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Sodium borohydride–iodine mediated reduction of γ-lactam carboxylic acids followed by DDQ mediated oxidative aromatisation: a simple approach towards *N*-aryl-formylpyrroles and 1,3-diaryl-formylpyrroles

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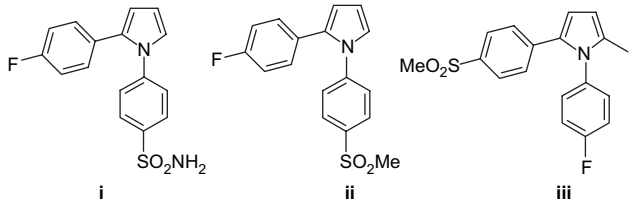
Abstract—A simple methodology for the conversion of substituted *N*-aryl-γ-lactam 2/3-carboxylic acids to substituted *N*-aryl-2/3-formyl-pyrroles has been developed. Several *N*-aryl-γ-lactam 2/3-carboxylic acids were reduced to substituted (*N*-aryl-pyrroliden-2/3-yl)-methanols in good yields by using the $NaBH_4$–I_2 system. Aromatisation and in situ oxidation of these alcohols using DDQ produced *N*-aryl-2/3-formyl-pyrroles, which act as key starting material and intermediates in the synthesis of several bioactive compounds.

1. Introduction

The pyrrole ring constitutes a basic heteroaromatic structure. Some substituted pyrroles are highly biologically active compounds, which make up an important class of synthetic pharmaceuticals[1a] and natural products with fungicidal[1b] and insecticidal[1c] activities. They also constitute the vital building blocks of the porphyrin ring systems present in chlorophyll, haeme, vitamin B_{12} and the bile pigments.[2] Additionally, there are a number of pyrrole-containing small molecules that exhibit interesting biological activities,[3a–d] for example, 3-substituted *N*-arylpyrroles act as potent aldose reductase (AR) inhibitors.[3e]

Among the substituted pyrroles, mono- and bi-arylpyrrole derivatives are of special interests to both chemists as well as biologists due to their remarkable bioactivities.[4] 1,5-Di-arylpyrrole-3-acetic acids and esters act as potent and highly selective cyclooxygenase-2 inhibitors.[5]

1,2-Diarylpyrrole **i** is an excellent inhibitor of COX-2 with an IC_{50} of 14 nm. Pyrrole **iii** is also a very potent (COX-2, IC_{50}= 60 nm) and selective (COX-1/COX-2>1700) inhibitor. Similarly, pyrrole **ii** inhibited COX-2 with an IC_{50}=0.5 μm while showing no inhibition of COX-1 at 100 μM.[6]



HIV-1 protease inhibitors with an *N*-aryl-pyrrole-containing moiety in the P_3 position **I** have excellent antiviral potency with improved aqueous solubility.[7] 3-(1*H*-Pyrrol-1-yl)-2-oxazolidinones **II** show antimycobacterial activity,[8] and *N*-phenyl-3-(aminomethyl)-pyrroles **III** act as potential antipsychotic agents.[9] In all cases (Fig. 1) the key synthetic intermediate was 3-formyl-*N*-phenyl pyrrole **IV**.[7–9] Generally *N*-arylpyrroles were prepared by the Clauson-Kaas reaction with 2,5-dimethoxytetrahydrofuran in refluxing acetic acid from commercially available anilines. But the reaction of pyrrole with the Vilsmeir reagent gave a mixture of 2-formyl-1-arylpyrroles and 3-formyl-1-aryl-pyrroles. Among them most 3-substituted arylpyrroles showed a higher 5-HT_7 affinity than the 2-substituted compounds.[10]

Although there are a number of potentially useful methods for the synthesis of *N*-arylpyrroles, 3-substituted *N*-arylpyrroles are the most difficult to synthesise since most electrophilic aromatic substitution reactions, as well as lithiation reactions, of *N*-substituted pyrroles occur at the 2-position,[11] and so functionalisation at the 3-position of pyrrole is a challenging goal in synthetic research.

Keywords: Lactam; Pyrrole; Reduction; Oxidative aromatisation.
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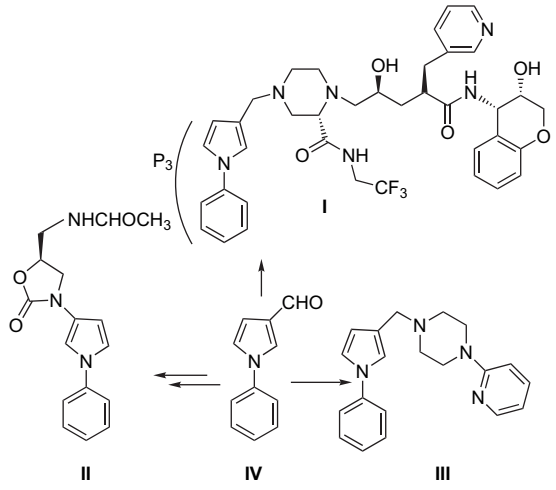
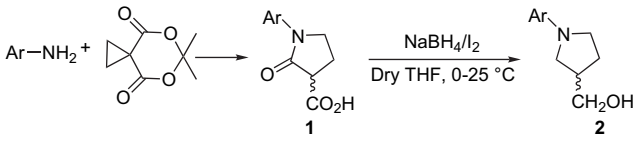


Figure 1.

As a part of our continued interest in selective reductions,[12] we initiated an investigation to find applications of the $NaBH_4$–I_2 reagent system[13] on *N*-aryl-γ-lactam derivatives, and discovered an efficient method[14] for the conversion of *N*-aryl-γ-lactam carboxylic acids[15] to the desired *N*-arylformylpyrrole derivatives. A part of this result has been reported recently in a communication,[14] and we wish to present here a comparative study of the effect of this reagent system on three different types of *N*-aryl-γ-lactam carboxylic acids, feasibility of the formation of *N*-arylformylpyrroles together with the experimental and spectral details of our earlier results.

2. Results and discussion

N-Aryl-2-oxo-pyrrolidine-3-carboxylic acids **1** were synthesised at room temperature by the reaction of substituted arylamines and 6,6-dimethyl-5,7-dioxaspiro[2.5]octane-4,8-dione.[16] γ-Lactam **1** upon treatment with $NaBH_4$–I_2 in dry THF at room temperature furnished (*N*-aryl-pyrrolidin-3-yl)-methanol **2** in good yield (Scheme 1,Table 1).



Scheme 1.

Table 1

2-Oxo-*N*-aryl-pyrrolidine-3-carboxylic acid	Ar	*N*-aryl-pyrrolidin-3-ylmethanol	Yield (%)
1a	4-CH_3–C_6H_4	**2a**	76
1b	4-Br–C_6H_4	**2b**	81
1c	4-Cl–C_6H_4	**2c**	82
1d	3,4-Cl,Cl–C_6H_3	**2d**	80
1e	3-Cl,4-F–C_6H_3	**2e**	78

To further examine the generality of the reaction, *N*-aryl-5-oxo-pyrrolidine-3-carboxylic acids **1′** were synthesised by the condensation of substituted arylamines with methylenesuccinic acid (itaconic acid).[17] Now on treatment with $NaBH_4$–I_2 in dry THF at 0–78 °C, γ-lactam **1′** afforded (*N*-aryl-pyrrolidin-3-yl)-methanol **2** in very good yield (Scheme 2 and Table 2).

Table 2

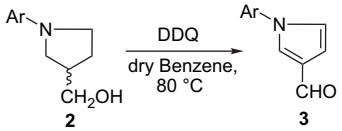
5-Oxo-*N*-aryl-pyrrolidine-3-carboxylic acid	Ar	*N*-aryl-pyrrolidin-3-ylmethanol	Yield (%)
1′a	4-CH_3–C_6H_4	**2a**	91
1′b	4-Br–C_6H_4	**2b**	94
1′c	4-Cl–C_6H_4	**2c**	96
1′d	3,4-Cl,Cl–C_6H_3	**2d**	88
1′e	3-Cl,4-F–C_6H_3	**2e**	85

In this case, the starting material itaconic acid is cheaper and air-stable than 6,6-dimethyl-5,7-dioxaspiro[2.5]octane-4,8-dione, but the reduction step in Scheme 2 is slower than that in Scheme 1. γ-Lactam carboxylic acids **1** were reduced to **2** at room temperature within 2 h, whereas nearly 3.5–4 h was required for the complete conversion of **1′** to **2** at room temperature. However, under refluxing condition (78 °C), *N*-aryl-5-oxo-pyrrolidine-3-carboxylic acids **1′** were reduced to (*N*-aryl-pyrrolidin-3-yl)-methanol **2** within 30 min, and the yield of alcohol **2** in Scheme 2 is better than that in Scheme 1.

(1-Substituted pyrrolidin-3-yl)methanols and their corresponding chlorides[18] are useful intermediates for the preparation of a number of physiologically active compounds of therapeutic value.

We hoped that DDQ[19] might bring about oxidative aromatisation of *N*-substituted pyrrolidin-3-ylmethanols to produce *N*-aryl-3-formylpyrroles, and this proved to be the case.

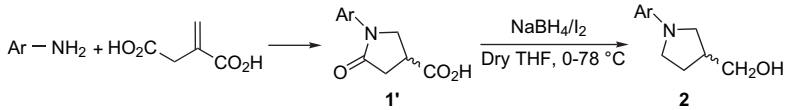
Aromatisation followed by in situ oxidation of **2** by DDQ furnished the desired compound **3** in one step and in good yield (Scheme 3, Table 3).



Scheme 3.

A recent study showed that *N*-aryl-2-formylpyrroles could act as key starting materials for the synthesis of isotactic-polypropylene (IPP) catalysts[20] and certain pyrrole Mannich bases that act as antipsychotic agents.[21]

The above reports and the pleasing outcome of the above reactions (Schemes 1–3) prompted us to extend this method to

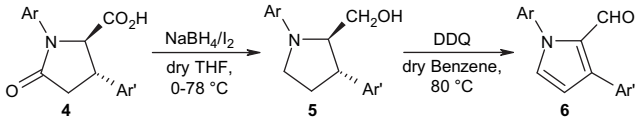


Scheme 2.

Table 3

Pyrrolidin-3-ylmethanol	Ar	3-Formylpyrrole	Yield (%)
2a	4-CH_3–C_6H_4	**3a**	62
2b	4-Br–C_6H_4	**3b**	64
2c	4-Cl–C_6H_4	**3c**	65
2d	3,4-Cl,Cl–C_6H_3	**3d**	62
2e	3-Cl,4-F–C_6H_3	**3e**	60

the synthesis of *N*-aryl-2-formylpyrroles. We selected *N*-aryl-5-oxo-3-aryl/heteroaryl-pyrrolidine-2-carboxylic acids **4**[15] to investigate the generality of the reaction, and assess the effect of steric crowding surrounding the carboxylic acid group at the 2-position of γ-lactam **4**. While the reduction was successful, it was much slower than those reported in Tables 1 and 2; it took nearly 2–3 h for the complete conversion of **4** to provide **5** in refluxing THF (Scheme 4, Table 4). But the rate of DDQ mediated oxidative aromatisation of (1,3-diaryl-pyrrolidine-2-yl)-methanols **5** to afford *N*-aryl-2-formyl-3-aryl/heteroaryl-pyrroles **6** (Scheme 4 and Table 5) is little faster than those reported in Table 3.



Scheme 4.

Table 4

γ-Lactam-carboxylic acid	Ar	Ar′	Pyrrolidin-2-ylmethanol	Yield (%)
4a	4-Cl–C_6H_4	2-Thienyl	**5a**	79
4b	4-CH_3–C_6H_4	Phenyl	**5b**	83
4c	4-Cl–C_6H_4	Phenyl	**5c**	85
4d	3,4-F,F–C_6H_3	Phenyl	**5d**	82
4e	3-Cl,4-F–C_6H_3	Phenyl	**5e**	80

Table 5

Pyrrolidin-2-ylmethanol	Ar	Ar′	2-Formylpyrrole	Yield (%)
5a	4-Cl–C_6H_4	2-Thienyl	**6a**	67
5b	4-CH_3–C_6H_4	Phenyl	**6b**	70
5c	4-Cl–C_6H_4	Phenyl	**6c**	72
5d	3,4-F,F–C_6H_3	Phenyl	**6d**	68
5e	3-Cl,4-F–C_6H_3	Phenyl	**6e**	69

All the compounds were characterised by interpretation of the usual spectroscopic and analytical data.

3. Conclusion

In conclusion we have disclosed that $NaBH_4$–I_2 can effectively reduce both the lactam carbonyl and the labile (β-carbonyl) carboxylic acid groups of *N*-aryl-2-oxo-pyrrolidine-3-carboxylic acids at room temperature and investigated the positional effect of carboxylic acid groups on the reaction temperature, rate and yield of the reduction. Furthermore, the reagent system used is safe, simple and inexpensive. We have also determined that DDQ is an efficient reagent for the oxidative aromatisation of *N*-arylpyrrolidin-3-ylmethanols in good yields, providing a simple and novel approach for the conversion of both *N*-aryl-2-oxo-pyrrolidine-3-carboxylic acids and *N*-aryl-5-oxo-pyrrolidine-3-carboxylic acids into *N*-aryl-3-formylpyrroles, which play a central role as key intermediates in the synthesis of several bioactive compounds.[7–9] This methodology has been successfully applied to the synthesis of a range of *N*-aryl-2-formylpyrroles. The operational simplicity and economic viability of this method definitely broaden the preview of further study in this area.

4. Experimental

4.1. General remarks

^{1}H NMR (200 MHz) spectra were recorded on a BRUKER-AC 200 MHz spectrometer. Chemical shifts are reported in parts per million from tetramethylsilane with the solvent resonance as the internal standard (deuterochloroform: 7.26 ppm). Data are reported as follows: chemical shifts, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, br=broad, m=multiplet), coupling constant (Hz). ^{13}C NMR (50 MHz) spectra were recorded on a BRUKER-AC 200 MHz spectrometer with complete proton decoupling. Chemical shifts are reported in parts per million from tetramethylsilane with the solvent resonance as the internal standard (deuterochloroform: 77.0 ppm). IR spectra were recorded on Perkin–Elmer 883 and Shimadzu FTIR-8300 infrared spectrometers. EIMS (70 eV) spectra were taken using a VG Autospec M mass spectrometer and ESI-MS spectra were taken using Waters LCT mass spectrometer. Elemental analysis was carried out by using an Elemental Analyzer VARIOEL instrument.

All reactions were carried out under an argon atmosphere. Chromatographic purification was done with either 60–120 or 100–200 mesh silica gel (SRL). For reaction monitoring, precoated silica gel 60 F_{254} TLC sheets (Merck) were used. Petroleum ether refers to the fraction boiling in the range 60–80 °C. Tetrahydrofuran was freshly distilled over benzophenone-sodium.

4.2. General procedure for the synthesis of *N*-aryl-2-oxo-pyrrolidine-3-carboxylic acids 1[16]

To 6,6-dimethyl-5,7-dioxaspiro[2.5]octane-4,8-dione (10 mmol) was added substituted arylamine (30 mmol). The mixture became a homogeneous solution after 20 min and was allowed to stir at room temperature for 11–14 h. The resulting crystalline mass was diluted with 150 mL of chloroform, washed three times with aqueous 10% hydrochloric acid (15 mL), washed once with brine (50 mL) and dried over anhydrous Na_2SO_4. Evaporation of solvent by rotavac furnished the crude acid, which was recrystallised from chloroform–hexane to afford **1** in 80–86% yield.

4.2.1. 2-Oxo-1-(*p*-tolyl)-pyrrolidine-3-carboxylic acid (1a). Colourless solid; yield 80%; mp 132–134 °C (ethanol).

IR (KBr) ν_{max} 1726.7, 1685.4 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.33 (s, 3H), 2.35–2.55 (m, 2H), 3.46–3.52 (t, 1H, J~9.2 Hz), 3.73–3.97 (m, 2H), 7.13 (d, 2H, J~8.2 Hz), 7.34 (d, 2H, J~6.9 Hz). ^{13}C NMR (50 MHz, DMSO-d_6+$CDCl_3$) δ 21.0, 47.2, 47.7, 120.6, 129.6, 135.4, 135.9, 169.8, 170.9. Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.63; H, 6.01; N, 6.32%. ESI-MS for $C_{12}H_{13}NO_3$ [M], $[M+H]^+$=220.10.

4.2.2. 1-(4-Bromophenyl)-2-oxopyrrolidine-3-carboxylic acid (1b). White solid; yield 73%; mp 147–150 °C (ethanol). IR (KBr) ν_{max} 1718.9, 1685.9 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.38–2.59 (m, 2H), 3.63–3.69 (t, 1H, J~9.4 Hz), 3.87–3.92 (m, 2H), 7.47–7.54 (m, 4H). ^{13}C NMR (50 MHz, DMSO-d_6+$CDCl_3$): δ 21.6, 46.7, 49.5, 117.1, 121.1, 131.3, 137.6, 169.3, 170.7. Anal. Calcd for $C_{11}H_{10}NO_3Br$: C, 46.50; H, 3.55; N, 4.93. Found: C, 46.65; H, 3.52; N, 4.87%. ESI-MS for $C_{11}H_{10}NO_3Br$ [M], $[M+H]^+$=283.97 (^{79}Br), 285.97 (^{81}Br).

4.2.3. 1-(4-Chlorophenyl)-2-oxopyrrolidine-3-carboxylic acid (1c). White solid; yield 83%; mp 136–138 °C (ethanol). IR (KBr) ν_{max} 1719.5, 1685.8 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.30–2.54 (m, 2H), 3.52–3.60 (t, 1H, J~8.7 Hz), 3.71–3.96 (m, 2H), 7.27 (d, 2H, J~8 Hz), 7.53 (d, 2H, J~8.5 Hz). ^{13}C NMR (50 MHz, DMSO-d_6+$CDCl_3$): δ 21.6, 46.6, 49.4, 120.7, 128.2, 129.2, 137.1, 169.2, 170.7. Anal. Calcd for $C_{11}H_{10}ClNO_3$: C, 55.13; H, 4.21; N, 5.84. Found: C, 55.22; H, 4.19; N, 5.80%. ESI-MS for $C_{11}H_{10}ClNO_3$ [M], $[M+H]^+$=240.05 (^{35}Cl,^{35}Cl), 242.05 (^{35}Cl,^{37}Cl).

4.2.4. 1-(3,4-Dichlorophenyl)-2-oxopyrrolidine-3-carboxylic acid (1d). White solid; yield 81%; mp 145–147 °C (ethanol). IR (KBr) ν_{max} 1718.7, 1685.5 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.29–2.51 (m, 2H), 3.48–3.56 (t, 1H, J~9.1 Hz), 3.66–3.91 (m, 2H), 7.29–7.44 (m, 2H), 7.76 (d, 1H, J~2.4 Hz). ^{13}C NMR (50 MHz, DMSO-d_6+$CDCl_3$): δ 21.9, 46.9, 49.8, 116.9, 121.4, 127.8, 130.2, 132.4, 138.4, 169.8, 170.9. Anal. Calcd for $C_{11}H_9NO_3Cl_2$: C, 48.20; H, 3.31; N, 5.11. Found: C, 48.29; H, 3.33; N, 5.06%. ESI-MS for $C_{11}H_9NO_3Cl_2$ [M], $[M+H]^+$=274.00 (^{35}Cl,^{35}Cl), 276.00 (^{35}Cl,^{37}Cl), 278.00 (^{37}Cl,^{37}Cl).

4.2.5. 1-(3-Chloro-4-fluorophenyl)-2-oxopyrrolidine-3-carboxylic acid (1e). White solid; yield 78%; mp 154–157 °C (ethanol). IR (KBr) ν_{max} 1719.2, 1685.6 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.24–2.54 (m, 2H), 3.49–3.57 (t, 1H, J~9.2 Hz), 3.67–3.89 (m, 2H), 7.01–7.10 (t, 1H, J~8.7 Hz), 7.35–7.43 (m, 1H), 7.70 (dd, 1H, J~2.6 Hz and 6.4 Hz). ^{13}C NMR (50 MHz, DMSO-d_6+$CDCl_3$) δ 21.7, 46.9, 49.6, 115.9, 116.1, 116.3, 119.3, 119.4, 1231.8, 135.5, 135.5, 142.4, 149.6, 156.8, 169.4, 170.9. Anal. Calcd for $C_{11}H_9O_3NFCl$: C, 51.28; H, 3.52; N, 5.44. Found: C, 51.41; H, 3.48; N, 5.36%. ESI-MS for $C_{11}H_9O_3NFCl$ [M], $[M+H]^+$=258.03 (^{35}Cl), 260.03 (^{37}Cl).

4.3. General procedure for the synthesis of *N*-aryl-5-oxopyrrolidine-3-carboxylic acids 1′[17]

To itaconic acid (10 mmol) substituted arylamine (10 mmol) was added and the dry reactants were maintained at the fusion point for 20 min in a flask attached to a reflux condenser. After that, the molten mass was cooled in ice-cold water and then dissolved in sodium bicarbonate solution, treated with charcoal, filtered and the filtrate was acidified with ice-cold dilute hydrochloric acid. The precipitated acid **1′** was recrystallised from aqueous ethanol.

4.3.1. 5-Oxo-1-(*p*-tolyl)-pyrrolidine-3-carboxylic acid (1′a). White solid; yield 90%; mp 186–188 °C (ethanol). IR (KBr) ν_{max} 1702.3, 1685.4 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.35 (s, 3H), 2.87–2.98 (m, 2H), 3.19–3.26 (m, 1H), 3.98–4.24 (m, 2H), 7.14–7.18 (m, 2H), 7.31–7.38 (m, 2H). ^{13}C NMR (50 MHz, DMSO-d_6+$CDCl_3$) δ 20.8, 35.4, 35.7, 50.6, 120.6, 129.3, 134.4, 136.2, 171.8, 174.3. Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.82; H, 5.95; N, 6.34%. ESI-MS for $C_{12}H_{13}NO_3$ [M], $[M+H]^+$=220.12.

4.3.2. 1-(4-Bromophenyl)-5-oxopyrrolidine-3-carboxylic acid (1′b). White solid; yield 78%; mp 172–174 °C (ethanol). IR (KBr) ν_{max} 1701.8, 1685.8, 1654.9 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.72–2.88 (m, 2H), 3.20–3.27 (m, 1H), 3.86–4.05 (m, 2H), 7.30–7.45 (m, 4H). ^{13}C NMR (50 MHz, DMSO-d_6+$CDCl_3$): δ 35.0, 35.1, 49.8, 116.7, 120.9, 131.2, 137.6, 171.5, 173.6. Anal. Calcd for $C_{11}H_{10}NO_3Br$: C, 46.50; H, 3.55; N, 4.93. Found: C, 46.59; H, 3.51; N, 4.90%. ESI-MS for $C_{11}H_{10}NO_3Br$ [M], $[M+H]^+$=283.97 (^{79}Br), 285.97 (^{81}Br).

4.3.3. 1-(4-Chlorophenyl)-5-oxopyrrolidine-3-carboxylic acid (1′c). White solid; yield 92%; mp 150–152 °C (ethanol). IR (KBr) ν_{max} 1702.5, 1686.1, 1655.2 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.75–3.01 (m, 2H), 3.25–3.34 (m, 1H), 3.92–4.13 (m, 2H), 7.22–7.31 (m, 2H), 7.49–7.55 (m, 2H). ^{13}C NMR (50 MHz, DMSO-d_6+$CDCl_3$) δ 35.3, 35.3, 50.2, 120.9, 128.5, 128.9, 137.4, 171.8, 173.5. Anal. Calcd for $C_{11}H_{10}ClNO_3$: C, 55.13; H, 4.21; N, 5.84. Found: C, 55.24; H, 4.23; N, 5.81%. ESI-MS for $C_{11}H_{10}ClNO_3$ [M], $[M+H]^+$=240.03 (^{35}Cl,^{35}Cl), 242.03 (^{35}Cl,^{37}Cl).

4.3.4. 1-(3,4-Dichlorophenyl)-5-oxopyrrolidine-3-carboxylic acid (1′d). White solid; yield 91%; mp 139–142 °C (ethanol). IR (KBr) ν_{max} 1701.9, 1685.9 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.76–2.97 (m, 2H), 3.18–3.28 (m, 1H), 3.96–4.14 (m, 2H), 7.28–7.45 (m, 3H). ^{13}C NMR (50 MHz, DMSO-d_6+$CDCl_3$) δ 34.9, 35.1, 49.8, 118.6, 120.9, 126.6, 130.3, 131.7, 138.3, 171.9, 173.7. Anal. Calcd for $C_{11}H_9NO_3Cl_2$: C, 48.20; H, 3.31; N, 5.11. Found: C, 48.12; H, 3.34; N, 5.15%. ESI-MS for $C_{11}H_9O_3NCl_2$ [M], $[M+H]^+$=274.00 (^{35}Cl,^{35}Cl), 276.00 (^{35}Cl,^{37}Cl), 278.00 (^{37}Cl,^{37}Cl).

4.3.5. 1-(3-Chloro-4-fluorophenyl)-5-oxopyrrolidine-3-carboxylic acid (1′e). White solid; yield 87%; mp 132–134 °C (ethanol). IR (KBr) ν_{max} 1703.2, 1686.5, 1655.4 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.75–2.83 (m, 2H), 3.19–3.27 (t, 1H, J~9.2 Hz), 3.84–4.01 (m, 2H), 7.03 (t, 1H, J~8.8 Hz), 7.31–7.39 (m, 1H), 7.63–7.68 (m, 1H). ^{13}C NMR (50 MHz, DMSO-d_6+$CDCl_3$): δ 35.1, 35.3, 50.3, 116.0, 116.5, 121.9, 125.7, 127.8, 135.8, 145.8, 152.1, 156.9, 171.9, 173.8. Anal. Calcd for $C_{11}H_9O_3NFCl$: C, 51.28; H, 3.52; N, 5.44. Found: C, 51.41; H, 3.48; N, 5.36%. ESI-MS for $C_{11}H_9O_3NFCl$ [M], $[M+H]^+$=258.03 (^{35}Cl), 260.03 (^{37}Cl).

4.4. General procedure for the synthesis of *N*-arylpyrrolidin-3-ylmethanols 2 from *N*-aryl-2-oxo-pyrrolidine-3-carboxylic acids 1

To a stirred solution of $NaBH_4$ (6 mmol) in dry THF (20 mL) a solution of iodine (3 mmol) in dry THF (5 mL) was added dropwise under argon at 0 °C over 45 min. Next, lactam-monoacid **1** (2 mmol) in dry THF (8 mL) was added and the mixture was stirred at room temperature (25 °C) for 2 h. The mixture was then cooled to 0 °C and the excess hydride was carefully destroyed by dropwise addition of methanol (10 mL). The solvents were removed under vacuum and the residue was taken up in 30 mL of 20% aqueous KOH and the mixture was extracted three times with ether (80 mL). The ether layer was washed with sodium thiosulfate solution and then with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude product **2** was purified by column chromatography [silica gel/petroleum ether (60–80 °C)–ethyl acetate (40:1)].

4.5. General procedure for the synthesis of *N*-arylpyrrolidin-3-ylmethanols 2 from *N*-aryl-5-oxo-pyrrolidine-3-carboxylic acids 1′

To a stirred solution of $NaBH_4$ (6 mmol) in dry THF (20 mL) a solution of iodine (3 mmol) in dry THF (5 mL) was added dropwise under argon at 0 °C over 45 min. Next, lactam-monoacid **1′** (2 mmol) in dry THF (8 mL) was added and the mixture was stirred at room temperature (25 °C) for 10 min. Then the mixture was refluxed for 30 min, cooled to 0 °C and the excess hydride was carefully destroyed by dropwise addition of methanol (10 mL). The solvents were removed under vacuum and the residue was taken up in 20% aqueous KOH (30 mL) and the mixture was extracted three times with ether (80 mL). The ether layer was washed with sodium thiosulfate solution and then with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude product **2** was purified by column chromatography [silica gel/petroleum ether (60–80 °C)–ethyl acetate (40:1)].

4.5.1. [1-(*p*-Tolyl)pyrrolidin-3-yl]methanol 2a. Colourless, viscous oily material; yield 76% from **1a**, 91% from **1′a**. IR (neat) ν_{max} 3394.5, 2921.4 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.76–1.85 (m, 1H), 2.02–2.11 (m, 1H), 2.33 (s, 3H), 2.42–2.49 (m, 1H), 3.08–3.15 (m, 1H), 3.27–3.45 (m, 3H), 3.57–3.68 (m, 2H), 6.64 (d, 2H, *J*~8.4 Hz), 7.05 (d, 2H, *J*~8.3 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.3, 27.9, 40.8, 47.5, 50.9, 65.3, 112.1, 125.3, 128.2, 146.0. Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.48; H, 8.92; N, 7.26%. ESI-MS for $C_{12}H_{17}NO$ [M], $[M+H]^+$=192.12.

4.5.2. [1-(4-Bromophenyl)pyrrolidin-3-yl]methanol 2b. Colourless, viscous oily material; yield 81% from **1b**, 94% from **1′b**. IR (neat) ν_{max} 3365.6, 2924.9 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.78–1.86 (m, 1H), 2.12–2.18 (m, 1H), 2.51–2.58 (m, 1H), 3.11–3.16 (m, 1H), 3.23–3.44 (m, 3H), 3.61–3.70 (m, 2H), 6.49–6.54 (m, 2H), 7.16–7.24 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.9, 40.8, 47.2, 50.6, 64.9, 107.5, 113.3, 131.7, 146.7. Anal. Calcd for $C_{11}H_{14}NOBr$: C, 51.58; H, 5.51; N, 5.47. Found: C, 51.49; H, 5.55; N, 5.50%. ESI-MS for $C_{11}H_{14}NOBr$ [M], $[M+H]^+$=256.03 (^{79}Br), 258.03 (^{81}Br).

4.5.3. [1-(4-Chlorophenyl)pyrrolidin-3-yl]methanol 2c. Colourless, viscous oily material; yield 82% from **1c**, 96% from **1′c**. IR (neat) ν_{max} 3359.4, 2924.3 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.79–1.86 (m, 1H), 2.12–2.16 (m, 1H), 2.55–2.59 (m, 1H), 3.07–3.13 (m, 1H), 3.25–3.39 (m, 3H), 3.63–3.69 (m, 2H), 6.44–6.52 (m, 2H), 7.14–7.25 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 27.8, 40.9, 47.3, 50.6, 65.1, 112.7, 120.5, 128.8, 146.4. Anal. Calcd for $C_{11}H_{14}NOCl$: C, 62.41; H, 6.67; N, 6.62. Found: C, 62.53; H, 6.65; N, 6.56%. ESI-MS for $C_{11}H_{14}NOCl$ [M], $[M+H]^+$=212.07 (^{35}Cl), 214.07 (^{37}Cl).

4.5.4. [1-(3,4-Dichlorophenyl)pyrrolidin-3-yl]methanol 2d. Colourless, viscous oily material; yield 80% from **1d**, 88% from **1′d**. IR (neat) ν_{max} 3357.4, 2925.1 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.77–1.87 (m, 1H), 2.06–2.19 (m, 1H), 2.22–2.27 (br s, 1H), 2.53–2.60 (m, 1H), 3.04–3.12 (m, 1H), 3.22–3.42 (m, 3H), 3.59–3.72 (m, 2H), 6.34–6.40 (dd, 1H, *J*~2.7 Hz and 8.8 Hz), 6.59 (d, 1H, *J*~2.7 Hz), 7.20 (d, 1H, *J*~8.8 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.8, 40.9, 47.2, 50.5, 64.8, 111.3, 112.9, 118.2, 130.3, 132.6, 147.1. Anal. Calcd for $C_{10}H_{13}Cl_2NO$: C, 53.68; H, 5.32; N, 5.69. Found: C, 53.53; H, 5.34; N, 5.73%. ESI-MS for $C_{11}H_{13}Cl_2NO$ [M], $[M+H]^+$=246.03 (^{35}Cl), 248.03 (^{35}Cl and ^{37}Cl), 250.03 (^{37}Cl).

4.5.5. [1-(3-Chloro-4-fluorophenyl)pyrrolidin-3-yl]-methanol 2e. Colourless, viscous oily material; yield 78% from **1e**, 85% from **1′e**. IR (neat) ν_{max} 3364.3, 2924.0 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.80–1.91 (m, 1H), 2.11–2.17 (m, 1H), 2.45–2.57 (m, 1H), 3.05–3.12 (m, 1H), 3.26–3.41 (m, 3H), 3.62–3.71 (m, 2H), 6.48–6.55 (m, 2H), 6.68–6.75 (m, 1H), 6.98–7.04 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.8, 40.9, 47.6, 50.9, 64.9, 110.6, 110.7, 112.7, 116.4, 116.9, 120.6, 121.0, 144.9, 147.7, 152.4. Anal. Calcd for $C_{11}H_{13}NOClF$: C, 57.52; H, 5.71; N, 6.10. Found: C, 57.63; H, 5.66; N, 6.06%. ESI-MS for $C_{11}H_{13}NOClF$ [M], $[M+H]^+$=230.07 (^{35}Cl), 232.07 (^{37}Cl).

4.6. General procedure for the synthesis of *N*-aryl-3-formylpyrroles 3

Compound **2** (1.4 mmol) was heated at reflux with DDQ (8 mmol) in dry benzene [*caution*: carcinogenic] (40 mL) for 8 h. After completion of the reaction, the organic layer was washed with aqueous $NaHCO_3$ solution, dried over anhydrous Na_2SO_4, the solvent was evaporated and the desired aldehyde **3** was purified by column chromatography [neutral alumina/petroleum ether (60–80 °C)–ethyl acetate (60:1)].

4.6.1. 1-(*p*-Tolyl)-3-formylpyrrole 3a. Colourless, viscous oily material; yield 62%. IR (neat) ν_{max} 1673.2 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.35 (s, 3H), 6.78 (d, 1H, *J*~2.7 Hz), 7.03 (d, 1H, *J*~2.7 Hz), 7.28–7.41 (m, 4H), 7.60 (s, 1H), 9.84 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.6, 110.1, 117.8, 120.1, 121.9, 129.8, 134.1, 137.9, 185.3. Anal. Calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.72; H, 5.96; N, 7.61%. ESI-MS for $C_{12}H_{11}NO$ [M], $[M+H]^+$=186.09.

4.6.2. 1-(4-Bromophenyl)-3-formylpyrrole 3b. Colourless, viscous oily material; yield 64%. IR (neat) ν_{max} 1672.6 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 6.81 (d, 1H,

J~2.7 Hz), 7.05 (d, 1H, *J*~2.8 Hz), 7.28–7.32 (m, 2H), 7.58–7.61 (m, 2H), 7.63 (s, 1H), 9.85 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 110.1, 120.8, 122.1, 122.6, 126.8, 128.5, 132.9, 138.6, 185.4. Anal. Calcd for $C_{11}H_8NOBr$: C, 52.83; H, 3.22; N, 5.60. Found: C, 52.95; H, 3.20; N, 5.64%. ESI-MS for $C_{11}H_8NOBr$ [M], $[M+H]^+$=249.98 (^{79}Br), 251.97 (^{81}Br).

4.6.3. 1-(4-Chlorophenyl)-3-formylpyrrole 3c. Colourless, viscous oily material; yield 65%. IR (neat) ν_{max} 1671.9 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.80 (d, 1H, *J*~2.8 Hz), 7.05 (d, 1H, *J*~2.7 Hz), 7.33–7.48 (m, 4H), 7.62 (s, 1H), 9.84 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 109.9, 122.2, 122.3, 126.8, 128.4, 129.9, 133.1, 138.1, 185.4. Anal. Calcd for $C_{11}H_8NOCl$: C, 64.23; H, 3.89; N, 6.81. Found: C, 64.12; H, 3.84; N, 6.87%. ESI-MS for $C_{11}H_8NOCl$ [M], $[M+H]^+$=206.01 (^{35}Cl), 208.01 (^{37}Cl).

4.6.4. 1-(3,4-Dichlorophenyl)-3-formylpyrrole 3d. Colourless, viscous oily material; yield 62%. IR (neat) ν_{max} 1672.2 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.81–6.83 (m, 1H), 7.03–7.06 (m, 1H), 7.29–7.31 (m, 1H), 7.54–7.58 (m, 2H), 7.63 (d, 1H, *J*~1.9 Hz), 9.84 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 110.1, 117.9, 120.9, 122.4, 123.8, 123.8, 127.0, 128.5, 185.35. Anal. Calcd for $C_{11}H_7NOCl_2$: C, 55.03; H, 2.94; N, 5.83. Found: C, 55.17; H, 2.96; N, 5.78%. ESI-MS for $C_{11}H_7NOCl_2$ [M], $[M+H]^+$=239.98 (^{35}Cl), 241.98 (^{35}Cl and ^{37}Cl).

4.6.5. 1-(3-Chloro-4-fluorophenyl)-3-formylpyrrole 3e. Colourless, viscous oily material; yield 60%. IR (neat) ν_{max} 1670.6 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.78 (d, 1H, *J*~1.8 Hz), 6.95–7.00 (m, 2H), 7.30–7.35 (m, 2H), 7.56–7.58 (t, 1H, *J*~1.9 Hz), 9.83 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 109.9, 122.2, 122.3, 126.9, 128.4, 129.9, 133.1, 138.1, 185.4. Anal. Calcd for $C_{11}H_7NOClF$: C, 59.08; H, 3.16; N, 6.26. Found: C, 58.96; H, 3.18; N, 6.21%. ESI-MS for $C_{11}H_7NOClF$ [M], $[M+H]^+$=224.02 (^{35}Cl), 226.02 (^{37}Cl).

4.7. General procedure for the synthesis of *N*-aryl-5-oxo-3-aryl/heteroaryl-pyrrolidine-2-carboxylic acids 4[15]

To a solution of 1-aryl-2,2-dicarbethoxy-5-oxo-3-aryl/heteroaryl-pyrrolidine (8 mmol) in ethanol (40 mL), a solution of KOH (17 mmol) in 10–15 mL water was added and refluxed for 5 h. Excess ethanol was distilled out and the residue was diluted further with 20 mL ice-cold water. It was then acidified with ice-cold dilute hydrochloric acid. The precipitate was dissolved in sodium bicarbonate solution and extracted with ether to remove neutral matter. The aqueous layer was again acidified with ice-cold dilute hydrochloric acid. The precipitated acid **4** was recrystallised from aqueous ethanol.

4.7.1. 1-(4-Chlorophenyl)-5-oxo-3-(2-thienyl)pyrrolidine-2-carboxylic acid 4a.[15b] White solid; yield 82%; mp 216–217 °C (ethanol). IR (KBr) ν_{max} 1736.1, 1648.8 cm^{-1}; ^{1}H NMR (DMSO-d_6+$CDCl_3$, 200 MHz): δ 2.72 (dd, 1H, *J*~3.7 Hz and 17.1 Hz), 3.16 (dd, 1H, *J*~8.8 Hz and 17.0 Hz), 3.78–3.86 (m, 1H), 4.61 (d, 1H, *J*~2.9 Hz), 6.90 (d, 2H, *J*~3.5 Hz), 7.18–7.21 (m, 1H), 7.29 (dd, 2H, *J*~2.4 Hz and 6.7 Hz), 7.39 (dd, 2H, *J*~2.4 Hz and 6.8 Hz). Anal. Calcd for $C_{15}H_{12}ClNO_3S$: C, 55.99; H, 3.76; N, 4.35. Found: C, 56.08; H, 3.74; N, 4.39%. ESI-MS for $C_{15}H_{12}ClNO_3S$ [M], $[M+H]^+$=321.02 (^{35}Cl), 323.02 (^{37}Cl).

4.7.2. 5-Oxo-3-phenyl-1-(*p*-tolyl)pyrrolidine-2-carboxylic acid 4b. White solid; yield 91%; mp 170–172 °C (ethanol). IR (KBr) ν_{max} 1739.5, 1654.7 cm^{-1}; ^{1}H NMR (DMSO-d_6+$CDCl_3$, 200 MHz): δ 2.19 (s, 3H), 2.55 (dd, 1H, *J*~3.2 Hz and 17.2 Hz), 3.15 (dd, 1H, *J*~9.2 Hz and 17.1 Hz), 3.53–3.59 (m, 1H), 4.46 (d, 1H, *J*~2.6 Hz), 7.02–7.05 (m, 2H), 7.13–7.35 (m, 7H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.8, 38.6, 41.3, 69.3, 121.9, 126.4, 127.5, 129.1, 129.5, 135.2, 135.6, 142.6, 172.9, 173.4. Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.27; H, 5.84; N, 4.72%. ESI-MS for $C_{18}H_{17}NO_3$ [M], $[M+H]^+$=296.12.

4.7.3. 1-(4-Chlorophenyl)-5-oxo-3-phenylpyrrolidine-2-carboxylic acid 4c. White solid; yield 92%; mp 209–212 °C (ethanol). IR (KBr) ν_{max} 1734.3, 1654.6 cm^{-1}; ^{1}H NMR (DMSO-d_6+$CDCl_3$, 200 MHz): δ 2.64 (dd, 1H, *J*~3.5 Hz and 17.4 Hz), 3.15 (dd, 1H, *J*~9.1 Hz and 17.3 Hz), 3.60–3.69 (m, 1H), 4.53 (d, 1H, *J*~2.8 Hz), 7.21–7.34 (m, 7H), 7.41–7.46 (m, 2H). ^{13}C NMR (50 MHz, DMSO-d_6+$CDCl_3$) δ 38.4, 40.9, 68.8, 122.6, 126.1, 127.4, 128.7, 128.9, 130.3, 136.6, 142.0, 172.3, 173.3. Anal. Calcd for $C_{17}H_{14}NO_3Cl$: C, 64.67; H, 4.47; N, 4.44. Found: C, 64.79; H, 4.44; N, 4.41%. ESI-MS for $C_{17}H_{14}NO_3Cl$ [M], $[M+H]^+$=316.07 (^{35}Cl), 318.07 (^{37}Cl).

4.7.4. 1-(3,4-Difluorophenyl)-5-oxo-3-phenylpyrrolidine-2-carboxylic acid 4d. White solid; yield 84%; mp 186–189 °C (ethanol). ^{1}H NMR (DMSO-d_6+$CDCl_3$, 200 MHz): δ 2.67 (dd, 1H, *J*~3.4 Hz and 17.3 Hz), 3.17 (dd, 1H, *J*~9.1 Hz and 17.3 Hz), 3.61–3.69 (m, 1H), 4.52 (d, 1H, *J*~2.8 Hz), 7.05–7.11 (m, 1H), 7.20–7.37 (m, 5H), 7.46–7.62 (m, 2H). ^{13}C NMR (50 MHz, DMSO-d_6+$CDCl_3$) δ 38.4, 40.9, 68.6, 110.9, 111.3, 116.7, 117.1, 120.0, 126.7, 127.3, 128.6, 128.9, 133.6, 142.7, 144.6, 146.9, 151.9, 172.0, 173.2. Anal. Calcd for $C_{17}H_{13}NO_3F_2$: C, 64.35; H, 4.13; N, 4.41. Found: C, 64.43; H, 4.11; N, 4.44%. ESI-MS for $C_{17}H_{13}NO_3F_2$ [M], $[M+H]^+$=318.09.

4.7.5. 1-(3-Chloro-4-fluorophenyl)-5-oxo-3-phenylpyrrolidine-2-carboxylic acid 4e. White solid; yield 88%; mp 158–161 °C (ethanol). ^{1}H NMR (DMSO-d_6+$CDCl_3$, 200 MHz): δ 2.71 (dd, 1H, *J*~3.5 Hz and 17.3 Hz), 3.16 (dd, 1H, *J*~9.2 Hz and 17.5 Hz), 3.56–3.65 (m, 1H), 4.53 (d, 1H, *J*~2.8 Hz), 7.08–7.24 (m, 2H), 7.27–7.45 (m, 5H), 7.62 (dd, 1H, *J*~2.7 Hz and 6.4 Hz). ^{13}C NMR (50 MHz, DMSO-d_6+$CDCl_3$) δ 37.4, 40.4, 68.1, 115.6, 116.0, 119.7, 120.1, 120.6, 123.3, 125.6, 126.8, 128.3, 134.2, 141.2, 151.9, 156.9, 171.4, 172.7. Anal. Calcd for $C_{17}H_{13}NO_3ClF$: C, 61.18; H, 3.93; N, 4.20. Found: C, 61.29; H, 3.90; N, 4.24%. ESI-MS for $C_{17}H_{13}NO_3ClF$ [M], $[M+H]^+$=334.06 (^{35}Cl), 336.06 (^{37}Cl).

4.8. General procedure for the synthesis of (1,3-diaryl-pyrrolidine-2-yl)-methanols 5

To a stirred solution of $NaBH_4$ (6 mmol) in dry THF (20 mL) a solution of iodine (3 mmol) in dry THF (5 mL) was added dropwise under argon at 0 °C over 45 min. Next, lactam-monoacid **4** (2 mmol) in dry THF (8 mL) was added and

the mixture was stirred at room temperature (25 °C) for 10 min. Then the mixture was heated at reflux for 2–3 h, cooled to 0 °C and the excess hydride was carefully destroyed by dropwise addition of methanol (10 mL). The solvents were removed under vacuum and the residue was taken up in 30 mL of 20% aqueous KOH and the mixture was extracted three times with ether (80 mL). The ether layer was washed with sodium thiosulfate solution and then with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude product **5** was purified by column chromatography [silica gel/petroleum ether (60–80 °C)–ethyl acetate (50:1)].

4.8.1. [1-(4-Chlorophenyl)-3-(2-thienyl)-pyrrolidin-2-yl]-methanol 5a. Colourless, viscous oily material; yield 79%. IR (liquid film) ν_{max} 3357.5, 2931.1 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.0–2.08 (br s, 1H), 2.44–2.54 (m, 1H), 3.34–3.57 (m, 3H), 3.73–3.92 (m, 4H), 6.61 (d, 2H, J~8.8 Hz), 6.74 (d, 1H, J~3.1 Hz), 6.86–6.91 (dd, 1H, J~3.4 Hz and 4.9 Hz), 7.11 (d, 1H, J~5.0 Hz), 7.18 (d, 2H, J~8.8 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 32.2, 42.0, 48.3, 62.1, 67.6, 113.5, 121.5, 123.4, 123.5, 126.0, 129.0, 145.8, 147.2. Anal. Calcd for $C_{15}H_{16}ClNOS$: C, 61.32; H, 5.49; N, 4.77. Found: C, 61.44; H, 5.46; N, 4.73%. EIMS m/z: 293 (M^+, 25.5%), 262 ($M^+-C_2H_5$, 100%).

4.8.2. [3-Phenyl-1-(*p*-tolyl)-pyrrolidin-2-yl]methanol 5b. Colourless, viscous oily material; yield 83%. IR (liquid film) ν_{max} 3392.8, 2931.4 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.97–2.03 (m, 1H), 2.28 (s, 3H), 2.38–2.52 (m, 1H), 3.37–3.49 (m, 1H), 3.53–3.63 (m, 2H), 3.66–3.72 (m, 1H), 3.78–3.81 (m, 1H), 3.86–3.92 (m, 1H), 6.66 (d, 2H, J~8.5 Hz), 7.06–7.13 (m, 4H), 7.12–7.35 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.01, 31.99, 46.66, 49.24, 60.38, 62.08, 114.16, 126.66, 127.00, 128.78, 129.21, 143.67, 145.48. Anal. Calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24. Found: C, 81.01; H, 7.87; N, 5.21%. EIMS m/z: 267 (M^+, 15.5%), 236 ($M^+-C_2H_5$, 100%).

4.8.3. [1-(4-Chlorophenyl)-3-phenyl-pyrrolidin-2-yl]-methanol 5c. Colourless, viscous oily material; yield 85%. IR (liquid film) ν_{max} 3376.8, 2930.1 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.34–2.52 (m, 2H), 3.31–3.40 (q, 1H, J~7.5 Hz), 3.48–3.57 (m, 2H), 3.68–3.80 (m, 2H), 3.83–3.89 (m, 1H), 6.54–6.62 (m, 2H), 7.08–7.16 (m, 2H), 7.20–7.34 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 32.0, 46.9, 48.7, 62.5, 66.8, 113.7, 121.6, 126.6, 127.0, 128.8, 129.1, 144.1, 145.8. Anal. Calcd for $C_{17}H_{18}NOCl$: C, 70.95; H, 6.30; N, 4.87. Found: C, 71.07; H, 6.27; N, 4.86%. ESI-MS for $C_{17}H_{18}NOCl$ [M], $[M+H]^+$=288.11 (^{35}Cl), 290.11 (^{37}Cl).

4.8.4. [1-(3,4-Difluorophenyl)-3-phenyl-pyrrolidin-2-yl]-methanol 5d. Colourless, viscous oily material; yield 82%. IR (liquid film) ν_{max} 3393.4, 2931.2 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.0–2.11 (m, 1H), 2.30–2.57 (m, 2H), 3.30–3.42 (q, 1H, J~8.1 Hz), 3.49–3.60 (m, 2H), 3.75 (d, 1H, J~4.9 Hz), 3.87–3.91 (m, 1H), 6.38–6.43 (m, 1H), 6.50–6.60 (m, 1H), 7.05–7.16 (m, 2H), 7.27–7.38 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 32.0, 46.7, 49.3, 59.2, 62.2, 67.4, 111.8, 114.0, 116.7, 117.1, 121.1, 121.5, 126.7, 126.9, 128.8, 143.7, 144.1, 148.5, 153.2. Anal. Calcd for $C_{17}H_{17}F_2NO$: C, 70.57; H, 5.92; N, 4.84. Found: C, 70.71; H, 5.87; N, 4.82%. EIMS m/z: 289 (M^+, 48.4%), 258 ($M^+-C_2H_5$, 100%).

4.8.5. [1-(3-Chloro-4-fluorophenyl)-3-phenyl-pyrrolidin-2-yl]methanol 5e. Colourless, viscous oily material; yield 80%. IR (liquid film) ν_{max} 3334.0, 2930.6 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.40–2.58 (m, 2H), 3.27–3.39 (q, 1H, J~7.5 Hz), 3.45–3.55 (m, 2H), 3.70–3.79 (m, 2H), 3.85–3.91 (m, 1H), 6.50–6.58 (m, 1H), 6.69–6.74 (q, 1H, J~2.9 Hz), 6.98 (s, 1H), 7.02–7.10 (m, 2H), 7.18–7.33 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): 31.9, 46.7, 49.0, 62.2, 67.1, 111.6, 113.7, 116.6, 117.0, 121.0, 121.4, 126.6, 126.9, 128.7, 143.8, 144.2, 148.3, 153.0. Anal. Calcd for $C_{17}H_{17}ClFNO$: C, 66.78; H, 5.60; N, 4.58. Found: C, 66.69; H, 5.63; N, 4.56%. EIMS m/z: 305 (M^+, 21.3%), 274 ($M^+-C_2H_5$, 100%).

4.9. General procedure for the synthesis of 1,3-diaryl-2-formylpyrroles 6

Compound **5** (1.4 mmol) was heated at reflux with DDQ (8 mmol) in dry benzene [*caution*: carcinogenic] (40 mL) for 5–6 h. After completion of the reaction, the organic layer was washed with aqueous $NaHCO_3$ solution, dried over anhydrous Na_2SO_4, the solvent was evaporated and the desired aldehyde **6** was purified by column chromatography [neutral alumina/petroleum ether (60–80 °C)–ethyl acetate (70:1)].

4.9.1. 1-(4-Chlorophenyl)-2-formyl-3-(2-thienyl)pyrrole 6a. Colourless, viscous oily material; yield 67%. IR (neat) ν_{max} 1655.0 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 6.52 (d, 1H, J~2.7 Hz), 6.99 (d, 1H, J~2.8 Hz), 7.11–7.14 (m, 1H), 7.27–7.31 (m, 3H), 7.36–7.45 (m, 3H), 9.83 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 111.6, 126.5, 127.3, 127.5, 127.8, 129.1, 130.8, 135.3, 180.0. Anal. Calcd for $C_{15}H_{10}ClNOS$: C, 62.61; H, 3.50; N, 4.87. Found: C, 62.75; H, 3.48; N, 4.83%. EIMS m/z: 287 (M^+, 99.9%), 258 (M^+-CHO, 59.6%).

4.9.2. 1-(*p*-Tolyl)-2-formyl-3-phenylpyrrole 6b. Colourless, viscous oily material; yield 70%. IR (neat) ν_{max} 1655.4 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.34 (s, 3H), 6.53 (d, 1H, J~2.8 Hz), 7.12 (d, 1H, J~2.9 Hz), 7.27–7.29 (m, 2H), 7.43–7.57 (m, 5H), 7.99 (d, 2H, J~7.6 Hz), 9.67 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) 20.9, 111.3, 126.5, 127.4, 128.3, 128.7, 129.2, 129.8, 130.3, 130.7, 134.4, 136.5, 139.7, 179.9. Anal. Calcd for $C_{18}H_{15}NO$: C, 82.73; H, 5.79; N, 5.36. Found: C, 82.89; H, 5.75; N, 5.33%. EIMS m/z: 261 (M^+, 100%).

4.9.3. 1-(4-Chlorophenyl)-2-formyl-3-phenylpyrrole 6c. Colourless, viscous oily material; yield 72%. IR (neat) ν_{max} 1658.3 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 6.49 (d, 1H, J~2.8 Hz), 7.01 (d, 1H, J~2.9 Hz), 7.22–7.28 (m, 3H), 7.43–7.49 (m, 6H), 9.64 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 111.8, 121.2, 125.6, 127.1, 127.3, 127.6, 128.1, 128.6, 128.8, 129.5, 129.7, 130.3, 131.8, 132.6, 136.2, 140.9, 179.7. Anal. Calcd for $C_{17}H_{12}ClNO$: C, 72.47; H, 4.29; N, 4.97. Found: C, 72.58; H, 4.27; N, 4.93%. EIMS m/z: 205 (M^+, 100%).

4.9.4. 1-(3,4-Difluorophenyl)-2-formyl-3-phenylpyrrole 6d. Colourless, viscous oily material; yield 68%. IR (neat) ν_{max} 1655.1 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 6.48

(d, 1H, *J*~2.9 Hz), 7.01 (d, 1H, *J*~ 3.0 Hz), 7.14–7.17 (m, 2H), 7.21–7.24 (m, 1H), 7.42–7.52 (m, 5H), 9.64 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 111.6, 115.8, 116.9, 117.3, 122.5, 127.5, 128.1, 128.6, 129.6, 130.0, 130.8, 133.2, 136.4, 140.8, 179.8. Anal. Calcd for $C_{17}H_{11}F_2NO$: C, 72.08; H, 3.91; N, 4.94. Found: C, 72.21; H, 3.87; N, 4.87%. EIMS *m/z*: 283 (M^+, 100%).

4.9.5. 1-(3-Chloro-4-fluorophenyl)-2-formyl-3-phenylpyrrole 6e. White solid; yield 69%; mp 154–157 °C (ethanol). IR (KBr) ν_{max} 1657.5 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.49 (d, 1H, *J*~2.8 Hz), 7.01 (d, 1H, *J*~2.9 Hz), 7.22–7.28 (m, 2H), 7.43–7.49 (m, 6H), 9.64 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 111.6, 116.5, 121.1, 126.1, 127.5, 128.0, 128.2, 128.4, 128.6, 129.6, 130.0, 130.8, 133.2, 136.2, 140.8, 179.6. Anal. Calcd for $C_{17}H_{11}NOClF$: C, 68.11; H, 3.67; N, 4.67. Found: C, 67.98; H, 3.75; N, 4.73%. ESI-MS for $C_{17}H_{11}NOClF$ [M], $[M+H]^+$=300.14 (100%) (^{35}Cl), 302.14 (33.2%) (^{37}Cl).

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References and notes

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