# Unequivocal Preparation of 4- and 5-Acyl-2-aminophenols

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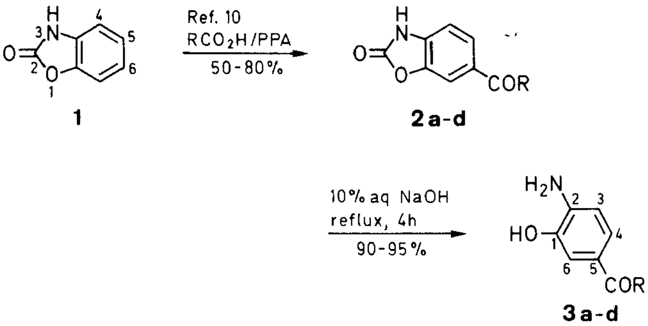
Unequivocal methods for the specific preparation of 4- or 5-acyl-2-aminophenols are reported. 5-Acyl-2-aminophenols are obtained by ring opening with dilute sodium hydroxide of 2(3*H*)-benzoxazolinones acylated at position 6. 4-Acyl-2-aminophenols are obtained by acylation of 2-acetamidophenol in the presence of aluminum chloride/dimethylformamide followed by a deprotection of the amino group.

Acyl-2-aminophenols are useful starting materials in organic chemistry for the preparation of various heterocycles. Moreover, they constitute a basis for chemical modulations in the field of agonists or antagonists of catecholaminergic receptors. Ring acylation of 2-aminophenols has been extensively studied[1-5] however it was difficult to determine the site of attack of electrophilic reagents. The donor effects of amino and phenol groups could be considered as more or less equivalent and in the presence of Friedel-Crafts catalysts, *C*-acylation could occur at position 4 and/or 5. Moreover, examination of the physicochemical data, including $^1$H-NMR spectral data, did not allow unambiguous assignment of regioisomers in the case of a direct acylation.

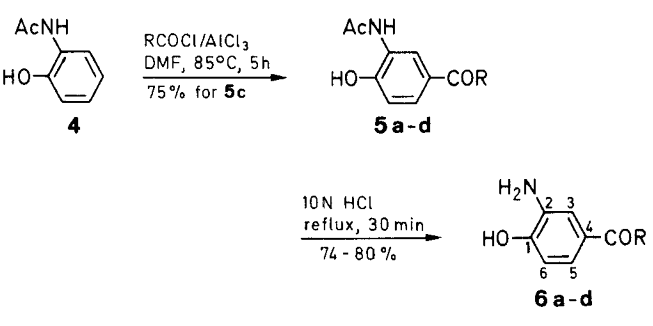
In order to obtain physicochemical information for the definitive identification of 4- or 5-acyl-2-aminophenols, we describe herein the specific preparation of 4-acyl derivatives and 5-acyl derivatives.

To obtain an unambiguous reference compound, 2-amino-5-benzoylphenol (**3c**) was prepared starting from 6-benzoyl-2-(3*H*)-benzoxazolinone (**2c**), the structure of which was clearly established by X-ray diffraction studies.[6]

The isomer 2-amino-4-benzoylphenol (**6c**) was prepared by a more classical method, involving Friedel-Crafts conditions (aluminum chloride/dimethylformamide). However, it is important to note that for preparation of a *C*-acyl derivative using such conditions with optimal yield, it is essential to protect the amino group by acetylation. After benzoylation and deacetylation, the acylated 2-aminophenol was compared to **3c** and the differences observed in the physicochemical data allowed us to conclude that benzoylation had occurred at position 4.



| 2, 3 | a | b | c | d |
|---|---|---|---|---|
| R | Me | Et | Ph | 2-thienyl |



| 5, 6 | a | b | c | d |
|---|---|---|---|---|
| R | Me | Et | Ph | 2-thienyl |

**Table 1.** 5-Acyl-2-aminophenols **3a-d** Prepared

| Product | Yield[a] (%) | mp (°C) | Molecular Formula[b] | IR (KBr) $\nu$(cm$^{-1}$) | $^1$H-NMR (DMSO-$d_6$/TMS) $\delta$, $J$(Hz) |
|---|---|---|---|---|---|
| **3a** | 90 | 170 | $C_8H_9NO_2$ (151.2) | 3390 (OH), 3295 (NH), 1660 (CO), 1600, 1580 (arom) | 2.35 (s, 3H, $CH_3$), 5.46 (s, 2H, $NH_2$), 6.58 (d, 1H, $J = 7.9$, H-3), 7.23 (d, 1H, $J = 2.0$, H-6), 7.31 (dd, 1H, $J = 7.9, 2.0$, H-4), 9.37 (s, 1H, OH) |
| **3b** | 90 | 139 | $C_9H_{11}NO_2$ (165.2) | 3490 (OH), 3400, 3330 (NH), 1650 (CO), 1610, 1570 (arom) | 1.05 (t, 3H, $CH_3$), 2.80 (q, 2H, $CH_2$), 5.44 (s, 2H, $NH_2$), 6.58 (d, 1H, $J = 7.9$, H-3), 7.27 (d, 1H, $J = 2.0$, H-6), 7.32 (dd, 1H, $J = 7.9$, $J = 2.0$, H-4), 9.37 (s, 1H, OH) |
| **3c** | 95 | 164 | $C_{13}H_{11}NO_2$ (213.2) | 3470 (OH), 3380 (NH), 1630 (CO), 1600, 1570 (arom) | 5.63 (s, 2H, $NH_2$), 6.63 (d, 1H, $J = 8.0$, H-3), 7.10 (dd, 1H, $J = 8.0, 1.8$, H-4), 7.20 (d, 1H, $J = 1.8$, H-6), 7.58 (m, 5H, H-2'-H-6'), 9.54 (s, 1H, OH) |
| **3d** | 95 | 185 | $C_{11}H_9NO_2S$ (219.3) | 3500 (OH), 3390 (NH), 1630 (CO), 1560 (arom) | 5.63 (s, 2H, $NH_2$), 6.64 (d, 1H, $J = 8.0$, H-3), 7.27 (dd, 1H, $J = 3.7, 4.9$, H-4'), 7.30 (dd, 1H, $J = 8.0, 2.0$, H-4), 7.32 (d, 1H, $J = 2.0$, H-6), 7.67 (dd, 1H, $J = 1.0, 3.7$, H-5'), 8.00 (dd, 1H, $J = 1.0, 4.9$, H-3'), 9.58 (s, 1H, OH) |

[a] Yield of isolated products **3a-d** based on **2**.

[b] Satisfactory microanalyses: C ±0.15, H ±0.19, H ±0.04.

Table 2. 4-Acyl-2-aminophenols **6a–d** Prepared

| Product | Yield[a] (%) | mp (°C) | Molecular Formula[b] | IR (KBr) $\nu$(cm$^{-1}$) | $^1$H-NMR (DMSO-$d_6$/TMS) $\delta$, $J$(Hz) |
|---|---|---|---|---|---|
| **6a** | 78 | 127–128 | $C_8H_9NO_2$ (151.2) | 3470 (OH), 3380, 3320 (NH), 1640 (CO), 1615, 1580 (arom) | 2.42 (s, 3H, CH$_3$), 5.65 (s, 2H, NH$_2$), 6.70 (d, 1H, $J$ = 7.9, H-6), 7.11 (dd, 1H, $J$ = 7.9, 2.0, H-5), 7.22 (d, 1H, $J$ = 2.0, H-3), 7.50 (s, 1H, OH) |
| **6b** | 74 | 145–146 | $C_9H_{11}NO_2$ (165.2) | 3480 (OH), 3380, 3300 (NH), 1630 (CO), 1610, 1580 (arom) | 1.05 (t, 3H, CH$_3$), 2.87 (q, 2H, CH$_2$), 5.00 (s, 2H, NH$_2$), 6.71 (d, 1H, $J$ = 7.9, H-6), 7.15 (dd, 1H, $J$ = 7.9, 2.0, H-5), 7.24 (d, 1H, $J$ = 2.0, H-3), 9.40 (s, 1H, OH) |
| **6c** | 80 | 164–165 | $C_{13}H_{11}NO_2$ (213.2) | 3460 (OH), 3360 (NH), 1640 (CO), 1610, 1580 (arom) | 5.15 (s, 2H, NH$_2$), 6.77 (d, 1H, $J$ = 8.9, H-6), 6.94 (dd, 1H, $J$ = 8.9, 2.2, H-5), 7.13 (d, 1H, $J$ = 2.2, H-3), 7.57 (m, 5H, H-2′–H-6′), 9.38 (s, 1H, OH) |
| **6d** | 75 | 153–154 | $C_{11}H_9NO_2S$ (219.3) | 3360 (OH), 3290 (NH), 1620 (CO), 1590 (arom) | 5.00 (s, 2H, NH$_2$), 6.78 (d, 1H, $J$ = 8.0, H-6), 7.06 (dd, 1H, $J$ = 8.0, 2.0, H-5), 7.25 (m, 1H, $J$ = 2, H-3), 7.27 (dd, 1H, $J$ = 3.7, 4.9, H-4′), 7.69 (dd, 1H, $J$ = 1, 3.7, H-5′), 7.99 (dd, 1H, $J$ = 1, 4.9, H-3′), 8.65 (s, 1H, OH) |

[a] Yield of isolated products **6a–d** based on **5**.

[b] Satisfactory microanalyses: C ±0.16, H ±0.15, N ±0.12.

A *C*-acylation using classical conditions could be expected to occur at position 3 (*ortho* position versus amino group) or at position 6 (*ortho* position versus phenol group). These two sites have been unambiguously excluded on the basis of the $^1$H-NMR data (no *ortho* coupling for one proton). Moreover, a chromatographic analysis performed on these products using various experimental conditions showed the absence of isomers and byproducts.

The above methods were applied to the preparation of a series of 5- and 4-acyl-2-aminophenols **3a–d, 6a–d** useful starting materials for the preparation of various condensed heterocycles including 2(3*H*)-benzoxazolinones acylated in position 5[7] and benzoxazinones acylated in position 7.[8,9]

Commercialy available reagents were used without purification. Melting points were taken using a Buchi 510 apparatus and are uncorrected. Microanalyses were obtained from the CNRS, Vernaison, France. IR spectra were recorded on a Perkin-Elmer 297 spectrophotometer. $^1$H-NMR spectra were obtained using a Brucker 80 MHz spectrometer.

**2-Amino-5-benzoylphenol (3c); Typical Procedure for 5-Acyl-2-aminophenols:**

A mixture of 6-benzoyl-2(3*H*)-benzoxazolinone (**2c**, 7.18 g, 0.03 mol) prepared by literature procedures,[10] and a 10% aq NaOH (60 mL) is refluxed for 4 h. After cooling, the solution is acidified with conc. HCl. The aminophenol is liberated from its hydrochloride by slow addition of a sat. aq $Na_2CO_3$ solution until a white precipitate is formed. The precipitated product is isolated by suction and washed well with water; yield: 6 g (95%) Table 1.

**2-Amino-4-benzoylphenol (6c); Typical Procedure for 4-Acyl-2-aminophenols:**

*2-Acetamido-4-benzoylphenol* (**5c**):

In a dried, nitrogen-filled round-bottom flask fitted with stirrer and addition funnel, is placed anhydrous aluminum chloride (53.3 g, 0.4 mol) and DMF (8.6 mL, 0.11 mol) is introduced dropwise with stirring. The mixture is heated at 35 °C and maintained at this temperature during the addition of 2-acetylaminophenol (7.6 g, 0.05 mol) and benzoyl chloride (9.8 g, 0.07 mol). Heating is increased to 85 °C. The solution is stirred at this temperature for 5 h then quenched with ice-cold 10 N HCl. The mixture is stirred for 1 h. The precipitated crude product 2-acetylamino-4-benzoylphenol is separated by filtration, washed with water, air dried; yield: 9.5 g (75%); mp 193–194 °C (EtOH).

| | | | | |
|---|---|---|---|---|
| $C_{15}H_{13}NO_3$ | calc. | C 70.58 | H 5.13 | N 5.48 |
| 255.2 | found | 71.33 | 5.13 | 5.42 |

$^1$H-NMR (DMSO-$d_6$/TMS): $\delta$ = 2.05 (s, 3H, COCH$_3$), 7.00 (d, 1H, $J$ = 8.7 Hz, H-6), 7.46 (dd, 1H, $J$ = 8.7, 2.2 Hz, H-5), 7.64 (m, 5H, H-2′-H-6′), 8.27 (d, 1H, $J$ = 2.2 Hz, H-3), 9.30 (s, 1H, OH), 10.78 (s, 1H, NH).

*2-Amino-4-benzoylphenol* (**6c**):

A mixture of the above compound 2-acetylamino-4-benzoylphenol (**5c**, 7.6 g, 0.03 mol) and 10 N HCl (30 mL) is heated at reflux for 30 min. After cooling, the solution is evaporated to dryness and aq $Na_2CO_3$ is added with caution under stirring until there is no further effervescence. Stirring is then maintained for 30 min. The precipitated crude compound is separated by filtration, washed with water and recrystallized; yield: 4.8 g (75%) (Table 2).

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