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

Juan Carlos Rodriguez Dominguez, Xiao Gang, Gilbert Kirsch*

Laboratoire d'Ingénierie Moléculaire et Biochimie Pharmacologique (LIMBP), Université Paul Verlaine-Metz, Institut Jean Barriol, 1 Boulevard Arago, 57078 Metz, France
Fax +33(3)87315801; E-mail: kirsch@univ-metz.fr

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-1*H*-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-1*H*-indol-3-yl acetates, 3-acetoxy-1-acetyl-1*H*-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-1*H*-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-1*H*-indoles have been used as the starting point for the preparation of 2-substituted 1-acetyl-1,2-dihydro-3*H*-indol-3-ones.[4]

On the other hand, only one compound, 3-acetoxy-1-acetyl-2-methyl-1*H*-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-1*H*-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-1*H*-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-1*H*-indoles **6** from 2-chlorobenzoic acids **1** and 2-substituted amino acids **2** or 5-aminopentanoic acid (**3**). We started by using the same reaction conditions given in previous papers and using 2-chlorobenzoic acids **1a–d** and amino acids **2a–c** or **3** to give Ullman compounds, 2-[(carboxymethyl)amino]benzoic acids **4a–g** and **5a–c** (Table 1) in very good yields. Subsequent Rossing cyclodecarboxylation of **4a–g** allowed us to obtain 2-substituted 3-acetoxy-1-acetyl-1*H*-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 ($CHCl_3$–EtOAc–AcOH, 8:6:1). Melting points were determined on a Stuart SMP3 apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a AC Bruker 250 MHz spectrometer in DMSO-d_6. 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.[5,6] 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).

^{1}H 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).

^{13}C 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 (4b)

Mp 258 °C (Lit.[8] 209–211 °C).

^{1}H 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).

^{13}C NMR: δ = 174.51, 169.28, 150.42, 139.25, 134.1, 114.82, 110.54, 109.37, 50.01, 17.83.

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

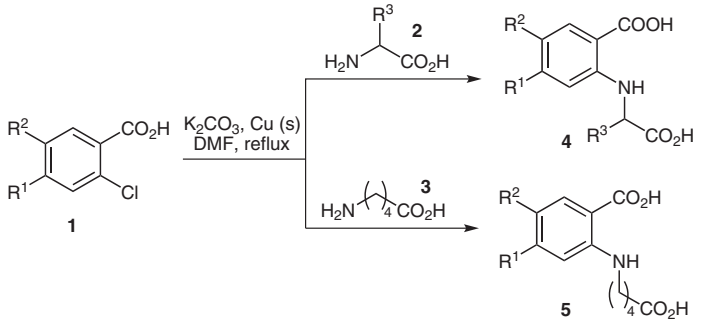
Mp 245 °C (Lit.[9] mp 251–252 °C).

^{1}H 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, 1 H), 4.31–4.2 (m, 1 H), 1.38 (d, *J* = 6.65 Hz, 3 H).

^{13}C NMR: δ = 177.36, 169.10, 150.28, 139.21, 133.48, 114.80, 110.93, 109.44, 50.04, 18.13.

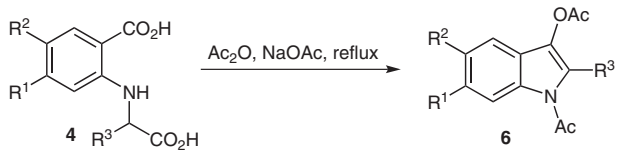
SYNTHESIS 2009, No. 14, pp 2345–2348
Advanced online publication: 29.05.2009
DOI: 10.1055/s-0029-1216851; Art ID: Z03009SS

Table 1 Ullman Compounds **4** and **5** from the Coupling of 2-Chlorobenzoic Acids **1** and Amino Acids **2** and **3**



Entry	Chlorobenzoic acid			Amino acid		Product	Yield (%)
		R^1	R^2		R^3		
1	**1a**	H	H	**2a**	Ph	**4a**	79
2	**1a**	H	H	**2b**	Me	**4b**	86
3	**1b**	Cl	H	**2b**	Me	**4c**	89
4	**1b**	Cl	H	**2a**	Ph	**4d**	85
5	**1b**	Cl	H	**3**	–	**5a**	79
6	**1c**	NO_2	H	**2b**	Me	**4e**	78
7	**1c**	NO_2	H	**3**	–	**5b**	75
8	**1d**	H	NO_2	**2b**	Me	**4f**	91
9	**1d**	H	NO_2	**3**	–	**5c**	82
10	**1d**	H	NO_2	**2c**	$(CH_2)_2SMe$	**4g**	90

Table 2 2-Substituted 3-Acetoxy-1-acetyl-1*H*-indoles **6** from the Rossing Cyclodecarboxylation Reaction of **4a**–**g**



Entry	Substrate	R^1	R^2	R^3	Product	Yield (%)
1	**4a**	H	H	Ph	**6a**	40
2	**4b**	H	H	Me	**6b**	43
3	**4c**	Cl	H	Me	**6c**	25
4	**4d**	Cl	H	Ph	**6d**	53
5	**4e**	NO_2	H	Me	**6e**	33
6	**4f**	H	NO_2	Me	**6f**	32
7	**4g**	H	NO_2	$(CH_2)_2SMe$	**6g**	44

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

^{1}H 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).

^{13}C 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.

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

^{1}H 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).

^{13}C 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 226–227 °C.

^{1}H NMR: δ = 8.41 (s, 1 H), 7.90 (d, *J* = 16.6 Hz, 1 H), 7.60 (s, 2 H), 4.36 (t, 1 H), 1.45 (d, *J* = 9.65 Hz, 3 H).

^{13}C NMR: δ = 174.10, 168.65, 151.2, 149.66, 133.47, 123.68, 108.66, 105.82, 50.24, 8.64.

2-(4-Carboxybutylamino)-4-nitrobenzoic Acid (5b)
Mp 183–185 °C.

^{1}H NMR: δ = 8.49 (d, *J* = 8.02 Hz, 1 H), 8.02 (d, *J* = 8.62 Hz, 1 H), 7.40–7.32 (m, 2 H), 4.20–4.14 (m, 1 H), 2.25–2.18 (m, 1 H), 1.01–0.97 (m, 6 H).

^{13}C NMR: δ = 172.98, 168.82, 151.23, 150.57, 133.46, 115.41, 108.60, 105.72, 60.27, 30.30, 18.86, 17.81.

2-(1-Carboxyethylamino])-5-nitrobenzoic Acid (4f)
Mp 253 °C.

^{1}H NMR: δ = 9.10 (d, *J* = 6.75 Hz, 1 H), 8.62 (d, *J* = 2.45 Hz, 1 H), 8.16 (dd, 1 H), 6.82 (d, *J* = 9.45 Hz, 1 H), 4.44 (t, 1 H), 1.44 (d, *J* = 6.85 Hz, 3 H).

^{13}C NMR: δ = 173.79, 168.91, 153.35, 135.19, 129.34, 128.51, 112.08, 110.12, 50.31, 17.96.

2-(4-Carboxybutylamino)-5-nitrobenzoic Acid (5c)
Mp 199–200 °C.

^{1}H NMR: δ = 9.18 (s, 1 H), 8.63 (s, 1 H), 8.14 (d, *J* = 9.17 Hz, 1 H), 6.87 (d, *J* = 7.92 Hz, 1 H), 4.31 (s, 1 H), 2.24 (s, 1 H), 1.01–0.94 (m, 6 H).

^{13}C NMR: δ = 173.1, 168.87, 151.75, 150.9, 130.35, 116.34, 108.52, 106.1, 60.1, 30.04, 18.71, 17.5.

2-{[1-Carboxy-3-(methylsulfanyl)propyl]amino}-5-nitrobenzoic Acid (4g)
Mp 142–144 °C.

^{1}H NMR: δ = 9.11 (d, *J* = 7.75 Hz, 1 H), 8.64 (d, *J* = 2.8 Hz, 1 H), 8.18 (dd, 1 H), 6.89 (d, *J* = 9.57 Hz, 1 H), 4.58–4.50 (m, 1 H), 2.54–2.49 (m, 2 H), 2.22–2.06 (m, 2 H), 2.03 (s, 3 H).

^{13}C NMR: δ = 172.5, 168.53, 153.64, 135.37, 129.41, 128.44, 112.02, 109.92, 53.83, 31.15, 29.04, 14.59.

1-Acetyl-2-phenyl-1*H*-indol-3-yl Acetates 6
These compounds were prepared according to the Rossing cyclodecarboxylation reaction.[10]

3-Acetoxy-1-acetyl-2-phenyl-1*H*-indole (6a)
Mp 130–131 °C.

^{1}H NMR: δ = 8.30 (d, *J* = 8.25 Hz, 1 H), 7.52–7.29 (m, 8 H), 2.21 (s, 3 H), 2.02 (s, 3 H).

^{13}C NMR: δ = 170.52, 168.86, 134.03, 132.59, 129.94, 129.52, 128.99, 128.73, 128.36, 125.79, 123.56, 122.78, 117.68, 115.87, 27.26, 20.08.

MS: *m*/*z* = 293, 251, 209, 180.

3-Acetoxy-1-acetyl-2-methyl-1*H*-indole (6b)
Mp 116–117 °C.

^{1}H NMR: δ = 7.32–7.24 (m, 4 H), 2.72 (s, 3 H), 2.49 (s, 3 H), 2.42 (s, 3 H).

^{13}C NMR: δ = 170.08, 168.72, 136.21, 133.67, 126.15, 124.64, 124.45, 123.7, 116.9, 115.56, 27.34, 20.49, 13.02.

MS: *m*/*z* = 231, 189, 147.

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

^{1}H NMR: δ = 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).

^{13}C NMR: δ = 169.81, 168.58, 134.05, 132.64, 130.74, 126.35, 123.98, 122.12, 117.57, 116.22, 27.17, 20.46, 13.08.

MS: *m*/*z* = 265, 223, 181.

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

^{1}H NMR: δ = 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).

^{13}C NMR: δ = 170.69, 168.79, 134.19, 132.06, 130.23, 129.59, 129.48, 129.29, 129.27, 128.80, 123.85, 121.64, 119.21, 115.74, 27.16, 20.07.

MS: *m*/*z* = 327, 285, 243, 207.

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

^{1}H NMR: δ = 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).

^{13}C NMR: δ = 171.01, 168.67, 144.14, 132.64, 131.70, 131.17, 127.77, 118.38, 117.26, 112.05, 26.8, 20.24, 12.6.

MS: *m*/*z* = 276, 234, 192, 162, 146.

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

^{1}H NMR: δ = 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).

^{13}C NMR: δ = 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: *m*/*z* = 276, 234, 192, 162, 146.

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

^{1}H NMR: δ = 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).

^{13}C NMR: δ = 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: *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

(1) Manafi, M. *Int. J. Food Microbiol.* **2000**, *60*, 205.
(2) Szameit, C.; Miech, C.; Balleininger, M.; Schmidt, B.; Von Figura, K.; Dierks, T. *J. Biol. Chem.* **1999**, *274*, 15375.
(3) Ono, K.; Tsuji, H.; Rai, S. K.; Yamamoto, A.; Masuda, K.; Endo, T.; Hotta, H.; Kawamura, T.; Uga, S. *Appl Environ. Microbiol.* **2001**, *67*, 3832.
(4) Pretka, J. E.; Lindwall, H. G. *J. Org. Chem.* **1954**, *19*, 1080.
(5) Balbuzano-Deus, A.; Rodríguez-Domínguez, J. C.; Fernández-Villalobo, A.; López-López, M.; Kirsch, G. *Org. Prep. Proced. Int.* **2006**, *38*, 87.

(6) Rodríguez-Domínguez, J. C.; Balbuzano-Deus, A.; López-López, M. A.; Kirsch, G. *J. Heterocycl. Chem.* **2007**, *44*, 273.
(7) Merour, J. Y.; Coadou, J. Y.; Tatiboueet, F. *Synthesis* **1982**, 1053.
(8) Hassner, A.; Haddadin, M. J. *J. Org. Chem.* **1963**, *28*, 224.
(9) Piper, J. R.; Stevens, F. J. *J. Org. Chem.* **1962**, *27*, 3134.
(10) Rössing, A. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 2988.