Reduction of electron-deficient pyrroles using group I and II metals in ammonia

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The preparation and Birch reduction of a series of electron-deficient pyrroles is described. This methodology allows the synthesis of a variety of C-2 substituted 3-pyrrolines‡ in good to excellent yields. The role of various activating groups (amide, ester, carbamate and urea) has been examined with regard to both stability under the Birch conditions and ease of deprotection after reduction. In addition, we discovered that the 3-pyrrole skeleton can be oxidised at C-5 with chromium trioxide–3,5-dimethylpyrazole to form the 3-pyrrolin-2-one nucleus. The identity of the Birch reduced products and also of the oxidised 3-pyrrolin-2-ones has been confirmed by X-ray crystallography on two derivatives.

Introduction

Development of new methods for the synthesis of substituted pyrroles has been a key element in the field of heterocyclic chemistry for many years. Extensive study into the reactivity pattern displayed by pyrrole has shown that it has a great propensity to act as a nucleophile in addition and substitution reactions. Correspondingly, chemistry which involves the pyrrole nucleus acting as an electron acceptor or electrophile is much less common. This is exemplified with redox chemistry: the oxidation of pyrroles has been the subject of much interest while the reduction of pyrroles remains a relatively unexplored area.²

As part of a general programme directed towards the stereo-selective reduction of aromatic heterocycles, we chose to investigate reduction of pyrrole to the pyrroline skeleton. Indeed, this synthetic transformation is precedented in the literature, being effected by the combination of a reducing agent (Zn, NaBH₃CN, H₃PO₄ etc.)¹ in the presence of acid, so as to activate the heterocycle (Scheme 1).

However, it appeared that a reduction protocol which did not involve acid as an activator was not known. The development of such a reaction would be useful in enabling the synthesis of substituted pyrroles containing acid sensitive functionality and in addition, may enable functionalisation of the pyrrole ring by reductive alkylation procedures.

![Scheme 1](image)

The most obvious choice of reduction conditions with which to accomplish this goal were those developed by Birch and which have come to bear his name, i.e. (typically) sodium in liquid ammonia solvent with tert-butyl alcohol added as a proton source.⁴ Although this reaction has been utilised extensively in the field of aromatic chemistry, its use in the reduction of pyrroles was unknown.⁷ Consideration of the basic tenants of the reaction provided us with at least two good reasons why this might be the case. Firstly, the pyrrole nucleus is electron-rich (as attested to by its high nucleophility) and this factor is generally a disadvantage when one is considering the addition of electrons to the aromatic system. Secondly, the presence of an acidic hydrogen atom on the pyrrole nitrogen (pKₐ 17) may present the opportunity for deprotonation under the reducing conditions (by an alkoxide for example): the resulting anion would be extremely resistant to further reduction (a similar situation is arrived at if one attempts the reduction of phenols under Birch conditions).

In order to circumvent such potential pitfalls we decided to synthesise some electron-deficient and N-protected pyrroles so as to investigate their reactivity under Birch conditions. Some of the work described in this paper has been the subject of preliminary communication and which we now wish to discuss in detail.⁸

Results and discussion

Compound 3 (Scheme 2) was chosen as our first target because it was easy to prepare and satisfied the criteria defined above: in addition, placing an electron withdrawing group in the 2-position of the pyrrole should control the regiochemistry of reduction and also provide an opportunity for reductive alkylation. Therefore, 3 was prepared from commercially available 2-trichloroacetylpyrrole (1) in two high yielding steps,⁹ and was subsequently subjected to a Birch reductive alkylation with sodium metal in ammonia, quenching with methyl iodide (Scheme 2). To our delight, we succeeded in isolating pyrrole 4 from the reaction mixture in 20–30% yield: the ¹H NMR spectrum of this compound clearly indicated that a significant transformation of the aromatic ring had taken place and showed two multiplets at 5.8, 5.6 ppm (2H, CH–CH) and one at 3.7 ppm (2H, CH₂CH–CH). In addition a N-methyl resonance appeared as a singlet at 2.3 ppm and another methyl singlet was observed at 1.2 ppm. These features, together with ¹³C NMR.
infra-red and mass spectra were all consonant with the proposed structure. Although we had achieved success in this reaction, we were dismayed to discover that the major product was in fact the volatile aldehyde 5, which had resulted from amide reduction rather than pyrrole reduction.10

Unfortunately, the ratio of 4:5 could not be increased despite attempted reduction under a variety of conditions (which included variation of co-solvent, proton source and metal). Presumably, this failure is a consequence of a lack of regioselectivity in the site of protonation of the radical-anion resulting from the addition of an electron to the aromatic system vide infra. It was reasoned that replacing the N-methyl group with a protecting group that was also capable of withdrawing electrons would alleviate this problem by promoting reduction of the aromatic portion of the molecule. Therefore, N-Boc pyrrole 6 was identified as a suitable substrate for reduction (Scheme 3). The target pyrrole was synthesised efficiently from

Scheme 3  Reagents: i, pyrrolidine, DMF; ii, NaH, (Boc)2O; iii, Na (3 equiv.), NH2/THF then RX (xs) – 78 °C

1 (via compound 2) and was then reduced under a variety of conditions. Success was achieved using a reductive alkylation protocol which did not involve the addition of an alcohol as a proton source (Scheme 3). Indeed, addition of a THF solution of 6 to a blue solution of sodium (3 equiv.) in ammonia at –78 °C resulted in rapid reduction: quenching of the reaction after 5 minutes with an electrophile dispersed the coloration and gave the α-alkylated material in good yield (Scheme 3). A range of primary alkyl halides were used as electrophiles and each reacted efficiently and regioselectively with the pyrroline enolate (Table 1). Unfortunately, quenching the reduction with isopropyl iodide gave only the protonated compound 13, as a result of an elimination process; this compound could be obtained more easily by quenching the reaction with an aqueous solution of ammonium chloride (entry 7, Table 1).

The identity of each of the Birch reduced compounds 7–13 was clarified by examination of their spectroscopic data. The 1H NMR spectra of each of the reduced products showed the presence of two olefinic protons at 5–6 ppm, together with incorporation of resonances due to the alkyl group of the electrophile. In each case, the position of the double bond was confirmed by the observation of a 2H multiplet at 4–4.5 ppm which was assigned to the methylene protons attached to C-5. All of the reduced compounds exhibited doubling of resonances in their 1H and 13C NMR spectra, presumably as a consequence of hindered rotation. In each case, the situation was clarified by performing the data collection in 1,2-dichlorobenzene at 120–140 °C which gave rise to a single set of signals (albeit somewhat broad). Moreover, each compound gave a satisfactory mass spectrum and elemental analysis, and compound 7 was further characterised by X-ray crystallography (Fig. 1).

We find the selective reduction of compound 6 particularly striking and worthy of comment. Firstly, the requirement that reduction is performed without an alcohol as a proton source is interesting. This observation leads us to believe that reduction is occurring via a mechanism which involves the intermediacy of a dianion (A, Scheme 4), formed by the capture of two electrons by the pyrrole nucleus. This should be basic enough to deprotonate ammonia thus yielding an enolate.11 Indeed, the pyrrole 6 is so electron-deficient that reduction occurs in less than 5 minutes at –78 °C. We made the observation that pyrrole 2 is a minor by-product (5–15%) in these reactions and speculate that it arises from nucleophilic attack of sodium amide (formed in the above mechanism) at the Boc carbonyl prior to reduction. In support of this, we found that 6 was

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Fig. 1 X-Ray crystal structure of (RS)-7. X-Ray crystallographic numbering shown.

Table 1  Birch reduction of 6

This reaction resulted in a product mixture that was similar to (and which should, therefore, promote reaction under conditions which do not include addition of an alcohol different mechanisms, we have some evidence that suggests that observed earlier with tert-butyl alcohol present (i.e. aldehyde 5 was the major compound formed). It is therefore more likely that the success of the Birch reduction of 6 is a consequence of a regioselective protonation of dianion A at C-5 rather than at the carbonyl group. We therefore have to ask why the dianion derived from 6 (A) should protonate so regioselectively while the radical anion (B) (or dianion) derived from 3 does not? In general terms it may be concluded that making the aromatic ring comparatively electron rich (compound 3) discourages reduction of that portion of the molecule and conversely, reducing electron density within it (compound 6) encourages aren reduction. This trend is in clear agreement with that observed during the Birch reduction of benzenoid systems. Assuming kinetic control we suggest that several factors may be responsible for the regiocontrol displayed by each radical anion (or dianion), and these would include: the total charge at each reactive position; the orbital coefficient of the HOMO of the radical-anion (or dianion) at each reactive position, and the steric hindrance at each possible site of protonation. Obviously it is not easy to assess quantitatively the difference that a change of nitrogen protecting group will have on each of these parameters and a more exacting explanation awaits further investigation of this system.

The effect of changing the reactive metal was next examined. The reductive alkylation of 6–7 was chosen as a representative example and was performed with three metals: in each case the reaction profile was identical and the isolated yields of 7 proved to be rather similar [Na (85%), Ca (75%), Li (71%)]. Clearly, the particular source of electrons and the nature of the cationic counterion is relatively unimportant to the success of this reaction. The success of lithium and calcium may have ramifications as far as the practicality of this reaction is concerned, as they are easier to handle than sodium.

Dialkylamides and isopropyl esters as activating groups for pyrrole

Alternative N-protecting and electron withdrawing groups for pyrrole were also examined for their stability during the Birch reduction. Thus, compound 14 was prepared from 2 via deprotonation and reaction with diethylcarbamoyl chloride (Scheme 6). This compound was then reduced under conditions that had proven to be successful for the N-Boc amide derivative. Birch reduced urea 15 was obtained as the sole product of the reaction in high yield. In fact, deprotected pyrrole 2 was not detected in this reduction at all, presumably because the N-protecting group (amide) shows greater resistance towards nucleophilic attack by sodamide.

The success of this reaction illustrates that a variety of electron withdrawing groups can be tolerated on the pyrrole nitrogen. However, this reaction sequence was not pursued further.
because of perceived difficulties in removing the urea group from the reduced product.

We also examined the reduction of N-Boc pyrroles substituted with an ester at C-2; this functionality was chosen because of the relative ease and selectivity with which the ester group could be removed after reduction. Ester 16 was prepared from 2-trichloroacetylpyrrole 1 in three steps and in excellent overall yield (Scheme 7). Reductive alkylation of 16 under standard conditions proceeded without complication and gave the two α-alkylated derivatives shown in the scheme. The two electrophiles that were chosen to quench the ester enolate illustrate that this activating group is equally useful for the synthesis of highly substituted pyrroles as the amide group described earlier.

Although excellent yields of 17 and 18 were obtained from the reduction, it was discovered that the substrate must be added rapidly to the reaction mixture: slow addition resulted in the formation of C-2 amide derivatives of the two pyrroles.

With the Birch reduced products in hand we next examined reductive alkylation of the two alkene methine resonances were observed. Presumably, under such acidic conditions the amine functionality is protonated thus disfavouring further protonation of the olefin at C-3 (this is a prerequisite step for olefin migration under acidic conditions).

We also examined the saponification of 17 and 18 with potassium hydroxide and formed the N-Boc amino acids in good yields (Scheme 8). The advantages of carrying an ester through the reduction procedure revolve around the relative ease of deprotection to the acid without removal of the Boc group.

In addition, we coupled acid 22 with pyrrolidine [promoted by bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl)] to produce a sample of 7 that was identical with the material that was produced in the Birch reduction of amide 6 (and whose identity was confirmed by X-ray crystallography). This correlation confirms the nature of acid 22 and therefore ester 17 unambiguously.

### Oxidation of the 3-pyrrole skeleton to form substituted 3-pyrrolin-2-ones

During an attempted recrystallisation of compound 7 from diethyl ether, we occasionally observed the formation of a new compound. Chromatography of the mother liquors on silica gel allowed the isolation of this compound, which was subsequently proven to be the γ-lactam 24 (Scheme 9). Presumably, this compound was formed by a free radical chain reaction involving atmospheric oxygen. However, the yield of 24 proved to be rather low and unpredictable and so we sought a more reproducible method of achieving this oxidation. Eventually, we discovered that the chromium trioxide–3,5-dimethylpyrazole combination was the most reliable method for effecting this transformation, and gave yields of 64–68% on three different substrates (Scheme 9).

The nature of the pyrrolin-2-ones (2,5-dihydropyrrol-2-ones) 24, 25 and 26 was determined by examination of the corresponding NMR and IR spectra. In each case, 1H NMR spectroscopy revealed that the two alkene methane resonances were shifted from δ 5–6 (pyrrole) to δ 6–7 ppm (pyrrolin-2-one). There was also an absence of the 2H multiplet at 4 ppm which shifted from δ 6–7 ppm (pyrrolin-2-one).

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2-(Pyrrolidin-1-ylcarbonyl)pyrrole 2

Freshly distilled pyridine (4.4 cm³, 52.0 mmol) was added dropwise to a solution of the trichloroacetilpyrrole 1 (5 g, 23.6 mmol) dissolved in DMF (15 cm³). After 10 h, water (40 cm³) was added, followed by 2 M HCl (20 cm³). The mixture was then extracted with EtOAc (3 × 50 cm³), dried (Na₂SO₄), filtered and concentrated under reduced pressure to afford the pyrrole amide 2 (3.17 g, 82%) as an off-white solid; mp 118–119 °C; ν_max (film)/cm⁻¹ 3224, 2974, 2870, 1585, 1453 and 1416; δ_H (300 MHz; CDCl₃) 10.4 (1 H, br s, NH), 6.97–6.91 (1 H, m, ArH), 6.63–6.57 (1 H, m, ArH), 6.30–6.23 (1 H, m, ArH), 3.81–3.61 (4 H, m, 2 × NCH₂CH₂); δ_C (75 MHz; CDCl₃) 160.5, 126.1, 121.1, 112.0, 109.6, 47.9, 47.0, 26.7 and 24.0; m/z (EI) 164 (M⁺, 35%), 108 (20), 94 (70) and 70 (100); (C₅H₃N₂O requires 164.0950). Found 164.0954.

2-(Pyrrolidin-1-ylcarbonyl)-N-methylpyrrole 3

A solution of the pyrrole amide 2 (5 g, 30.5 mmol) in THF (10 cm³) was added to NaH (1.46 g, 60.9 mmol) in THF (10 cm³) at room temperature. After 1 h, methyl iodide (4.75 cm³, 76.3 mmol) was added and the reaction heated at 60 °C for 12 h. After cooling, the reaction mixture was washed with brine and extracted with EtOAc (3 × 20 cm³) and dried (Na₂SO₄). Flash chromatography (eluting with petrol–EtOAc, 5:1) afforded the N-methylpyrrole 3 (4.1 g, 75%) as a yellow oil; ν_max (film)/cm⁻¹ 2953, 2873, 1744, 1531, 1433; δ_H (300 MHz; CDCl₃) 6.70–6.65 (1 H, m, ArH), 6.55–6.48 (1 H, m, ArH), 6.15–6.05 (1 H, m, ArH), 3.85 (3 H, s, NMe), 3.65 (4 H, br s, 2 × NCH₂); δ_C (75 MHz; CDCl₃) 162.3, 127.0, 126.5, 113.9, 107.0, 49.8, 46.7, 36.9, 27.0 and 24.6; m/z (EI) 178 (M⁺, 100%), 108 (100), 81 (40), and 70 (35); (C₅H₃N₂O requires 178.1106. Found 178.1101.

1,2-Dimethyl-2-(pyrrolidin-1-ylcarbonyl)-2,5-dihydropyrrole 4

A solution of N-methylpyrrole amide 3 (320 mg, 1.8 mmol) in THF (10 cm³) was added to a mixture of ammonia (100 cm³), and sodium (124 mg, 5.4 mmol) at −78 °C. tert-Butyl alcohol (120 mg) was added and the reaction stirred for 1 h. Methyl iodide (1 cm³) was then added followed by NH₄Cl (excess) after a further 2 h. The reaction mixture was diluted with brine, extracted with dichloromethane and dried (Na₂SO₄). Flash chromatography (eluting with petrol–EtOAc 1:1) gave the dihydropyrrole 4 (90 mg, 26%) as a yellow oil; ν_max (film)/cm⁻¹ 2969, 1626, and 1413; δ_H (300 MHz; CDCl₃) 5.80 (1 H, dt, J 6.0 and 2.0, CH₂–CH), 5.63 (1 H, dt, J 6.0 and 2.0, CH₂–CH), 3.85 (2 H, m, NCH₂CH₂), 3.65 (2 H, m, NCH₂CH₂), 3.30 (2 H, s, NMe); δ_C (100 MHz; CDCl₃) 172.6, 134.7, 128.5, 74.4, 60.0, 48.3, 47.3, 34.8, 27.6, 23.8 and 17.6; m/z (CI) 195 (M⁺ + 1, 99%), 193 (100) and 96 (25); (C₅H₇N₂O requires 195.1497. Found 195.1500.

N-(tert-Butyloxycarbonyl)-2-(pyrrolidin-1-ylcarbonyl)pyrrole 6

A solution of the pyrrole amide 2 (5 g, 30.5 mmol) in THF (15 cm³) was added to NaH (1.46 g, 60.9 mmol) in THF (15 cm³) at room temperature. After 30 min, di-tert-butyl dicarbonate (10.5 cm³, 45.7 mmol) was added dropwise and the reaction was heated at 45 °C for 12 h. The reaction mixture was then diluted with water (10 cm³), extracted with EtOAc (3 × 30 cm³), dried (Na₂SO₄) and concentrated in vacuo. Flash chromatography (eluting with petrol–EtOAc 1:2) afforded the N-Boc pyrrole amide 6 (7.25 g, 90%) as a colourless solid; mp 102–103 °C (Found: C, 63.59; H, 7.72; N, 10.49. Calc. for C₁₇H₁₇N₂O₂C₆: C, 63.62; H, 7.63; N, 10.60%). eλ_max (film)/cm⁻¹ 2976, 2876, 1744, 1640, 1555 and 1460; δ_H (300 MHz; CDCl₃) 7.23 (1 H, dd, J 3.6 and 3.6, ArH), 6.30 (1 H, dd, J 1.6 and 3.6, ArH), 6.17 (1 H, t, J 3.6, ArH), 3.60 (2 H, t, J 6.6, NCH₂CH₂), 3.30 (2 H, t, J 6.6, NCH₂CH₂).
NCH$_2$(CH$_3$)$_2$, 2.00–1.80 (4 H, m, 2 × NCH$_2$CH$_2$) and 1.55 (9 H, s, CMe$_3$); $\delta$ (75 MHz, CDCl$_3$) 162.8, 148.3, 129.0, 121.6, 113.0, 110.6, 84.4, 48.3, 45.6, 27.8, 25.8 and 24.6; m/z (CI) 265 (M$^+$ + 1, 75%); 285 (100), 165 (25), 94 (10) and 70 (15); (C$_{14}$H$_{28}$NO$_4$) requires 264.1744. Found 264.1746.

**N-(tert-Butoxycarbonyl)-2-(pyrrolidin-1-ylcarbonyl)-2-methyl-2,5-dihydroxypropele 7**

A solution of N-Boc-pyrorole amide 6 (500 mg, 1.9 mmol) in THF (10 cm$^3$) was added rapidly to a mixture of ammonia (150 cm$^3$), THF (40 cm$^3$) and sodium (131 mg, 5.7 mmol) at −78 °C. After 1 h, methyl iodide (1 cm$^3$) was added and after a further 2 h, NH$_3$(excess) was added. The mixture was slowly warmed to room temperature, while the ammonia was removed with a stream of nitrogen. Brine was added and the product extracted with EtOAc (3 × 50 cm$^3$), dried (Na$_2$SO$_4$), filtered and concentrated under reduced pressure. Flash chromatography (eluting with petrol–acetone 5:1) gave the dihydroxypropele 9 (451 mg, 85%) as a colourless solid; mp 95–98 °C (Found: C, 64.45; H, 8.54; N, 9.85. Calc. for C$_{16}$H$_{26}$NO$_4$: C 64.26; H, 8.63; N, 9.99%); $\text{v}_{\text{max}}$(film/cm$^{-1}$) 2974, 2874, 1606, 1639 and 1391; $\delta$(300 MHz, CDCl$_3$) 5.87, 5.81 (1 H, dt, J 6.2 and 1.9, CH=CH), 5.62 (1 H, dt, J 6.2 and 1.9, CH=CH), 4.30–4.08 (2 H, m, NCH$_2$CH$_2$H), 3.57–3.00 (4 H, m, 2 × NCH$_2$CH$_2$H), 2.00–1.65 (4 H, m, 2 × NCH$_2$CH$_2$H), 1.48 (15 H, s, CMe$_3$); $\delta$(75 MHz, CDCl$_3$) 140.5, 140.0, 137.6, 137.0, 136.0, 129.3, 128.9, 127.7, 126.7, 126.2, 126.0, 80.6, 79.7, 75.8, 75.7, 54.1, 48.4, 48.3, 45.0, 40.6, 39.4, 28.6, 28.4, 27.4, 27.3, 23.3 and 23.2; m/z (CI) 281 (M$^+$ + 1, 100%), 225 (40), 181 (25) and 82 (40); (C$_{16}$H$_{28}$NO$_4$) requires 280.1787. Found 280.1775.

**N-(tert-Butoxycarbonyl)-2-(pyrrolidin-1-ylcarbonyl)-2-benzyl-2,5-dihydroxypropele 8**

A solution of N-Boc-pyrorole amide 6 (500 mg, 1.9 mmol) in THF (10 cm$^3$) was added rapidly to a mixture of ammonia (150 cm$^3$), THF (40 cm$^3$) and sodium (131 mg, 5.69 mmol) at −78 °C. After 1 h, ethyl iodide (1 cm$^3$) was added and after a further 2 h, NH$_3$(excess) was added. After work-up, which was identical to that described for 7, flash chromatography (eluting with petrol–acetone 5:1) gave the dihydroxypropele 9 (357 mg, 71%) as a colourless solid (Found: C, 66.78; H, 8.62; N, 8.90. Calc. for C$_{16}$H$_{28}$NO$_4$: C 66.64; H, 8.55; N, 9.14%); $\text{v}_{\text{max}}$(film/cm$^{-1}$) 1696, 1627, and 1391; $\delta$(75 MHz, CDCl$_3$) 5.96–5.84 (1 H, m, CH=CH), 5.64–5.48 (2 H, m, CH=CH$_2$), 5.06–4.96 (2 H, m, CH=CH$_2$), 4.13–3.98 (2 H, m, NCH$_2$CH$_2$), 3.62–3.34 (2 H, m, NCH$_2$CH$_2$), 3.30–3.16 (1 H, m, CH$_3$CH=CH$_2$), 3.08–2.98 (2 H, m, NCH$_2$CH$_2$), 2.78–2.68 (1 H, dd, J 4.0 and J 7.5, CH$_3$CH=CH$_2$), 1.94–1.50 (4 H, m, 2 × NCH$_2$CH$_2$) and 1.39, 1.38 (9 H, s, CMe$_3$); $\delta$(75 MHz, CDCl$_3$) 168.9, 153.0, 133.2, 132.8, 129.5, 129.1, 126.8, 126.7, 118.9, 118.7, 80.2, 74.7, 54.7, 54.4, 48.2, 44.9, 39.6, 38.1, 28.2, 27.3 and 23.2; m/z (CI) 307 (M$^+$ + 1, 40%) and 207 (100); (C$_{16}$H$_{28}$NO$_4$) requires 306.1943. Found 306.1939.

**N-(tert-Butoxycarbonyl)-2-(pyrrolidin-1-ylcarbonyl)-2-ethyl-2,5-dihydroxypropele 10**

A solution of N-Boc-pyrorole amide 6 (500 mg, 1.89 mmol) in THF (10 cm$^3$) was added rapidly to a mixture of ammonia (150 cm$^3$), THF (40 cm$^3$) and sodium (131 mg, 5.69 mmol) at −78 °C. After 1 h, ethyl iodide (1 cm$^3$) was added and after a further 2 h, NH$_3$(excess) was added. After work-up, which was identical to that described for 7, flash chromatography (eluting with petrol–acetone 5:1) gave the dihydroxypropele 9 (357 mg, 71%) as a colourless solid (Found: C, 66.78; H, 8.62; N, 8.90. Calc. for C$_{16}$H$_{28}$NO$_4$: C 66.64; H, 8.55; N, 9.14%); $\text{v}_{\text{max}}$(film/cm$^{-1}$) 1696, 1627, and 1391; $\delta$(75 MHz, CDCl$_3$) 5.96–5.84 (1 H, m, CH=CH), 5.64–5.48 (2 H, m, CH=CH$_2$), 5.06–4.96 (2 H, m, CH=CH$_2$), 4.13–3.98 (2 H, m, NCH$_2$CH$_2$), 3.62–3.34 (2 H, m, NCH$_2$CH$_2$), 3.30–3.16 (1 H, m, CH$_3$CH=CH$_2$), 3.08–2.98 (2 H, m, NCH$_2$CH$_2$), 2.78–2.68 (1 H, dd, J 4.0 and J 7.5, CH$_3$CH=CH$_2$), 1.94–1.50 (4 H, m, 2 × NCH$_2$CH$_2$) and 1.39, 1.38 (9 H, s, CMe$_3$); $\delta$(75 MHz, CDCl$_3$) 168.9, 153.0, 133.2, 132.8, 129.5, 129.1, 126.8, 126.7, 118.9, 118.7, 80.2, 74.7, 54.7, 54.4, 48.2, 44.9, 39.6, 38.1, 28.2, 27.3 and 23.2; m/z (CI) 307 (M$^+$ + 1, 40%) and 207 (100); (C$_{16}$H$_{28}$NO$_4$) requires 306.1943. Found 306.1943.

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H 4.64–4.46 (2 H, m, NC\(_2\times\)NC\(_{\text{CHMe}}\)) 5.97, 5.89 (1 H, m, NCH\(_2\)), 4.15–4.05 (2 H, m, NC\(_{\text{CH}}\)) 5.52–5.35 (4 H, m, 2 × NCH\(_2\ )); δ\(_{\text{C}}\) 75 MHz, CDCl\(_3\)) 169.3, 159.4, 131.6, 125.0, 74.1, 54.6, 48.1, 44.5, 43.3, 27.2, 23.8, 23.1 and 14.0; \(\text{m/z (Cl)}\), 323 (M\(^{+} + 1\), 100%), 211 (50), 167 (35) and 68 (30); (C\(_{\text{CH}}\) 2.10–1.50 (6 H, m, 2 × NCH\(_2\ )); δ\(_{\text{C}}\) 75 MHz, CDCl\(_3\)) 160.3, 153.2, 130.9, 130.4, 126.4, 80.2, 79.6, 75.6, 75.3, 54.7, 48.5, 44.7, 43.0, 28.4, 27.4, 25.3, 24.6, 23.2 and 23.0; \(\text{m/z (Cl)}\), 323 (M\(^{+} + 1\), 100%), 267 (30), 223 (10) and 124 (25); (C\(_{\text{H}}\)\(_{2}\)\(_{2}\)\(_{N}\)\(_{2}\)O\(_{2}\) requires 323.2335. Found 323.2339.

**N-(tert-Butyloxycarbonyl)-2-(pyrrolidin-1-ylcarbonyl)-2,5-di hydropyrole 13**

As a solution of the N-Boc-pyrole amide 6 (500 mg, 1.9 mmol) in THF (10 cm\(^3\)) was added rapidly to a mixture of ammonia (150 cm\(^3\)), THF (40 cm\(^3\)) and sodium (152 mg, 6.6 mmol) at −78 °C. After 1 h, saturated NH\(_4\)Cl solution (5 cm\(^3\)) was added. The mixture was slowly warmed to room temperature, while the ammonia was removed with a stream of nitrogen. After work-up, which was identical to that described for 7, flash chromatography (eluting with petrol–acetone 1 : 2) afforded the dihydropyrole 13 [358 mg, 71%] as a pale yellow oil (Found: C, 63.06; H, 8.45; N, 10.39. Calc. for C\(_{15}\)H\(_{17}\)N\(_{2}\)O\(_{2}\); C, 63.17; H, 8.33; N, 10.53%). δ\(_{\text{C}}\) (film/cm\(^{-1}\)) 2974, 2875, 1704, 1659 and 1398; δ\(_{\text{H}}\) (500 MHz, CDCl\(_3\)) 5.62–5.49 (2 H, m, CH\(_{2}\)), 4.18–4.12 (2 H, m, NCH\(_2\)); δ\(_{\text{C}}\) (75 MHz, CDCl\(_3\)) 167.3, 159.4, 131.6, 125.0, 74.1, 54.6, 48.1, 44.5, 43.3, 27.2, 23.8, 23.1 and 14.0; \(\text{m/z (Cl)}\), 323 (M\(^{+} + 1\), 100%), 211 (50), 167 (35) and 68 (30); (C\(_{\text{H}}\)\(_{2}\)\(_{2}\)\(_{N}\)\(_{2}\)O\(_{2}\) requires 323.2335. Found 323.2339.]

Isopropyl N-(tert-butyloxycarbonyl)pyrole-2-carboxylate 14

A solution of the pyrole amide 2 (5 g, 33.7 mmol) in THF (75 cm\(^3\)) was added dropwise to the mixture in an ice bath and after 30 min the reaction was refluxed for 3 h. Excess oxalyl chloride was removed in vacuo and the acid chloride was then dissolved in dichloromethane (15 cm\(^3\)). Oxalyl chloride (3.1 cm\(^3\), 35.5 mmol) was added dropwise to the mixture in an ice bath and after 30 min, the reaction was refluxed for 3 h. Excess oxalyl chloride was removed in vacuo and the acid chloride was then dissolved in isopropyl alcohol (10 cm\(^3\)) and heated at reflux for 12 h. Excess isopropyl alcohol was evaporated to afford the pyrole isopropyl ester (2.73 g, 75%) as a dark viscous oil.

A solution of the pyrole isopropyl ester (2.5 g, 16.3 mmol) in THF (5 cm\(^3\)) was added to NaH (782 mg, 32.6 mmol) in THF (10 cm\(^3\)) at room temperature. After 30 min, di-tert-butyl dicarbonate (9.0 cm\(^3\), 39.1 mmol) was added slowly and the reaction heated at 45 °C for 12 h. The reaction mixture was then diluted with water (10 cm\(^3\)), extracted with dichloromethane (3 × 30 cm\(^3\)), dried (Na\(_{2}\)SO\(_{4}\)) and filtered concentrated in vacuo. Flash chromatography (eluting with petrol–EtOAc 1 : 5) afforded the N-Boc-pyrole isopropyl ester 16 [40.0 g, 97%] as a pale yellow oil: \(\text{v}_{\text{max}}\) (film/cm\(^{-1}\)) 2980, 2930, 1753, 1724 and 1450; δ\(_{\text{H}}\) (300 MHz, CDCl\(_3\)) 7.35 (1 H, dd, J = 3.5, 1.8, ArH), 6.85 (1 H, dd, J = 3.5, 1.8, ArH), 6.20 (1 H, J = 3.5, ArH), 5.20 (1 H, sp, J = 6.3, CMe\(_{2}\)) 1.65, 1.55 (9 H, s, CMe\(_{2}\)) and 1.09 (6 H, d, J = 6.3, CMe\(_{2}\)); δ\(_{\text{C}}\) (75 MHz, CDCl\(_3\)) 213.5, 212.8, 160.4, 148.4, 126.5, 126.1, 110.0, 85.2, 84.6, 68.3, 27.7, 27.4 and 21.9; \(\text{m/z (Cl)}\), 280 (M\(^{+} + 1\), 30%), 215 (55), 198 (100), 111 (35) and 94 (30); (C\(_{\text{H}}\)\(_{2}\)\(_{2}\)\(_{N}\)O\(_{2}\) requires 253.1314. Found 253.1316.)
N-(tert-Butoxycarbonyl)-2-(isopropoxycarbonyl)-2-methyl-2,5-dihydropyrrole 17

A solution of the N-Boc pyrrole isopropyl ester 16 (500 mg, 2.0 mmol) in THF (10 cm³) was added rapidly to a mixture of ammonia (150 cm³), THF (40 cm³) and sodium (136 mg, 6.0 mmol) at −78 °C. After 5 min, methyl iodide (1 cm³) was added and after a further 2 h, NH₄Cl (excess) was added. The mixture was slowly warmed to room temperature, while the ammonia was removed with a stream of nitrogen. After work-up, which was identical to that described for 7, flash chromatography (eluting with petrol-acetone 9:1) afforded the dihydropyrrole 17 as a colourless oil (463 mg, 87%) (Found: C, 62.44; H, 8.62; N, 5.21%).

N-Methyl-2-(isopropoxycarbonyl)-2-methyl-2,5-dihydropyrrole 18

A solution of the N-Boc pyrrole isopropyl ester 16 (500 mg, 2.0 mmol) in THF (10 cm³) was added rapidly to a mixture of ammonia (150 cm³), THF (30 cm³) and sodium (136 mg, 6.0 mmol) at −78 °C. After 5 min, isopropyl iodide (1 cm³) was added and after a further 2 h, NH₄Cl (excess) was added. The mixture was slowly warmed to room temperature, while the ammonia was removed with a stream of nitrogen. After work-up, which was identical to that described for 7, flash chromatography (eluting with petrol-acetone 9:1) afforded the dihydropyrrole 18 as a colourless oil (473 mg, 76%) (Found: C, 65.62; H, 9.19; N, 4.62%).

2-(Pyroridin-1-ylcarbonyl)-2-methyl-2,5-dihydropyrrole 19

A solution of the pyrrole 7 (60 mg, 0.21 mmol) in dichloromethane (10 cm³) was cooled in an ice bath and treated with trifluoroacetic acid (0.5 cm³). After 6 h at room temperature, the reaction mixture was poured into NaOH solution (0.5 m) and extracted with dichloromethane (3 × 10 cm³). The organic extracts were dried (Na₂SO₄), filtered and concentrated in vacuo to afford the dihydropyrrole 19 (32.4 mg, 84%) as a colourless solid; mp 68–69 °C (Found: C, 66.6; H, 8.9; N, 15.5%).
A solution of the dihydroxystyryl 18 (103 mg, 0.74 mmol) in methanol (5 cm³) was treated with concentrated KOH solution (3 cm³) and the mixture heated at 60°C for 48 h. The reaction mixture was then cooled in an ice bath, acidified (HCl, 2 m) to pH (6–5) and extracted with EtOAc (3 × 15 cm³). The organic extracts were dried (Na₂SO₄), filtered and concentrated in vacuo. Flash chromatography (eluting with petrol–acetone 6:1) afforded 22 (68 mg, 76%) as a colourless oil (Found: C, 62.67; H, 8.99; N, 5.11. Calc. for C₃H₅NO₂: C, 62.43; H, 8.61; N, 5.20%; vmax(film)/cm⁻¹ 3100, 1740, 1706 and 1625; δd(300 MHz, CDCl₃) 6.10–6.00 (2 H, m, CH=CH), 4.60–4.45 (2 H, m, NCH₂CH₃), 1.71, 1.64 (3 H, s, CMe) and 1.50, 1.46 (9 H, s, CMe₃); δs(75 MHz, CDCl₃) 178.1, 176.3, 154.9, 153.6, 131.7, 131.1, 127.6, 81.2, 80.8, 71.7, 54.6, 28.4, 22.6 and 21.8; m/z (CI) 228 (M⁺ + 1, 35%), 189 (100), 172 (70), 120 (82) and 60; (C₆H₄NO₂ requires 228.1236. Found 228.1242).

N-(tert-Butoxycarbonyl)-2-isobutyl-2,5-dihydroxystyryl-2-carboxylic acid 23

The complex between chromium trioxide and 3,5-dimethylpyrazole was prepared at low temperature (~−30°C to ~−20°C) by rapid addition of 3,5-dimethylpyrazole (621 mg, 6.21 mmol) to pre-dried chromium trioxide (597 mg, 6.21 mmol), suspended in dry dichloromethane (5 cm³). After stirring for 30 min, the substrate 12 (100 mg, 0.311 mmol) was added and the temperature slowly raised to 0°C. After 2 h the mixture was treated with (aq.) KOH (3 m, 3 cm³) and stirred for a further 1 h at room temperature and concentrated under reduced pressure. The red solid residue was then dissolved in EtOAc (15 cm³) and washed with ice cold 2 m HCl (5 × 10 cm³). The organic layer was then treated with saturated aqueous NaHCO₃, dried (Na₂SO₄), filtered and evaporated in vacuo. Flash chromatography, eluting with petrol–acetone (4:1) afforded 26 (70.5 mg, 67%) as a colourless oil (Found: C, 59.18; H, 7.42; N, 5.03. Calc. for C₂H₅NO₂: C, 59.35; H, 7.47; N, 4.94%; vmax(film)/cm⁻¹ 1782, 1739 (br) and 1607; δs(200 MHz, CDCl₃) 6.95 (1 H, d, J 6.9, CH-CH), 6.17 (1 H, d, J 6.9, CH-CH), 5.0 (1 H, sept, J 6.9, CH₂Me), 1.72 (2 H, m, CH₂Me), 1.35 (9 H, s, CMe), 1.22 (3 H, d, J 6.9, MeCHMe) and 1.18 (3 H, d, J 6.9, MeCHMe); (CI) 168.6, 168.1, 150.0, 148.6, 126.8, 83.60, 70.25, 70.17, 28.00, 21.54, 20.49 and 175.2; m/z (CI) 284 (M⁺ + 1, 10%) and 184 (100); (C₆H₄NO₂ requires 284.1498). Found 284.1498).

Crystal data: (RS)-7

C₆H₅NO₂, M = 280.37. Monoclinic, space group P2₁/c (No. 14), crystal dimensions 0.18 × 0.23 × 0.37 mm, colourless prismatic crystal, a = 8.388(2), b = 13.930(3), c = 13.570(3) Å, β = 90 °(2). A by least-squares refinement on diffractometer settings for 25 carefully centered reflections in the range 15.28 ° < 2θ < 21.71°, Z = 4, D = 1.208 g cm⁻³, F(000) = 608.00.

Data collection and processing. Rigaku AFC5R diffractometer, graphite monochromated Mo-Kα radiation (λ = 0.71073 Å), μ(Mo-Kα) 0.791 cm⁻¹, 3054 reflections measured, maximum 20 value of 50.1°, segment (+h, +k, ±l), 2851 unique reflections measured (Rint = 0.024), 1728 of these with I > 3σ(I) used in refinement. An empirical absorption correction based on azimuthal scans of several reflections was applied which resulted in transmission factors ranging from 0.97 to 1.00. The intensities of three representative reflections measured after every 150 reflections showed no sign of decay.

Structure solution and refinement. Solution by direct methods,\textsuperscript{8} hydrogen atoms included in idealised positions (C–H 0.95 Å) with isotropic thermal parameters 20% greater than the equivalent B value of the relevant carbon. The structure was refined by full-matrix least-squares refinement on \(F\) with all non-hydrogen atoms anisotropic and the hydrogen atoms fixed, \(R = 0.041, \ R_g = 0.037, \ \omega = 1/[\sigma^2(F_o^2) + 0.0002F_o^2] \) for 181 refined parameters. Max/min peaks in final difference map 0.15/0.13.

Crystal data: (RS)-24

\[ \text{C}_{11}\text{H}_{22}\text{N}_2\text{O}_4 \]

\( M = 294.35 \) Orthorhombic, space group \( Pna2_1 \) (No. 33), crystal dimensions \( 0.50 \times 0.18 \times 0.18 \) mm, colourless block crystal, \( a = 16.585(3) \), \( b = 8.566(2) \), \( c = 11.409(3) \) Å, \( U = 1620(1) \) Å\(^2\) by least-squares refinement on diffractometer angles for 25 carefully centered reflections in the range \( 15.15 < 2\theta < 19.67^\circ \), \( Z = 4 \), \( D_\text{calc} = 1.21 \text{ g cm}^{-3} \), \( F(000) = 632.00 \).

Data collection and processing. Rigaku AFC5R diffractometer, graphite monochromated Mo-K\( \alpha \) radiation (\( \lambda = 0.71069 \) Å), \( \mu (\text{Mo-K}\alpha) 0.9 \text{ cm}^{-1} \), 1676 unique reflections measured, maximum 2\( \theta \) value of 50.0\( ^\circ \), segment (+h, +k, +l), 1113 of these with \( I > 3 \sigma (I) \) used in refinement. An empirical absorption correction based on azimuthal scans of several reflections was applied which resulted in transmission factors ranging from 0.96 to 1.00. The intensities of three representative reflections measured after every 150 reflections showed no sign of decay.

Structure solution and refinement. Solution by direct methods,\textsuperscript{9} hydrogen atoms included in idealised positions (C–H 0.95 Å) with isotropic thermal parameters 20% greater than the equivalent B value of the relevant carbon. The structure was refined by full-matrix least-squares refinement on \(F\) with all non-hydrogen atoms anisotropic and the hydrogen atoms fixed, \( R = 0.046, \ R_g = 0.035, \ \omega = 1/[\sigma^2(F_o^2)] \) for 190 refined parameters. Max/min peaks in final difference map 0.15/–0.15. Calculations for both crystal structures were performed using TEXSAN.\textsuperscript{8}

\( ^8 \) Full crystallographic details, including structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see ‘Instructions for Authors’, \textit{J. Chem. Soc. Perkin Trans. 1}, available via the RSC Web page (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/178.

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