C before removing the stopper. The solution was diluted with ether (30 ml) and washed briefly with cold saturated $NaHCO_3$. The organic phase was washed with water, dried and evaporated to give *tert*-butyl *O*-acetyl 2-nitromandelate as a pale yellow oil (5.16 g, 58%) which was used without further purification; δ_H (90 MHz) 7.95–8.05 (1 H, m, Ar-H), 7.42–7.68 (3 H, m, Ar-H), 6.75 (1 H, s, C*H*OH), 2.20 (1 H, s, $COCH_3$) and 1.40 (9 H, s, CMe_3). A solution of this material (5.0 g, 16.9 mmol) in ethanol (50 ml) was treated with 2.5 M potassium hydroxide (5 ml) and the mixture was stirred at room temp. for 1 h. Acetic acid (15 ml) and water (25 ml) were added and the solution was extracted with EtOAc (3 × 50 ml). The combined organic phases were washed with saturated $NaHCO_3$, dried and evaporated. Flash chromatography [EtOAc–light petroleum (1:4)] and recrystallisation from light petroleum afforded the *tert*-butyl ester **6** as yellow crystals (1.94 g, 45%), mp 51 °C (Found: C, 57.1; H, 6.0; N, 5.5. $C_{12}H_{15}NO_5$ requires C, 56.9; H, 6.0; N, 5.5%); ν_{max} (Nujol)/cm^{-1} 3385, 1720, 1535, 1355; δ_H (90 MHz) 7.89–8.00 (1 H, m, Ar-H), 7.36–7.69 (3 H, m, Ar-H), 5.83 (1 H, s, C*H*OH), 3.72 (1 H, s, OH) and 1.38 (9 H, s, CMe_3).

1-Acetyl-2,1-benzisoxazol-3(1*H*)-one 7 from *O*-acetyl 2-nitromandelic acid

A solution of *O*-acetyl 2-nitromandelic acid **5** (1.88 g, 7.8 mmol) and *tert*-butyl alcohol (0.95 ml, 10 mmol) in dry pyridine (5 ml) was mixed with a solution of $POCl_3$ (0.93 ml, 10 mmol)

in CH_2Cl_2 (52 ml) and kept at 0 °C for 1 h then allowed to warm to room temp. over 30 min. Water (50 ml) was added and the aqueous layer was washed with CH_2Cl_2. The combined organic phases were washed with water, dried and evaporated to give a dark oil (1.49 g). Flash chromatography [EtOAc–light petroleum (1:4)] gave the benzisoxazolone **7** as pale yellow needles (1.00 g, 72%), mp 119–120 °C (cyclohexane) (lit.[11a] 119–120 °C); λ_{max} (EtOH)/nm 253.5 (ε/$M^{-1}cm^{-1}$ 8800), 314 (6300). The ^1H NMR and IR spectra agreed with published data.[11a] An authentic sample prepared by acetylation[11a] of 2,1-benzisoxazol-3(1*H*)-one[29] had identical properties.

Reactions of amines with (2-nitrophenyl)[(trimethylsilyl)oxy]-acetonitrile 10

a) Morpholine. A solution of **10**[30] (6.22 g, 25 mmol) and morpholine (2.20 g, 25.3 mmol) in MeOH (38 ml) was refluxed for 2 h and the solvent was evaporated under reduced pressure. The residue was dissolved in EtOAc and washed with water, then dried and evaporated. The residue was triturated with a mixture of CCl_4 and $CHCl_3$ (3:1; 50 ml), allowed to stand for ~1 h then filtered (see below) and the solid was washed with CCl_4. The combined filtrate and washings were evaporated and flash chromatographed [EtOAc–light petroleum (1:4)] to give (morpholin-4-yl)(2-nitrophenyl)acetonitrile **11a** as a pale yellow oil (0.89 g, 14%) (Found: $(M + H)^+$ 248.1040. ($C_{12}H_{13}N_3O_3$ + H) requires 248.1035); ν_{max} ($CHCl_3$)/cm^{-1} 1525, 1350; δ_H (90 MHz) 7.53–7.90 (4 H, m, Ar-H), 5.69 (1 H, s, CHCN), 3.47–3.74 (4 H, m, CH_2O), 2.28–2.71 (4 H, m, CH_2N).

The solid isolated from the crude reaction mixture was crystallised (acetone–light petroleum) to give *N*-(3-cyanomorpholin-4-yl)-2-aminobenzoic acid **12a** (1.54 g, 25%), mp 191–192 °C (Found: C, 58.0; H, 5.1; N, 17.0. $C_{12}H_{13}N_3O_3$ requires C, 58.3; H, 5.3; N, 17.0%); λ_{max} (EtOH)/nm 248 (ε/$M^{-1}cm^{-1}$ 9200) and 321 (3600); ν_{max} (Nujol)/cm^{-1} 3300–2500, 2230 (w), 1670, 1255; δ_H (500 MHz, DMSO-d_6) 12.90 (1 H, br s, COOH), 8.67 (1 H, s, NH), 7.82 (1 H, dd, $J_{5,6}$ 7.3, $J_{4,6}$ 1.4, H-6), 7.44 (1 H, td, $J_{3,4}$ 9.0, $J_{4,5}$ 8.0, H-4), 7.35 (1 H, dd, $J_{3,5}$ 0.5, H-3), 6.75 (1 H, td, H-5), 4.29 (1 H, dd, J_{vic} 2.5 and 2.8, H-3′), 3.98 (1 H, dd, J_{gem} 11.8, H-2′$_{eq}$), 3.87 (1 H, ddd, J_{gem} 11.6, J_{vic} 3.1 and 2.4, H-6′$_{eq}$) superimposed on 3.85 (1 H, dd, H-2′$_{ax}$), 3.67 (1 H, ddd, J_{vic} 10.1, H-6′$_{ax}$), 2.90 (1 H, ddd, J_{gem} 11.4, H-5′$_{ax}$), 2.81 (1 H, ddd, H-5′$_{eq}$); δ_C (125 MHz, DMSO-d_6) 169.3 (COOH), 149.1 (C-2), 134.3 (C-4), 131.3 (C-6), 117.2 (C-5), 116.4 (CN), 113.3 (C-3), 111.1 (C-1), 67.3 (C-2′), 66.3 (C-6′), 55.2 (C-3′), 51.7 (C-5′).

b) Piperidine. Reaction and work up as in (a) gave a solid and a filtrate after trituration with CCl_4–$CHCl_3$. The evaporated filtrate was flash chromatographed [EtOAc–light petroleum (15:85)] and the eluted material was crystallised (×2 from aq. MeOH) to give (2-nitrophenyl)(piperidin-1-yl)acetonitrile **11b** (10%), mp 89–90 °C (Found: C, 63.7; H, 6.2; N, 17.0. $C_{13}H_{15}N_3O_2$ requires C, 63.65; H, 6.2; N, 17.1%); ν_{max} (Nujol)/cm^{-1} 1530, 1355; δ_H (90 MHz) 7.72–8.08 (4 H, m, Ar-H), 5.63 (1 H, s, CHCN), 2.21–2.65 (4 H, m, CH_2N) and 1.45 (6 H, br s, CH_2).

The solid filtered from the crude reaction products was crystallised from aq. MeOH to give *N*-(2-cyanopiperidin-1-yl)-2-aminobenzoic acid **12b** (35%), mp 162–164 °C (decomp.) (Found: C, 63.4; H, 6.2; N, 17.0. $C_{13}H_{15}N_3O_2$ requires C, 63.65; H, 6.2; N, 17.1%); ν_{max} (Nujol)/cm^{-1} 3300–2500, 2220 (w), 1670, 1260; δ_H (400 MHz, DMSO-d_6) 8.63 (1 H, s, NH), 7.80 (1 H, dd, $J_{5,6}$ 8.0, $J_{4,6}$ 1.5, H-6), 7.43 (1 H, td, $J_{3,4}$ 8.3, H-4), 7.28 (1 H, dd, $J_{3,5}$ 1.2, H-3), 6.72 (1 H, td, H-5), 4.26 (1 H, br s, CHCN), 2.87 and 2.66 (2 H, 2 × br s, CH_2N), 1.93 (2 H, m, piperidine-H), 1.58–1.69 (3 H, m, piperidine-H) and 1.43 (1 H, br s, piperidine-H).

c) 2-Methylpiperidine. A solution of **10** (6.22 g, 25 mmol) and 2-methylpiperidine (2.51 g, 25.3 mmol) in MeOH (40 ml) was refluxed for 2 h and the solvent was evaporated under reduced pressure. The residue was dissolved in EtOAc and washed with water, then dried and evaporated. The residue was triturated with a mixture of CCl_4 and $CHCl_3$ (3:1; 50 ml), allowed to stand for ~1 h then filtered and the solid was washed with CCl_4 and dried. The filtrate was washed with aq. $NaHCO_3$, dried and evaporated. Flash chromatography [EtOAc–light petroleum (1:4)] gave (2-methylpiperidin-1-yl)(2-nitrophenyl)acetonitrile **11c** (81 mg, 1%) as a viscous oil (Found: $(M - CN)^+$ 233.1292. ($C_{14}H_{17}N_3O_2$–CN) requires 233.1290); ν_{max} ($CHCl_3$)/cm^{-1} 2225 (w), 1530, 1355; δ_H (90 MHz) 7.25–7.86 (4 H, m, Ar-H), 5.46 and 6.07 [1 H (diastereoisomers, ratio ~15:85), 2 × s, CHCN], 1.7–2.5 (3 H, m, CH_2N and MeC*H*N), 1.2–1.7 (6 H, m, CH_2), 0.98 and 1.22 [3 H (diastereoisomers, ratio ~15:85), 2 × d, *J* 6.4, Me].

The combined aqueous extracts from above were acidified to pH 4 with 4 M aq. HCl and extracted with EtOAc. The organic extract was washed with brine, dried and evaporated and the residue was flash chromatographed [EtOAc–light petroleum (3:7 + 1% AcOH)] to give two crystalline solids. The less polar component was *N*-(*trans*-2-cyano-6-methylpiperidin-1-yl)-2-aminobenzoic acid **12d** (699 mg, 11%) as white crystals, mp 162–164 °C (from EtOAc–light petroleum after decolourisation with charcoal) (Found: C, 64.8; H, 6.6; N, 16.2. $C_{14}H_{17}N_3O_2$ requires C, 64.85; H, 6.6; N, 16.2%); ν_{max} (Nujol)/cm^{-1} 3220, 2240 (w), 1680, 1580, 1215; δ_H (600 MHz, DMSO-d_6) 8.68 (1 H, s, NH), 7.79 (1 H, dd, $J_{5,6}$ 7.8, $J_{4,6}$ 1.2, H-6), 7.39 (1 H, td, $J_{3,4}$ 7.8, H-4), 7.24 (1 H, dd, $J_{3,5}$ 1.2 Hz, H-5), 6.67 (1 H, td, H-3), 4.30 (1 H, t, *J* 3, H-2′), 2.73 (1 H, m, H-6′), 1.93 (2 H, m, CH_2), 1.80 (1 H, m, CH), 1.68 (1 H, m, CH), 1.44–1.51 (1 H, m, CH), 1.30–1.36 (1 H, m, CH) and 0.97 (3 H, d, *J* 6, Me).

The more polar component was identical to the solid recovered by trituration of the crude reaction products with CCl_4–$CHCl_3$ and gave *N*-(*cis*-2-cyano-6-methylpiperidin-1-yl)-2-aminobenzoic acid **12c** (981 mg, 15%), as white crystals, mp 160–162 °C (from EtOAc–light petroleum after decolourisation with charcoal) (Found: C, 64.4; H, 6.7; N, 16.0. $C_{14}H_{17}N_3O_2$ requires C, 64.85; H, 6.6; N, 16.2%); ν_{max} (Nujol)/cm^{-1} 3280, 2240 (w), 1670, 1580; δ_H (600 MHz, DMSO-d_6) 8.60 (1 H, s, NH), 7.76 (1 H, dd, $J_{5,6}$ 7.8, $J_{4,6}$ 1, H-6), 7.36–7.39 (2 H, m, H-4,5), 6.64 (1 H, td, $J_{3,4}$ 8.4, $J_{3,5}$ 1.2, H-3), 3.93 (1 H, dd, *J* 12.0, 2.7, H-2′), 2.65 (1 H, m, H-6′), 2.09 (1 H, m, CH), 1.66–1.87 (3 H, m, CH), 1.28–1.38 (2 H, m, CH_2) and 0.89 (3 H, d, *J* 6.1, Me).

d) Pyrrolidine. A solution of **10** (4.51 g, 18 mmol) in MeOH (30 ml) was cooled in an ice-bath and a solution of pyrrolidine (1.29 g, 18.2 mmol) in MeOH (10 ml) was added over 15 min. The mixture was stirred at 4 °C for 1 h , then at room temp. for a further 3.5 h. The solvent was evaporated and the residue was dissolved in EtOAc and washed with saturated aq. $NaHCO_3$ and brine, dried and evaporated. Flash chromatography [EtOAc–light petroleum (1:4)] afforded two products. The less polar product was (pyrrolidin-1-yl)(2-nitrophenyl)acetonitrile **11d** (326 mg, 8%) as white crystals, mp 42–43 °C (from aq. MeOH) (Found: $(M + H)^+$ 232.1093. ($C_{12}H_{13}N_3O_2$ + H) requires 232.1086. Found: $(M - CN)^+$ 205.1093. $C_{11}H_{13}N_2O_2$ requires 205.0977); ν_{max} (Nujol)/cm^{-1} 1525, 1360; δ_H (90 MHz) 7.46–7.98 (4 H, m, Ar-H), 5.99 (1 H, s, CHCN), 2.31–2.80 (4 H, m, NCH_2) and 1.59–1.91 (4 H, m, CH_2). The more polar product was hydroxy(2-nitrophenyl)acetonitrile (855 mg, 27%), mp 88–90 °C (from $CHCl_3$–light petroleum) (lit.[31] 95 °C).

The bicarbonate solution from the original work up was acidified to pH 4 with 4 M aq. HCl and extracted with EtOAc. The combined organic phases were washed with brine, dried and evaporated. The residue was flash chromatographed [EtOAc–light petroleum (3:7 + 2% AcOH)] to give a viscous oil that crystallised on trituration with CCl_4–$CHCl_3$ (3:1; 50 ml) and gave *N*-(2-cyanopyrrolidin-1-yl)-2-aminobenzoic acid **12e** (0.93 g, 22%) as white crystals, mp 134–136 °C (from aq. MeOH)

(Found: C, 62.1; H, 5.7; N, 18.0. $C_{12}H_{13}N_3O_2$ requires C, 62.3; H, 5.7; N, 18.2%); ν_{max} (Nujol)/cm^{-1} 2500–3300, 2230 (w), 1660, 1580, 1260; δ_H (90 MHz, DMSO-d_6) 8.55 (1 H, s, NH), 7.81 (1 H, d, *J* 7.5, H-6), 7.24–7.50 (2 H, m, H-4,5), 6.68 (1 H, td, *J* 8, 2.6, H-3), 4.21 (1 H, dd, *J* 7.2 and 4.6, H-2′), 2.96 (2 H, m, H-5′), 1.6–2.4 (4 H, m, CH_2).

NMR details for the structural assignment of 12a. Two dimensional and one dimensional ^{1}H NMR spectra were measured at 11.7 T on a Varian Unityplus 500 spectrometer using a triple ^{1}H-[^{13}C,^{15}N] probe equipped with PerformaII *z*-axis pulsed field gradients. All gradient pulses were 1 ms in length with a 500 μs recovery period. One dimensional ^{13}C NMR spectra were measured at 9.4 T on a Bruker AM400 WB spectrometer, using a dedicated probe.

The 1D ^{1}H NMR spectrum was recorded with a 9000 Hz spectral width, 2 s acquisition time and a 30° excitation pulse for a total of 64 transients. One dimensional ^{13}C NMR spectra were measured over a 20 kHz spectral width, a 1 s acquisition time and a 45° excitation pulse for a total of 8192 transients. WALTZ-16[32] was used for broad band ^{1}H decoupling.

1D DPFGSE-TOCSY[33] spectra were obtained using 40 ms Gaussian shaped selective 180° pulses. MLEV-17[34] was used for the isotropic mixing periods and the mixing times were varied from 20 to 140 ms in 20 ms steps. Gradient strengths were 17 and 5 G cm^{-1}.

1D NOE experiments were measured with the DPFGSE method described by Stott *et al*.[35] The selective 180° pulses were of 40 ms duration and Gaussian shaped. The gradient strengths were 7 and 3 G cm^{-1} for the DPFGSE. The mixing time was 2 s. The FIDs were multiplied by a cosine squared window function prior to Fourier transformation.

The 2D ^{1}H–^{13}C HSQC spectrum was recorded in pure phase absorption mode as a hypercomplex data set[36] using the gradient enhanced method of Wider and Wüthrich.[37] 16 transients were measured for each of 150 complex data pairs. The spectral widths in F_2 (^{1}H) and F_1 (^{13}C) were 5302 and 15094 Hz respectively, with representative acquisition times in t_2 and t_1 of 151 and 10 ms respectively. The experiment was optimised for a ^1J(^{13}C–^{1}H) of 139 Hz.

The 2D ^{1}H–^{13}C HMBC spectrum was measured as a phase sensitive experiment in F_1, using the gradient selection method originally devised for the HMQC experiment.[38] Delays for the evolution of long range ^{1}H–^{13}C couplings and for the suppression of one-bond ^{1}H–^{13}C couplings were 70 and 3.6 ms respectively, corresponding to couplings of 7.1 and 139 Hz. The spectral widths were 5302 Hz in F_2 (^{1}H) and 17 kHz in F_1 (^{13}C) and 256 data pairs were measured. Acquisition times were 193 and 14 ms in t_2 and t_1 respectively, with a 2.2 s relaxation delay. Gradient amplitudes were 20, 20 and 10 G cm^{-1}, corresponding to the usual 2 : 2 : 1 ratio.[38]

For both two dimensional experiments, the number of points in the F_1 dimension was doubled by linear prediction and both dimensions were zero filled once, prior to Fourier transformation. A cosine squared window function was applied in both dimensions.

Acknowledgements

We thank Dr V. R. N. Munasinghe for running NMR spectra and for the preparation of compound **4**, and Dr K. J. Welham for high resolution mass spectrometric measurements. We are grateful to the MRC Biomedical NMR Centre for access to facilities. This work was supported in part by the MRC Neurosciences Initiative in Human Health.

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Paper 9/04676C