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# An Expeditious Synthesis Some Pyrrolo[1,2-a]Quinoline Derivatives

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**Abstract:** Starting from 2-nitrophenylacetic acid, the synthesis of some pyrrolo[1,2-a]quinoline derivaives has been reduced to an experimentally simple three-step operation.
**Keywords:** Pyrrolo[1,2-a]quinoline, 2-nitrophenylacetic acid, 2-aminophenylacetic acid, Pd/C catalysed hydrogenolysis, ammonium formate.

## Introduction and Experimental

The interest in pyrrolo[1,2-*a*]quinolines is due to their potential biological activity and attractive physicochemical properties[1-4]. Also the skeleton of pyrrolo[1,2-*a*]quinoline is present in gephyrotoxin, a natural alkaloid which was the subject of many investigations[5-8]. We undertook the synthesis of the novel heterocycle pyrrolo[1,2-a]quinoline in one of our previous works with a view to bring new findings to these investigations. The route to the target compound cannot sidestep 2-aminobenzoic acid as the central moiety to any further elaboration, where the product 2-(1-pyrrolyl)phenylacetic acid stands as a key precursor[9]. Difficulties hitherto encountered relate in particular to the instability of the 2-(1-pyrrolyl)benzoyl chloride intermediate and to the use of the highly toxic, as well as explosive, diazomethane used for conversion of the latter to the phenylacetic structure *via* chain-lengthening[10]. We present here an expeditious synthesis of some pyrrolo [1,2-a]quinoline derivatives where choice of 2-nitrophenylacetic acid as the commercially available starting material, instead of 2-aminophenylbenzoic acid, helps prevent such problems and leads straightforwardly to the critical 2-(1-pyrrolyl)phenylacetic acid system.

Melting points were determined on a Boëtius hot plate microscope and are uncorrected. The IR spectra were recorded on a Nicolet Impact 410 spectrometer, in KBr pellets. The NMR spectra were recorded on a Varian Gemini 300 BB instrument, operating at 300 MHz for $^{1}$H-NMR and 75 MHz for $^{13}$C-NMR, the multiplicities were determined through DEPT. Mass spectra were recorded on a Varian MAT 311 spectrometer.

***1. Preparation of 2-aminophenylacetic acid derivatives 2(a-c)***

Substituted ortho-nitrophenylacetic acid 1 (a-b) (5.52 mmol) was added to a solution of Pd/C (20 %) and an excess of ammonium formate in 20 ml of EtOH. The mixture was stirred and refluxed for 2 hours, then filtered and concentrated *in vacuo*. The reaction mixture was poured into H2O and extracted with $Et_2O$. The organic solution was dried over $MgSO_4$ and evaporated. The residue was recrystallized from petroleum ether.

***a. 2-aminophenylacetic acid 2a***

Yield=72%; mp =124 °C. $^1$H NMR ($CDCl_3$ , 300 MHz): 6.46 (dd, 1H, H3); 6.94 (t, 1H, H4); 6.62 (t, 1H, H5); 6.93 (dd, 1H, H6); 3.62 (s, 2H, $CH_2$); 4,3 (br s, 2H, $NH_2$); 5.0 (br s, 1H, OH). $^{13}$C.NMR ($CDCl_3$ , 75 MHz); 121.9 (C1); 148.4 (C2); 115.8 (C3); 128.4 (C4); 119.3 (C5); 130.9 (C6); 32.6 ($CH_2$); 178,5 (CO). IR (KBr) : 3200 (OH), 1685 (C=O), 3300 ($NH_2$), 3400 ($NH_2$). HRMS, m/z: 151(M), calcd. for $C_8H_9NO_2$ : 151.060, found: 251.093.

***b. (2-Amino-5-methyl-phenyl)-acetic acid 2b***

Yield=72%; mp =146°C. $^1$H NMR ($CDCl_3$ , 300 MHz): 6.33 (d, 1H, H3); 6.74 (d, 1H, H4); 6.74 (s, 1H, H6); 2.47 (s, 3H, $CH_3$); 3.60 (s, 2H, $CH_2$); 4,27 (br s, 2H, $NH_2$); 5.2 (br s, 1H, OH). $^{13}$C.NMR ($CDCl_3$ , 75 MHz); 122.4 (C1); 146.0 (C2); 116.3 (C3); 129.2 (C4); 129.3 (C5); 132.5 (C6); 23.1 ($CH_3$); 33.5 ($CH_2$); 178,1 (CO). IR (KBr) : 3200 (OH), 1685 (C=O), 3300 ($NH_2$), 3400 ($NH_2$). HRMS, m/z: 165(M), calcd. for $C_9H_{11}NO_2$ : 165.070, found: 165.079.

***c. (2-Amino-5-chloro-phenyl)-acetic acid 2c***

Yield=72%; mp =153 °C. $^1$H NMR ($CDCl_3$ , 300 MHz): 6.19 (d, 1H, H3); 6.79 (d, 1H, H4); 6.83 (s, 1H, H6); 3.45 (s, 2H, $CH_2$); 4,27 (br s, 2H, $NH_2$); 5.1 (br s, 1H, OH). $^{13}$C.NMR ($CDCl_3$ , 75 MHz); 123.5 (C1); 146.7 (C2); 117.3 (C3); 128.2 (C4); 124.5 (C5); 131.2 (C6); 31.5 ($CH_2$); 177,9 (CO). IR (KBr) : 3200 (OH), 1685 (C=O), 3300 ($NH_2$), 3400 ($NH_2$). HRMS, m/z: 185(M), calcd. for $C_8H_8ClNO_2$ : 185.020, found: 185.024.

***2. Preparation of 2-(1-pyrrolyl)phenylacetic acid derivatives 3(a-c)***

2-aminophenylacetic acid derivatives 2(a-c) (1.98 mmol) was stared and refluxed for 3 hours with 4-chloropyridinium chlorohydrate (7.9 mmole), and 2,5-dimethoxytetrahydrofurane (15 mmol) in 20 ml of dioxane. Having removed the solvent *in vacuo*, The reaction mixture was poured into H2O and extracted with $Et_2O$. The organic solution was dried over $MgSO_4$ and evaporated. The residue was recrystallized from petroleum ether.

***a. 2-(1-pyrrolyl)phenylacetic acid 3a***

Yield=65%; mp= 40°C. $^1$H NMR ($CDCl_3$ , 300 MHz): 6.76 (dd, 1H, H3); 7.24 (t, 1H, H4); 6.92 (t, 1H, H5); 7.23 (dd, 1H, H6); 3.42 (s, 2H, $CH_2$); 6,85 (d, 2H, H2'H5'); 6.26 (t, 2H, H3'H4'); 4.9 (br s, 1H, OH).

$^{13}$C.NMR ($CDCl_3$ , 75 MHz); 126.6 (C1); 142.4 (C2); 120.4 (C3); 127.5 (C4); 125.5 (C5); 130.6 (C6); 34.1 ($CH_2$); 179,0 (CO); 119.5 (C2'); 110.6 (C3'); 110.6 (C4'); 119,5 (C5'). IR (KBr) : 3500 (OH), 1720 (C=O). HRMS, m/z: 201(M), calcd. for $C_{12}H_{11}NO_2$: 201.070, found: 201.079.

***b. 5-Methyl-2-(1-pyrrolyl)phenyl acetic acid 3b***

Yield=47%; mp= 86°C. $^1$H NMR ($CDCl_3$ , 300 MHz): 6.93 (d, 1H, H3); 7.34 (d, 1H, H4); 7.34 (s, 1H, H6); 2.67 (s, 3H, $CH_3$); 3.80 (s, 2H, $CH_2$); 6,94 (d, 2H, H2'H5'); 6.39 (t, 2H, H3'H4'); 5.7 (br s, 1H, OH). $^{13}$C.NMR ($CDCl_3$ , 75 MHz); 126.8 (C1); 138.2 (C2); 120.7 (C3); 128.3 (C4); 134.6 (C5); 131.6 (C6); 34.1 ($CH_2$); 22.1 ($CH_2$); 178,4 (CO); 119.2 (C2'); 110.4 (C3'); 110.4 (C4'); 119,2 (C5'). IR (KBr) : 3350 (OH), 1720 (C=O). HRMS, m/z: 215(M), calcd. for $C_{12}H_{11}NO_2$: 215.090, found: 215.091.

***c. 5-Chloro-2-(1-pyrrolyl)phenyl acetic acid 3c***

Yield=57%; mp= 106°C. $^1$H NMR ($CDCl_3$ , 300 MHz): 6.39 (d, 1H, H3); 7.01 (d, 1H, H4); 7.15 (s, 1H, H6); 3.75

(s, 2H, $CH_2$); 6,75 (d, 2H, H2'H5'); 6.36 (t, 2H, H3'H4'); 4.9 (br s, 1H, OH). $^{13}$C.NMR ($CDCl_3$ , 75 MHz); 128.3 (C1); 139.8 (C2); 122.1 (C3); 128.3 (C4); 131.0 (C5); 131.1 (C6); 32.4 ($CH_2$); 178,2 (CO); 119.2 (C2'); 110.3 (C3'); 110.3 (C4'); 119,2 (C5'). IR (KBr): 3500 (OH), 1720 (C=O). HRMS, m/z: 235(M), calcd. for $C_{12}H_{10}ClNO_2$: 235.038, found: 235.04.

### *3. Preparation of pyrrolo[1,2-a]quinoline derivatives 4(a-c)*

2-(1-pyrrolyl)phenylacetic acid derivatives **3(a-c)** (0.5 mmole) was stired and refluxed for 4 hours with 2 ml of acetic anhydride. Having removed the solvent *in vacuo*, the reaction mixture was stirred with 4 ml of saturated $NaHCO_3$ solution for 1 hour. After the mixture was diluted with $H_2O$ and the aqueous mixture was extracted twice with ether, the ether fraction were combined, washed with water, and dried over $MgSO_4$, and the solvent was removed in *vacuo*. The residue was recrystallized from petroleum ether.

#### *a. 4-Acetoxy pyrrolo[1,2-a]quinoline 4a*

Yield=47%. $^1$H NMR ($CDCl_3$ , 300 MHz): 8.29 (d, 1H, H1); 6.89 (t, 1H, H2); 6.53 (d, 1H, H3); 7.12 (s, 1H, H5); 7,97 (d, 1H, H6); 7.8 (t, 2H, H7H8); 8.37 (d, 1H, H9); 3.05 (s, 3H, $CH_3$). $^{13}$C.NMR ($CDCl_3$ , 75 MHz); 113.2 (C1); 114.3 (C2); 99.6 (C3); 145.4 (C4); 143.3 (C5); 126.2 (C6); 128.1 (C7); 127,4 (C8); 126.7 (C9); 128.9 (C10); 129.0 (C11); 146,1 (C12); 168.4 (CO); 17.1 ($CH_3$). IR (KBr): 1750 (CO); 1650; 1540; 1460. HRMS, m/z: 225(M), calcd. for $C_{14}H_{11}NO_2$: 225.070, found: 225.079.

#### *b. 4-Acetoxy-7-methyl pyrrolo[1,2-a]quinoline 4b*

Yield=56%; mp= 78°C. $^1$H NMR ($CDCl_3$ , 300 MHz): 7.23 (d, 1H, H1); 6.73 (t, 1H, H2); 6.33 (d, 1H, H3); 7.72 (s, 1H, H5); 7,57 (s, 1H, H6); 7.46 (d, 1H, H8); 8.37 (d, 1H, H9); 3.15 (s, 3H, $CH_3$); 3.24 (s, 3H, $CH_3$). $^{13}$C.NMR ($CDCl_3$: 75 MHz); 113.3(C1); 114.2 (C2); 99.5 (C3); 144.4 (C4); 143.7 (C5); 125.2 (C6); 128.4 (C7); 125,8 (C8); 136.3 (C9); 129.9 (C10); 128.1 (C11); 143,7 (C12); 168.1 (CO); 17.3 ($CH_3$); 21.5 ($CH_3$).

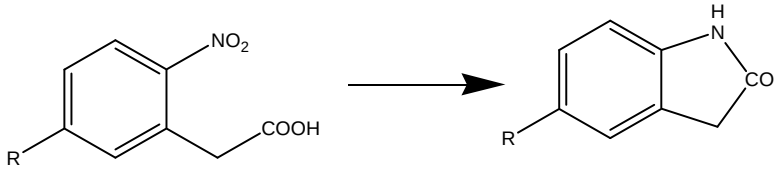
IR (KBr): 1750 (CO); 1490; 1420; 1360. HRMS, m/z: 239(M), calcd. for $C_{15}H_{13}NO_2$: 239.090, found: 239.095.

#### *c. 4-Acetoxy-7-chloro pyrrolo[1,2-a]quinoline 4c*

Yield=66%; mp= 40°C. mp =108 °C. $^1$H NMR ($CDCl_3$ , 300 MHz): 7.19 (d, 1H, H1); 6.69 (t, 1H, H2); 6.23 (d, 1H, H3); 7.82 (s, 1H, H5); 7,78 (s, 1H, H6); 7.57 (d, 1H, H8); 8.11 (d, 1H, H9); 2.24 (s, 3H, $CH_3$). $^{13}$C.NMR ($CDCl_3$ , 75 MHz): 113.2 (C1); 114.4 (C2); 99.4 (C3); 145.3 (C4); 144.3 (C5); 125.7 (C6); 128.9 (C7); 126,1 (C8); 132.8 (C9); 129.9 (C10); 139.1 (C11); 144,1 (C12); 168.2 (CO); 17.0 ($CH_3$). IR (KBr): 1750 (CO); 1490; 1430; 1360; 1250; 1200. HRMS, m/z: 259(M), calcd. for $C_{15}H_{13}NO_2$: 259.038, found: 259.040.

## Results and Discussion

The reduction of 2-nitrophenylacetic acid derivatives **1(a-c)** to the corresponding amine **2(a-c)** using classical reducing reagents such as Iron in acidic media[11], Sodium hydrosulfite[12], Tin(II) chloride (Faul et al., 2005), Samarium[13], Sodium sulfide[14], Raney nickel and hydrazine at 0-10 °C (Ayyangar et al., 1984) and Zinc metal in aqueous ammonium chloride[15] gave the oxyindol with intramolecular cyclisation (Scheme 1).




1a R = H
1b R = $CH_3$
1c R = Cl

2a R = H
2b R = $CH_3$
2c R = Cl

**Scheme 1**

This problem was overcome, with a good yield, by Pd/C catalysed hydrogenolysis using ammonium formate as a source of hydrogen[16]. With a Clauson-Kaas reaction[17], 2-aminophenylacetic acid derivatives 2(a-c) was then heated to reflux with stirring in dioxane, in the presence of 4-chloropyridinium chlorohydrate and 2,5-dimethoxytetrahydrofurane to obtain 2-(1-pyrrolyl) phenylacetic acid derivatives **3(a-c)**, whose cyclisation was accomplished by heating at reflux in acetic anhydride[18], finally leading to the target compound pyrrolo[1,2-a]quinoline derivatives **4(a-c)**.

### *1. Preparation of 2-aminophenylacetic acid* derivatives 2(a-c)

2-aminophenylacetic acid derivatives **2(a-c)** were prepared starting from 2-nitrophenylacetic acid derivatives **1(a-c)** via catalytic hydrogenation using and an excess of ammonium formate in EtOH. The mixture was stirred and refluxed for 2 hours then filtered and concentrated *in vacuo* (Scheme 2). After dilution of the reaction mixture with ethyl acetate, washing with brine, and evaporation, the reaction mixture, was crystallized from hexane, affording 2-aminophenylacetic acid derivatives **2(a-c)** in 72% yield.

The identification of the aminophenylacetic acid derivatives **2(a-c)** was based on spectroscopic data. In the $^1$HNMR spectra of these products, we noted the appearance of the signal as the massif at 3.6 due to protons of amine group $NH_2$.

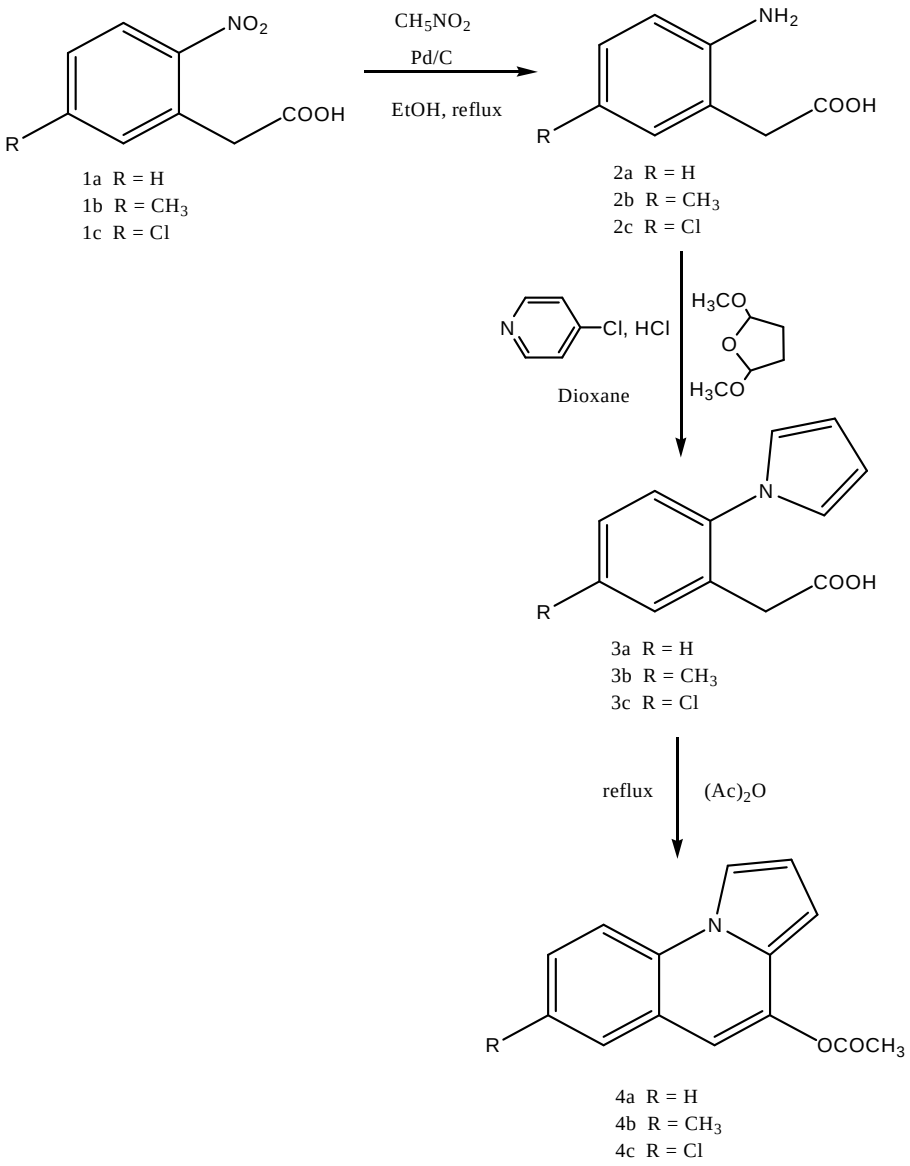
### *2. Preparation of 2-(1-pyrrolyl)phenylacetic acid* derivatives 3(a-c)

For the synthesis of the *2-(1-pyrrolyl)phenylacetic acid* derivatives 3(a-c), we have used the Clauson-Kaas reaction( Clauson-Kaas et al., 1952), the reaction between the 2-aminophenylacetic acid derivatives **2(a-c)** and 2,5-dimethoxytetrahydrofurane was heated to reflux and stirring in dioxane, in the presence of 4-chloropyridinium chlorohydrate to obtain 2-(1-pyrrolyl)phenylacetic acid derivatives **3(a-c)**. (Scheme 2)

The identification of the 2-(1-pyrrolyl)phenylacetic acid derivatives 3(a-c) was based on spectroscopic data. In the $^1$HNMR spectra of these products, we noted the disappearance of the massif at 3.6 due to protons $NH_2$ and the appearance of two singlets at 9.16 and 9.91 due to protons of the pyrrolyle group.

### *3. Preparation of pyrrolo[1,2-a]quinoline* derivatives 4(a-c)

2-(1-pyrrolyl)phenylacetic acid derivatives 3(a-c), whose cyclisation was accomplished by heating at reflux in acetic anhydride, finally leading to the target compound pyrrolo[1,2-a]quinoline derivatives 4(a-c) (Scheme 2). The identification of the *pyrrolo[1,2-a]quinoline* derivatives 4(a-c) was based on spectroscopic data. In the $^1$HNMR spectra of these products, we noted the appearance of the singlet at 2.45 due to protons of methyl of acetoxyl group.




**Scheme 2**

## Conclusion

In conclusion, by Pd/C catalysed hydrogenolysis with conversion of 2-nitrophenylacetic derivatives to the corresponding amine in excellent yield, the synthesis of novel heterocycle pyrrolo[1,2-a]quinoline has been reduced to an experimentally simple tree-step operation. The structures of obtained products were established with spectroscopic data of proton and carbon 13 NMR, mass.

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