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Sodium borohydride–iodine mediated reduction of γ-lactam carboxylic acids followed by DDQ mediated oxidative aromatisation: a facile entry to *N*-aryl-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-pyrrolidine-2/3-yl)-methanols in good yields at room temperature using sodium borohydride–iodine. Controlled oxidation and aromatisation of these alcohols using DDQ produced *N*-aryl-2/3-formyl-pyrroles.

Some substituted pyrroles are highly biologically active compounds, which constitute an important class of synthetic pharmaceuticals[1a] and natural products with fungicidal[1b] and insecticidal[1c] activities and which also constitute the building blocks of the porphyrin ring systems present in chlorophyll, heme, 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] 3-Substituted *N*-aryl pyrroles act as potent aldose reductase (AR) inhibitors.[3e]

3-Substituted pyrroles 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[4] and so functionalisation at the 3-position of pyrrole is a challenging goal in synthetic research.

HIV-1 protease inhibitors with an *N*-aryl-pyrrole-containing moiety in the P_3 position **I** have excellent antiviral potency,[5] 3-(1*H*-pyrrol-1-yl)-2-oxazolidinones **II** show antimycobacterial activity,[6] and *N*-phenyl-3-(aminomethyl)-pyrroles **III** act as potential antipsychotic agents.[7] In all cases (Fig. 1) the key synthetic intermediate was 3-formyl-*N*-phenyl pyrrole **IV**.[5–7]

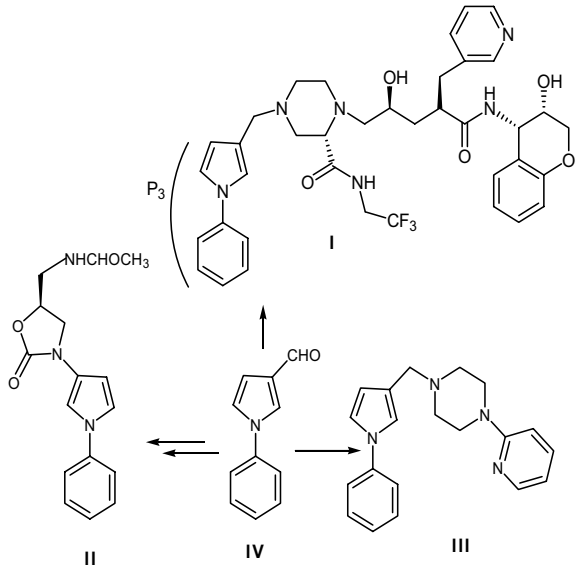

Figure 1.

Encouraged by the above reports we aimed to develop a novel and simple approach for the synthesis of *N*-aryl 3-formyl-pyrroles whose ultimate utility might extend to unexpected applications.

Related to our studies of bioactive *N*-aryl-γ-lactams[8,9] we set out to discover an efficient method for the conversion of γ-lactam carboxylic acids to the desired pyrrole

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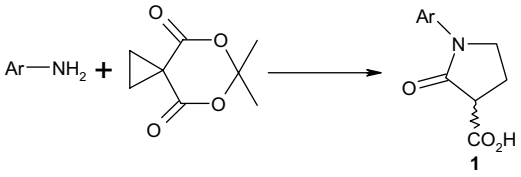


Scheme 1.

derivatives, keeping in mind that modification of the heterocyclic ring is crucial in determining the biological activity of these derivatives.[10]

N-Aryl-2-oxo-pyrrolidine-3-carboxylic acids **1** were synthesised by the reaction of substituted arylamines and 6,6-dimethyldioxaspiro[2,5]octane-4,8-dione[11] at room temperature (Scheme 1).

Lithium aluminium hydride could reduce both the lactam carbonyl and carboxylic acid group of compound **1** but this reagent suffers from disadvantages of cost, inflammability and often problematical work-ups. Thus we turned our attention to other reducing agents and (*N*-aryl-pyrrolidine-3-yl)-methanol **2** was easily synthesised in very good yield (Table 1) by reaction of **1** with $NaBH_4$–I_2[12] in dry THF at room temperature (Scheme 2). The reagent system is safe, simple and inexpensive.

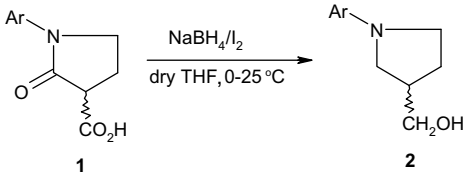
(1-Substituted pyrrolidin-3-yl)methanols and their corresponding chlorides[13] are useful intermediates for the preparation of a number of physiologically active compounds of therapeutic value.

We hoped that DDQ[14] might bring about oxidative aromatisation of *N*-subsituted pyrrolidin-3-ylmethanols to produce *N*-aryl-3-formylpyrroles and this proved to be the case.

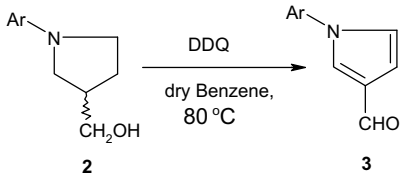
Controlled oxidation and aromatisation of **2** by DDQ furnished the desired compound **3** in one step and in good yield (Scheme 3, Table 2).

Table 1.

2-Oxopyrrolidine-3-carboxylic acid	Ar	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



Scheme 2.



Scheme 3.

Table 2.

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 pleasing outcome of the above reactions prompted us to extend this methodology to the synthesis of *N*-aryl-2-formyl-3-aryl/heteroaryl-pyrroles (Scheme 4, Tables 3 and 4) starting from *N*-aryl-5-oxo-3-aryl/heteroaryl-pyrrolidine-2-carboxylic acids **4**.[9,12a] A recent study showed that *N*-aryl-2-formylpyrroles can act as key starting materials for the synthesis of isotactic-polypropylene (IPP) catalysts[15] and certain pyrrole Mannich bases that act as antipsychotic agents.[16]

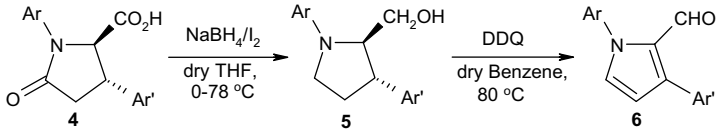
All the compounds were characterised by the usual spectroscopic data.

In conclusion we have shown that $NaBH_4$–I_2 can effectively reduce both the lactam carbonyl and the carboxylic acid groups of *N*-aryl-2-oxo-pyrrolidine-3-carboxylic acids at room temperature and that DDQ effects the oxidative aromatisation of *N*-arylpyrrolidin-3-ylmethanols in good yields, providing a simple and novel approach for the conversion of γ-lactam carboxylic acids into *N*-aryl-3-formylpyrroles. This methodology has been successfully applied to the synthesis of a range of *N*-aryl-2-formylpyrroles.

Typical experimental procedure:

(a) Synthesis of *N*-arylpyrrolidin-3-ylmethanols **2**.

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 (2 mmol) **1** in dry THF (8 mL) was added and the mixture was stirred at rt (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 3times 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 was purified by column chromatography [silica gel/petroleum ether (60–80 °C)-ethyl acetate (40:1)].



Scheme 4.

Table 3.

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 4.

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

(b) Synthesis of *N*-aryl-3-formylpyrroles **3**.
Compound **2** (1.4 mmol) was refluxed 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 evaporated and the product aldehyde **3** was purified by column chromatography [neutral alumina/petroleum ether (60–80 °C)-ethyl acetate (60:1)].

Spectral data of representative compounds.

(a) [*N*-(4-Chlorophenyl)pyrrolidin3-yl]methanol **2c**: ^{1}H 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), 3.42–3.63 (m, 2H), 6.44–6.52 (m, 2H), 7.14–7.25 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 27.87, 40.91, 47.26, 50.64, 65.08, 112.75, 120.50, 128.84, 146.40. Anal. Calcd for $C_{11}H_{14}NOCl$: C, 62.41; H, 6.62; 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 (100%) (^{35}Cl), 214.07 (33%) (^{37}Cl).

(b) *N*-(4-Chlorophenyl)-3-formylpyrrole **3c**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.80 (d,1H, $J \sim 2.8$ Hz), 7.05 (d, 1H, $J \sim 2.7$ Hz), 7.33–7.48 (m, 4H), 7.62 (s, 1H), 9.84 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 109.97, 122.20, 122.34, 126.85, 128.37, 129.99, 133.06, 138.08, 185.41. Anal. Calcd for $C_{11}H_8$-NOCl: C, 64.23; H, 3.89; N, 6.81%. Found: C, 64.12; H, 3.82; N, 6.87%. ESI-MS: for $C_{11}H_8NOCl$ [M], $[M + H]^+$ = 206.01(100%) (^{35}Cl), 208.01 (34%) (^{37}Cl).

(c) *N*-(3-Chloro-4-fluorophenyl)-2-formyl-3-phenylpyrrole **6e**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.49 (d, 1H, $J \sim 2.8$ Hz), 7.01 (d, 1H, $J \sim 2.9$ 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 111.56, 116.49, 121.13, 126.09, 127.53, 128.04, 128.23, 128.38, 128.58, 129.61, 130.01, 130.80, 133.23, 136.24, 140.80, 179.61. Anal. Calcd for $C_{17}H_{11}NOFCl$: C, 68.11; H, 3.67; N, 4.67%. Found: C, 67.98; H, 3.75; N, 4.73%. ESI-MS: for $C_{17}H_{11}NOFCl$ [M], $[M + H]^+$ = 300.14 (100%) (^{35}Cl), 302.14 (33%) (^{37}Cl).

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