The Ullmann Coupling between 2-Chlorobenzoic Acids and Amino Acids; A Valuable Reaction for Preparing 2-Substituted 1-Acetyl-1H-indol-3-yl Acetates

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Received 25 February 2009; revised 23 March 2009
Dedicated to Dr. Michel Wierzbicki on the occasion of his 60th birthday

Abstract: 2-Substituted 3-acetoxy-1-acetyl-1H-indoles were prepared by condensing 2-chlorobenzoic acids with amino acids under Ullmann conditions in good yields, and further cyclodecarboxylation using the Rössing method in moderate to good yields.

Key words: Ullmann coupling, chlorobenzoic acids, amino acids, cyclodecarboxylation, 2-substituted indoles

N,O-Diacetylindoxyls (1-acetyl-1H-indol-3-yl acetates, 3-acetoxy-1-acetyl-1H-indoles) are present as precursors of some aglicons in chromogenic compounds that are very useful in the identification of various microorganisms.1–3 However, 2-substituted 3-acetoxy-1-acetyl-1H-indoles are rarely found in literature and there are no procedures available that describe the synthesis of these compounds from the corresponding unactivated amino acid and 2-chlorobenzoic acids by the Ullman procedure. Nevertheless, 2-substituted 3-acetoxy-1-acetyl-1H-indoles have been used as the starting point for the preparation of 2-substituted 1-acetyl-1,2-dihydro-3H-indol-3-ones.4

On the other hand, only one compound, 3-acetoxy-1-acetyl-2-methyl-1H-indole, has been prepared from the corresponding N-acetylated 2-[(carboxymethyl)amino]benzoic acid, but it was not prepared using the Ullman conditions.4

In previous work we reported a simple two-step procedure for the preparation of 3-acetoxy-1-acetyl-6-chloro-1H-indole from 2,4-dichlorobenzoic acid and an unactivated amino acid in good yield.5 Encouraged by this result, we decided to carry out the preparation of other substituted 3-acetoxy-1-acetyl-1H-indoles starting from the corresponding 2-chlorobenzoic acids.6 These papers made us think about the possibility of using the same procedure to prepare 2-substituted 3-acetoxy-1-acetyl-1H-indoles from 2-chlorobenzoic acids and amino acids or 2-[(carboxymethyl)amino]benzoic acids 4a–g and 5a–c (Table 1) in very good yields. Subsequent Rössing cyclodecarboxylation of 4a–g allowed us to obtain 2-substituted 3-acetoxy-1-acetyl-1H-indoles 6a–g in moderate to good yields (Table 2).

Reagents were purchased from Acros Organics. TLC was carried out using silica gel plates Alugram Sil G/UV 254 (CHCl3–EtOAc–AcOH, 8:6:1). Melting points were determined on a Stuart SMP3 apparatus and are uncorrected. 1H and 13C NMR spectra were recorded on a AC Bruker 250 MHz spectrometer in DMSO-d6. MS spectra were performed on an Agilent Technologies GC-MS instrument equipped with a 7683 injector, 6890N gas chromatograph and a 5973 mass selective detector. The mass spectrometer was operated in EI mode at 70 eV and MS spectra were recorded from m/z 50 to 650.

2-[(Carboxymethyl)amino]benzoic Acids 4 and 5

These compounds were prepared according to a previously reported procedure.3,5 Mass spectra were not possible to obtain due to rapid thermal decomposition once they were injected into the equipment.

2-[(Carboxy(phenyl)methyl)amino]benzoic Acid (4a)

Mp 210–212 °C (Lit.7 226 °C). 1H NMR: δ = 12.94 (s, 2 H), 8.88 (s, 1 H), 7.79 (d, J = 7.70 Hz, 1 H), 7.51–7.18 (m, 8 H), 6.57–6.47 (m, 2 H), 5.29 (s, 1 H).

2-[(Carboxy(phenyl)ethyl)amino]benzoic Acid (4b)

Mp 211–214 °C (Lit.7 226 °C). 1H NMR: δ = 12.94 (s, 2 H), 8.88 (s, 1 H), 7.79 (d, J = 7.70 Hz, 1 H), 7.51–7.18 (m, 8 H), 6.57–6.47 (m, 2 H), 5.29 (s, 1 H).

2-[(Carboxy(phenyl)ethyl)amino]benzoic Acid (4c)

Mp 214–217 °C (Lit.7 226 °C). 1H NMR: δ = 171.95, 169.58, 148.58, 138.29, 134.13, 131.67, 128.51, 127.02, 126.82, 115.09, 112.43, 111.17, 58.99.

2-(1-Carboxyethylamino)benzoic Acid (4d)

Mp 258 °C (Lit.9 209–211 °C). 1H NMR: δ = 7.75 (d, J = 8.47 Hz, 1 H), 6.67–6.66 (m, 2 H), 6.62 (d, J = 1.95 Hz, 1 H), 6.59 (d, J = 1.95 Hz, 1 H), 4.28–4.22 (m, 1 H), 1.39 (d, J = 6.8 Hz, 3 H).

2-(1-Carboxyethylamino)benzoic Acid (4e)

Mp 245 °C (Lit.9 mp 251–252 °C). 1H NMR: δ = 8.28 (d, J = 7.32 Hz, 1 H), 7.79 (d, J = 4.25 Hz, 1 H), 6.66 (d, J = 1.93 Hz, 1 H), 6.61 (dd, J = 4.51–4.2 Hz, 1 H), 1.38 (d, J = 6.65 Hz, 3 H).

2-(1-Carboxyethylamino)-4-chlorobenzoic Acid (4f)

Mp 245 °C (Lit.9 mp 251–252 °C). 1H NMR: δ = 8.28 (d, J = 7.32 Hz, 1 H), 7.79 (d, J = 4.25 Hz, 1 H), 6.66 (d, J = 1.93 Hz, 1 H), 6.61 (dd, J = 4.51–4.2 Hz, 1 H), 1.38 (d, J = 6.65 Hz, 3 H).

SYNTHESIS 2009, No. 14, pp 2345–2348
Advanced online publication: 29.05.2009
DOI: 10.1055/s-0029-1216851; Art ID: Z03009SS
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Table 1  Ullman Compounds 4 and 5 from the Coupling of 2-Chlorobenzoic Acids 1 and Amino Acids 2 and 3

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<th>Entry</th>
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<td>1a</td>
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Table 2  2-Substituted 3-Acetoxy-1-acetyl-1H-indoles 6 from the Rossing Cyclodecarboxylation Reaction of 4a–g

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2-[(Carboxy(phenyl)methyl)amino]-4-chlorobenzoic Acid (4d) Mp 236–237 °C.

2-(4-Carboxybutylamino)-4-chlorobenzoic Acid (5a) Mp 177–179 °C.

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1H NMR: δ = 8.79 (d, J = 5.97 Hz, 1 H), 7.53 (d, J = 8.42 Hz, 1 H), 7.22–7.04 (m, 5 H), 6.35–6.38 (m, 2 H), 5.12 (d, J = 5.85 Hz, 1 H).

13C NMR: δ = 171.81, 168.99, 149.38, 138.86, 137.80, 133.38, 131.09, 128.77, 128.68, 127.59, 115.06, 111.83, 110.02, 58.65.

1H NMR: δ = 8.37 (d, J = 8.32 Hz, 1 H), 7.78 (d, J = 8.5 Hz, 1 H), 6.68 (d, J = 1.92 Hz, 1 H), 6.60 (dd, 1 H), 4.08–4.03 (m, 1 H), 2.20–2.12 (m, 1 H), 0.99–0.94 (m, 6 H).

13C NMR: δ = 173.23, 169.32, 151.23, 139.24, 133.47, 114.74, 110.86, 109.44, 60.10, 30.34, 18.87, 17.84.
2-(1-Carboxyethylamino)-4-nitrobenzoic Acid (4e)
Mp 130–131 °C.

\[ \text{H NMR: } \delta = 8.26 (d, J = 1.67 Hz, 1 H), 7.39 (d, J = 8.35 Hz, 1 H), 7.29 (dd, 1 H), 2.69 (s, 3 H), 2.45 (s, 3 H), 2.39 (s, 3 H). \]

\[ \text{C NMR: } \delta = 169.81, 168.58, 134.05, 132.64, 126.74, 126.35, 126.98, 122.12, 117.57, 116.22, 27.17, 20.46, 13.08. \]

MS: \text{m/z} = 265, 223, 181.

3-Acetoxy-1-acetyl-6-chloro-2-methyl-III-indole (6c)
Mp 133 °C.

\[ \text{H NMR: } \delta = 8.26 (d, J = 1.67 Hz, 1 H), 7.39 (d, J = 8.35 Hz, 1 H), 7.29 (dd, 1 H), 2.69 (s, 3 H), 2.45 (s, 3 H), 2.39 (s, 3 H). \]

\[ \text{C NMR: } \delta = 169.81, 168.58, 134.05, 132.64, 126.74, 126.35, 126.98, 122.12, 117.57, 116.22, 27.17, 20.46, 13.08. \]

MS: \text{m/z} = 265, 223, 181.

3-Acetoxy-1-acetyl-6-chloro-2-phenyl-III-indole (6d)
Mp 136–137 °C.

\[ \text{H NMR: } \delta = 8.34 (d, J = 1.62 Hz, 1 H), 7.56–7.43 (m, 6 H), 7.38 (dd, 1 H), 2.21 (s, 3 H), 1.97 (s, 3 H). \]

\[ \text{C NMR: } \delta = 170.69, 168.79, 134.19, 132.06, 130.23, 129.59, 129.48, 129.29, 129.27, 128.80, 128.85, 128.81, 119.21, 115.74, 27.16, 20.07. \]

MS: \text{m/z} = 327, 285, 243, 207.

3-Acetoxy-1-acetyl-2-methyl-6-nitro-III-indole (6e)
Mp 137 °C.

\[ \text{H NMR: } \delta = 9.10 (d, J = 1.77 Hz, 1 H), 8.11 (dd, 1 H), 7.58 (d, J = 8.7 Hz, 1 H), 2.74 (s, 3 H), 2.55 (s, 3 H), 2.41 (s, 3 H). \]

\[ \text{C NMR: } \delta = 171.01, 168.67, 144.14, 132.64, 131.70, 131.17, 127.77, 118.38, 117.26, 112.05, 26.88, 20.24, 12.6. \]

MS: \text{m/z} = 276, 234, 192, 162, 146.

3-Acetoxy-1-acetyl-2-methyl-5-nitro-III-indole (6f)
Mp 156–157 °C.

\[ \text{H NMR: } \delta = 8.38–8.31 (m, 2 H), 8.13 (dd, 1 H), 2.74 (s, 3 H), 2.49 (s, 3 H), 2.44 (s, 3 H). \]

\[ \text{C NMR: } \delta = 170.98, 168.79, 143.17, 135.91, 131.54, 129.85, 123.24, 119.23, 116.38, 112.96, 26.94, 20.36, 12.35. \]

MS: \text{m/z} = 276, 234, 192, 162, 146.

3-Acetoxy-1-acetyl-2-[2-(methylsulfanyl)ethyl]-III-indole (6g)
Mp 129–130 °C.

\[ \text{H NMR: } \delta = 8.37 (d, J = 1.2 Hz, 1 H), 8.14 (d, J = 2.25 Hz, 2 H), 3.16 (t, 2 H), 2.84 (s, 3 H), 2.69 (t, 2 H), 2.43 (s, 3 H), 2.06 (s, 3 H). \]

\[ \text{C NMR: } \delta = 170.54, 168.84, 143.03, 135.62, 132.65, 131.08, 123.14, 119.15, 116.30, 113.76, 31.98, 27.36, 24.5, 20.39, 14.53. \]

MS: \text{m/z} = 336, 294, 252, 220, 178.

Acknowledgment

We want to thank to Prof. Pierre Seck for his valuable help with performing mass spectra, and Mrs. Veronique Poddig for recording the NMR spectra.

References


