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An unexpected simple synthesis of *N*-substituted 2-acetoxy-5-arylpyrroles and their hydrolysis to 3 and 4-pyrrolin-2-ones

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Abstract—The unexpected synthesis of *N*-substituted 2-acetoxy-5-arylpyrroles, from the reaction of 3-aroyl-propionamides with a large excess of refluxing acetyl chloride, and their alkaline hydrolysis to 3- and 4-pyrrolin-2-ones, is described.

The importance of the pyrrole ring system has continued to stimulate a great deal of interest in the development of new methodologies for its synthesis. Several recent reviews on this topic are available.[1–3] Pyrroles, which occur in porphyrins,[4] pigments,[5] and other natural products[6] have found applications in materials science[7] and are common components in molecular recognition and self-assembly ensembles.[8–10] On the other hand, 3-pyrrolin-2-ones are important structural units in organic and medicinal chemistry including the synthesis of alkaloids, nucleosides, antineoplastic agents or immunosuppressants.[11] The α,β-unsaturated lactam moiety can be utilized as a Michael acceptor for a variety of nucleophiles including stabilized carbanions,[12] and nitrogen nucleophiles.[13,14] Therefore the synthesis of such building blocks is currently receiving considerable attention.[15,16]

Here we wish to report a simple and unexpected synthesis of *N*-substituted 2-acetoxy-5-arylpyrroles **2** from the corresponding 3-aroylpropionamides **1**, via a cyclocondensation–acetylation reaction, conducted with a large excess of acetyl chloride under reflux,[17] and their alkaline hydrolysis to the corresponding 3- and 4-pyrrolin-2-ones **4** and **5** (Scheme 1). The starting *N*-substituted 3-aroylpropionamides **1** were prepared from the corresponding 3-aroylpropionic acids.[18–20] The alkaline hydrolysis of 2-acetoxypyrroles **2** was shown to give a mixture of 3- and 4-pyrrolin-2-ones **4** and **5**, respectively, in a ratio between 70:30 to 80:20, evidently through the unstable[21,22] 2-hydroxypyrroles **3** (Scheme 1). After recrystallization of the pyrrolinone mixture, the pure 3-pyrolin-2-ones **4a**,**b** and **4d** could be separated.[23] We have not yet used other special physical methods for the separation of the other pyrrolinones. It must be pointed out that the transformation of 3-pyrrolin-2-ones **4a**,**b** and **4d** to the corresponding acetoxypyrroles **2** was accomplished by resubjection to acetyl chloride. This transformation was also successful for the 3- and 4-pyrrolin-2-one mixtures. An isomerization study between 3- and 4-pyrrolin-2-ones has been reported,[24] as well as the non-existence of the pure isomers, at room temperature.

A proposed mechanism for 2-acetoxypyrrole **2** formation could involve: tautomerization of the 3-aroylpropionamides **1** to the corresponding 5-hydroxypyrrolidinones **6**, their subsequent dehydration to the 4-pyrrolin-2-ones **5**, which after acetylation of these or their tautomers, 2-hydroxypyrroles **3**, proceed to the 2-acetoxypyrroles **2** (Scheme 2). Both the tautomerization and dehydration routes could be acid catalyzed by traces of hydrogen chloride present in the acetyl chloride. The elimination of **6** to **5** could proceed via the O-acetate of **6**.

In conclusion, acetyl chloride is an excellent reagent for the cyclocondensation–acetylation reaction of 3-aroylpropionamides to the corresponding *N*-substituted

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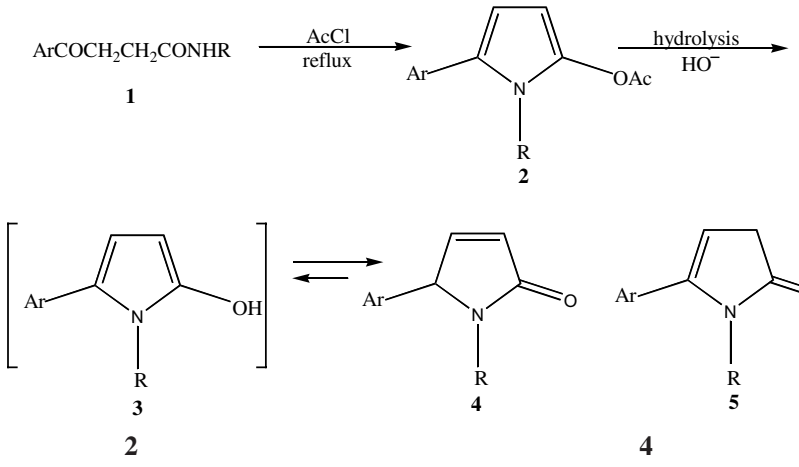

2

Ar	R	yield(%)
(a): C_6H_5-	C_6H_5-	61
(b): *p*-$CH_3C_6H_4$-	C_6H_5-	59
(c): *p*-ClC_6H_4-	C_6H_5-	62
(d): C_6H_5-	$C_6H_5CH_2$-	81
(e): *p*-$CH_3OC_6H_4$-	$C_6H_5CH_2$-	73
(f): *P*-$CH_3C_6H_4$-	$C_6H_5CH_2$-	75
(g): *p*-BrC_6H_4-	$C_6H_5CH_2$-	67

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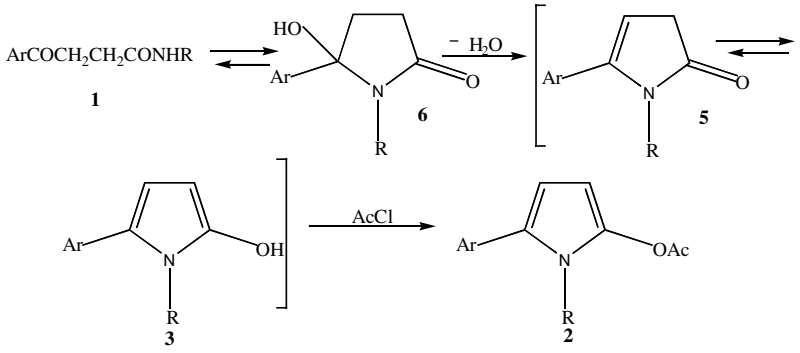
Ar	R	yield(%)
(a): C_6H_5-	C_6H_5-	66
(b): *p*-$CH_3C_6H_4$-	C_6H_5-	70
(d): C_6H_5-	$C_6H_5CH_2$-	71

Scheme 1.



Scheme 2.

5-aryl-2-acetoxypyrroles. The latter is likely to be a useful synthon for the preparation of 3-pyrrolin-2-ones. The application of this method to γ-keto amides with other substituents present on the functional groups and methylene chain, as well as the separation of all the 3-pyrrolin-2-ones and the 4-pyrrolin-2-ones, is currently being investigated.

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17. Typical procedure for the preparation of 2-acetoxypyrroles **2**. A mixture of the γ-keto amide **1** (20 mmol) and acetyl chloride (100–150 mL) (depending on the γ-keto

amide solubility), was refluxed for 1–4 h. The solution was concentrated under vacuum to a residue, which proved to be almost pure (^{1}H NMR) compound **2**. After recrystallization, an analytical sample was obtained in 59–81% yield. 2-Acetoxy-1,5-diphenylpyrrole **2a**: yield 61%, mp 112–113 °C. Anal. Calcd for $C_{18}H_{15}NO_2$: C, 77.95; H, 5.46; N, 5.05%. Found: C, 77.99; H, 5.71; N, 5.04%. IR (Nujol mull, cm^{-1}): 1770, 1603, 1565, 1515 and 1499; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.07 (s, 3H, CH_3CO), 6.06 (d, J = 4 Hz, 1H, –CH=), 6.42 (d, J = 4 Hz, 1H, –CH=), 7.12–7.52 (m, 10H, arom). ^{13}C NMR (75.5 MHz, $CDCl_3$): 20.39, 96.81, 107.70, 126.40, 127.90, 128.22, 128.33, 128.42, 128.95, 129.21, 132.96, 133.74, 136.98, 170.85. HRMS (EI) calcd for $C_{18}H_{15}NO_2$: 277.3172. Found: 277.3214. 2-Acetoxy-5-(4-methylphenyl)-1-phenylpyrrole **2b**: yield, 59%, mp 79–81 °C. Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81%. Found: C, 78.11; H, 5.76; N, 4.68%. IR (Nujol mull, cm^{-1}): 1779, 1597, 1560, 1526 and 1500; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.07 (s, 3H, CH_3CO), 2.28 (s, 3H, CH_3Ar), 6.02 (d, J = 4 Hz, 1H, –CH=), 6.33 (d, J = 4 Hz, 1H, –CH=), 6.95–7.47 (m, 9H, arom). HRMS (EI) calcd for $C_{19}H_{17}NO_2$; 291.3438. Found 291.3465. 2-Acetoxy-5-(4-chlorophenyl)-1-phenylpyrrole **2c**: yield, 62%, mp 126–128 °C. Anal. Calcd for $C_{18}H_{14}ClNO_2$: C, 69.35; H, 4.53; Cl, 11.37; N, 4.49%. Found: C, 69.49; H, 4.60; Cl, 11.57; N, 4.36%. IR (Nujol mull, cm^{-1}): 1773, 1598, 1560, 1510 and 1500; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.07 (s, 3H, CH_3CO), 6.03 (d, J = 4 Hz, 1H, –CH=), 6.37 (d, J = 4 Hz, 1H, –CH=), 6.87–7.50 (m, 9H, arom). 2-Acetoxy-1-benzyl-5-phenylpyrrole **2d**: yield 81%, mp 74–76 °C. Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81%. Found: C, 78.27; H, 5.75; N, 4.73%. IR (Nujol mull, cm^{-1}). 1773, 1603, 1565, 1511 and 1497; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.05 (s, 3H, CH_3CO), 5.05 (s, 2H, –CH_2Ph), 6.03 (d, J = 4 Hz, 1H, –CH=), 6.25 (d, J = 4 Hz, 1H, –CH=), 6.87–7.50(m, 10H, arom). ^{13}C NMR (75.5 MHz, $CDCl_3$): 20.55, 47.03, 96.12, 106.84, 126.23, 127.30, 127.49, 128.76, 128.95, 129.00, 129.42, 139.26, 137,87, 138.51, 167.97. 2-Acetoxy-1-benzyl-5-(4-methoxyphenyl)pyrrole **2e**: yield, 73%, mp 78–79 °C. Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.74; H, 5.96; N, 4.36%. Found: C, 74.67; H, 5.97; N, 4.32%. IR (Nujol mull, cm^{-1}): 1778, 1613, 1563 and 1521; ^{1}H NMR (300 MHz, $CDCl_3$): 2.02 (s, 3H, CH_3CO), 3.73 (s, 3H, CH_3O), 5.00 (s, 2H, –CH_2Ph), 5.94 (d, J = 4 Hz, 1H, –CH=), 6.13 (d, J = 4 Hz, 1H, –CH=), 6,70–7.43 (m, 9H, arom). ^{13}C NMR (75.5 MHz, $CDCl_3$): 20.56, 46.90, 55.41, 95.78, 106.15, 114.14, 125.80, 126.24, 127.46, 128.94, 129.12, 130.49, 137.34, 138.62, 159.21, 168.05. 2-Acetoxy-1-benzyl-5-(4-methylphenyl)pyrrole **2f:** yield 75%, mp 89–91 °C. Anal. Calcd for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59%. Found: C, 78.51; H, 6.11; N, 4.48%. IR (Nujol mull, cm^{-1}): 1778, 1613, 1572, 1560, 1517 and 1495; ^{1}H NMR (300 MHz, $CDCl_3$): 2.05 (s, 3H, CH_3CO), 2.35 (s, 3H, CH_3Ar), 5.03 (s, 2H, –CH_2Ph), 6.00 (d, J = 4 Hz, 1H, –CH=), 6.19 (d, J = 4 Hz, 1H, –CH=), 6.87–7.50 (m, 9H, arom). ^{13}C NMR (75.5 MHz, $CDCl_3$): 20.56, 21.23, 64.99, 95.96, 106.44, 126.23, 127.45, 128.34, 128.93, 129.00, 129.46, 130.36, 137.12, 137.61, 138.62, 168.00. 2-Acetoxy-1-benzyl-5-(4-bromophenyl)pyrrole **2g**: yield 67%, mp 113–114 °C. Anal. Calcd for $C_{19}H_{16}BrNO_2$: C, 61.64; H, 4.36; Br, 21.58; N, 3.78%. Found: C, 61.75; H, 4.40; Br, 21.32; N, 3.72%. IR (Nujol mull, cm^{-1}): 1776, 1567, 1555, 1503 and 1493; ^{1}H NMR (300 MHz, $CDCl_3$): 2.08 (s, 3H, CH_3CO), 5.01 (s, 2H, –CH_2Ph), 6.02 (d, J = 4 Hz, 1H, –CH=), 6.22 (d, J = 4 Hz, 1H, –CH=), 6.83–7.53 (m, 9H, arom). ^{13}C NMR (75.5 MHz, $CDCl_3$): 20.57, 47.00, 96.35, 107.32, 121.36, 126.12, 127,64, 128.14, 129.06, 130.41, 131.92, 132.15, 138.23, 167.90.

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23. General procedure for the preparation of 3-pyrrolin-2-ones **4**. To a refluxing solution of 2-acetoxypyrrole **2** (10 mmol) in methanol (80–130 mL), a solution of 0.01 N potassium hydroxide (20 mL) was added dropwise. Reflux was continued (40–75 min), until reaction was complete (TLC). The solution was then concentrated under vacuum and the residue was recrystallized from benzene/petrol ether, to give an analytical sample of 3-pyrrolin-2-one **4**, in 66–71% yields, or a pure mixture of 3- and 4-pyrrolin-2-ones **4** and **5**, in 74–86% yields, (as proved[25] from ^{1}H NMR and elemental analysis). 1,5-Diphenyl-3-pyrrolin-2-one **4a**: yield, 66%, mp 166–168 °C, lit.[26] 167–168 °C. IR (Nujol mull, cm^{-1}): 1686, 1598, 1503; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.65 (t, J = 1.8 Hz, 1H, C5), 6.20 (dd, J = 6 Hz and J = 1.8 Hz, 1H, C4), 6.83–7.60 (m, 11H, 10 arom and C3). ^{13}C NMR (75.5 MHz, $CDCl_3$): 67.70, 121.71, 124.89, 126.46, 127.02, 128.76, 129.11, 129.43, 135.33, 137.64, 148.63, 171.01. 5-(4-Methylphenyl)-1-phenyl-3-pyrrolin-2-one **4b**: yield 70%, mp 127–129 °C. Anal. Calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.61%. Found: C, 81.86; H, 6.13; N, 5.44%. IR (Nujol mull, cm^{-1}): 1680, 1593, 1498; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.28 (s, 3H, CH_3Ar), 5.63 (t, J = 1.8 Hz, 1H, C5), 6.24 (dd, J = 6 Hz and 1.8 Hz, 1H, C4), 6.93–7.62 (m, 10H, 9 arom and C3). ^{13}C NMR (75.5 MHz, $CDCl_3$): 21.18, 67.51, 121.76, 124.84, 126.35, 126.95, 129,10, 130.12, 132.19, 137.69, 138.62, 148.78, 171.04. 1-Benzyl-5-phenyl-3-pyrrolin-2-one **4d**: yield 71%, mp 125–127 °C. Anal. Calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.61%. Found: C, 82.06; H, 6.25; N, 5.44%. IR (Nujol mull, cm^{-1}): 1678, 1598, 1494; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.61 and 5.20 (dd, J = 15 Hz, 2H, –CH_aH_bPh), 4.88 (t, J = 1.8 Hz, 1H, C5), 6.21 (dd, J = 6 Hz and 1.8 Hz, 1H, C4), 6.85–7.50 (m, 11H, 10 arom and C3). ^{13}C NMR (75.5 MHz, $CDCl_3$): 43.59, 66.06, 126.43, 127.71, 128.51, 128.82, 129.10, 129.46, 133.57, 134.63, 137.64, 148.49, 171.72.

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25. An analytical sample (mp 159–163 °C, after recrystallization), of a mixture of pyrrolinones **4a** and **5a** showed the 3-pyrrolin-2-one **4a** signals and of those at δ 3.39 (d, J = 2.5 Hz, 1H, C3) and 5.68 (t, J = 2.5 Hz, 1H, C4), which agree[24] with the 4-pyrrolin-2-one structure **5a**. Analogous sets of signals appeared in all the pyrrolinone mixtures.

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