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General Method for the Synthesis of 5-Arylpyrrole-2-carboxylic Acids

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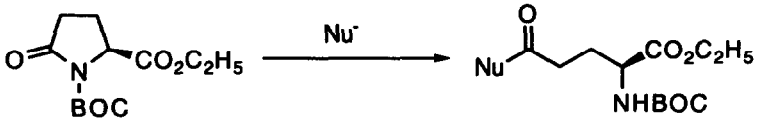
Abstract: *5-Arylpyrrole-2-carboxylic acids are prepared by DDQ oxidative aromatization of the corresponding ethyl 2-aryl-Δ^1-pyrroline-5-carboxylate followed by basic hydrolysis.*

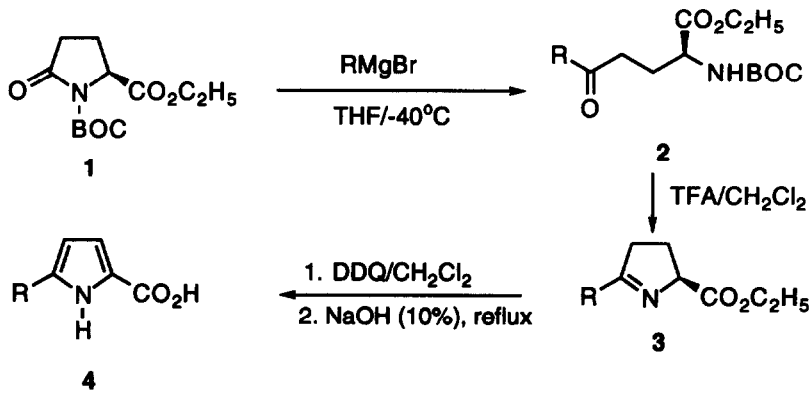
Many different approaches have been used for the synthesis of 5-substituted pyrrole-2-carboxylates. Methyl azidoacetate,[1] 4-amino-1,3-dienes,[2] glycine,[3] diethylaminomalonate,[4] 5,6-dihydro-4*H*-1,2-oxazines[5] and 3-aryl-3-chloropropeniminium salts[6] have all been used as starting materials. The viability of these methods is highly dependant on the availability of the suitable substituted starting material, several of which pose special handling problems. In this paper we would like to report a general method for the preparation of the title compounds by oxidation of precursors in which the five membered nitrogen-containing ring already exists but not at the aromatic oxidation level. Although this oxidative aromatization has been extensively used for the synthesis of indoles and carbazoles it has not been used for the preparation of substituted pyrroles.[7]

To prepare 5-arylpyrrole-2-carboxylic acids we have chosen pyroglutamic acid as our starting material. Pyroglutamic acid can be viewed as an internal protection of the γ-carboxyl group of the glutamic acid, allowing an easy differentiation of the two carboxyl groups. Thus, ring opening of the N-urethane protected pyroglutamate can be achieved with a variety of nucleophiles[8] (Scheme 1).



1

Scheme 1



Scheme 2

The nuclephilic ring opening of the ethyl N-BOC protected pyroglutamate[9] **1** with aryl Grignard reagents[10] (Scheme 2) proceeds in good yield with excellent regioselectivity. Removal of the BOC group gave rise to the corresponding ethyl Δ^1-pyrroline-2-carboxylate **3**.[11] Finally DDQ oxidation of these pyrrolines followed directly by basic hydrolysis, yielded the 5-arylpyrrole-2-carboxylic acids **4**.[12] In table I are summarised the reaction yields for the four steps.

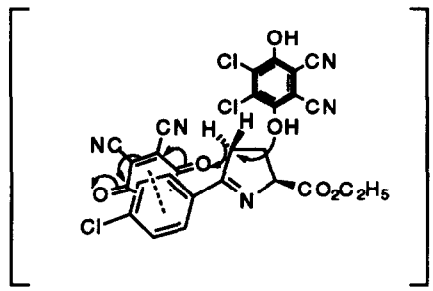
Table I

Entry	R	2 (%Yield)	3 (%Yield)	4 (%Yield)	4 m.p (°C)
a	C_6H_5-	83	93	72	>160 (dec.)
b	4-Cl-C_6H_4-	97	90	75	171-172
c	4-F-C_6H_4-	91	93	70	160-161
d	4-$CH_3C_6H_4$-	78	87	73	155-156
e	CH_3CH_2-	74	98	–	–

This method has proven to be effective when aryl Grignard reagents are used. However, with alkyl magnesium halides (entry e), the corresponding Δ^1-pyrroline intermediate gave a mixture of degradation products after the DDQ oxidative reaction.

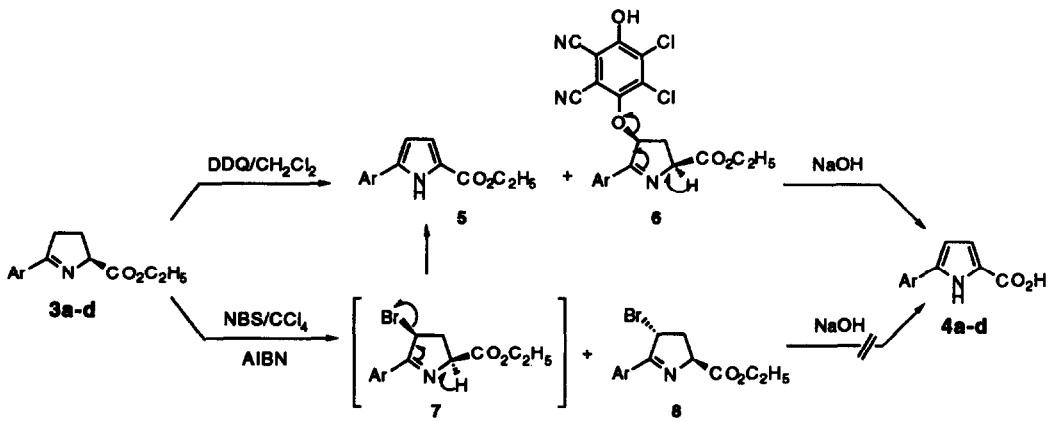
A careful study of the oxidation reaction step on compound **3b** allowed us to isolate 20% of the pyrrole **5b** together with 60% of the adduct **6b**[13] (Scheme 4). This result suggests that two different mechanims are operating in the reaction, the oxidation of the pyrrolines **3** and the nucleophilic attack of DDQ hydroquinone. This latter process could be the result of the displacement of the α-hydrogen at the three position of the Δ^1-pyrroline by the reduced DDQ present in the medium. First, a π-donor-acceptor complex must be formed between DDQ and the aromatic substituent of the substrate on the less hindered face, allowing the selective removal of the α-hydrogen *via* a concerted process.[14] Nucleophilic attack by DDQ hydroquinone can then occur

at the more hindered face of the π-donor-acceptor complex intermediate, to give **6**. A suggested transition state for this transformation is presented in the scheme 3.



Scheme 3

The intermediates **6a-d** were isolated and characterized in all cases. However, with the pyrroline **3e** it was not possible to isolate the intermediate compound **6**, probably because it is not possible to form the π-donor-acceptor complex between the substrate and the DDQ.



Scheme 4

The intermediates **6** gave rise to the corresponding pyrroles when treated under basic conditions. This elimination should be a concerted proccess through four centres, as the proton α to the ester group is the most acidic[15] (Scheme 4). In order to confirm this assumption, pyrrolines **3a-d** were brominated with NBS/AIBN yielding a mixture of the pyrroles **5** (60-70% yield) and the *trans*-ethyl 2-aryl-3-bromo-Δ^1-pyrroline-5-carboxylates **8**[16] (15-20% yield). The pyrrole **5** probably arises by the facile base elimination of the hydrogen bromide from the intermediate **7**. However, the isomeric intermediate **8** is base stable.

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10 These reactions were performed as described in *ref.* 8a

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12 **General procedure**. A mixture of the corresponding pyrroline (1 mmol) and DDQ (1 mmol) in CH_2Cl_2 (10 ml) was stirred at room temperature for 1 hour. The solvent was removed under reduced pressure and the residue was suspended in a 10% NaOH solution (20 ml) and refluxed for 12 hours. The solution was poured into cold water and neutralized with 10% HCl (20 ml). The precipitate formed was filtered, washed with cold water and recrystallized from a suitable solvent.

13 The reaction was run as described in the general method but it was not hydrolyzed. Flash chromatography of the reaction crude residue gave the pyrrole ester **5** (13-20% yield) and the pyrroline **6** (40-60% yield). For **6b**: Yield m.p.: 119-120°C (dec) from ethanol. ^{1}H NMR (200 MHz, $CDCl_3$-CD_3OD) δ (ppm) 7.85 and 7.35 (AA'BB' system, 4H); 6.16 (dd, J = 4.8 and 7.5 Hz, 1H); 4.87 (dd, J = 5.9 and 8.4 Hz, 1H); 4.25 (q, J = 7 Hz, 2H); 2.76 (dt, J = 8.1 and 14.4 Hz, 1H); 2.45 (dt, J = 5.3 and 14.4 Hz, 1H); 1,28 (t, J = 7.1 Hz, 3H). ^{13}C NMR (50 MHz, DMSO-d_6) δ (ppm) 171.0, 170.9, 155.4, 136.0, 133.3, 131.1, 130.3, 129.2, 128.6, 126.9, 113.8, 113.2, 108.1, 101.7, 87.6, 71.2, 60.9, 33.5, 14.1. IR (KBr pellet) 3446, 2230, 1734, 1215, 1092 cm^{-1}. HRMS calc for $C_{21}H_{14}N_3O_4Cl_3$: 477.0050, found: 477.0028.

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16 For **8b** m.p.: 81-82°C (dec)from ethanol. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.91 and 7.42 (AA'BB' system, 4H); 5.28 (d, J = 6.6 Hz, 1H); 4.95 (t, J = 7.3 Hz, 1H); 4.30 (q, J = 7.1 Hz, 2H); 2.83-2.62 (m, 2H); 1.34 (t, J = 7.1 Hz, 3H). IR (KBr pellet) 3314, 1684, 1280, 1263 cm^{-1}. HRMS calc for $C_{13}H_{13}NO_2ClBr$: 328.9818, found: 328.9799.

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