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# Hydrolysis-free synthesis of 3-aminocoumarins

Amit A. Kudale, Jamie Kendall, C. Chad Warford, Natasha D. Wilkins and Graham J. Bodwell*

*Department of Chemistry, Memorial University, St. John's, NL, Canada A1B 3X7*

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**Abstract**—A commonly encountered problem in the synthesis of 3-aminocoumarins is the formation of 3-hydroxycoumarins. A solution to this problem, which involves non-aqueous formation of the 3-aminocoumarin system, is described.


The coumarin system is present in a very broad range of natural and non-natural products of biological interest.[1] The 3-aminocoumarin motif, while considerably less prevalent, can nonetheless be found in a number of naturally occurring antibiotics, such as novobiocin **1**,[2] clorobiocin **2**[3] and coumermycin $A_1$ **3**[4] (Fig. 1).

Derivatives of 3-aminocoumarins have been found to possess biological activity, including CNS depressant,[5] antibacterial,[6] antiallergic[7] and insect-growth regulatory.[8] Moreover, 3-aminocoumarin and its derivatives are also known to exhibit interesting photochemical behavior and have found application as fluorescent markers.[9]

Although various methods have been reported for the synthesis of 3-aminocoumarins or related compounds,[10] reproducibility has sometimes been a problem, as

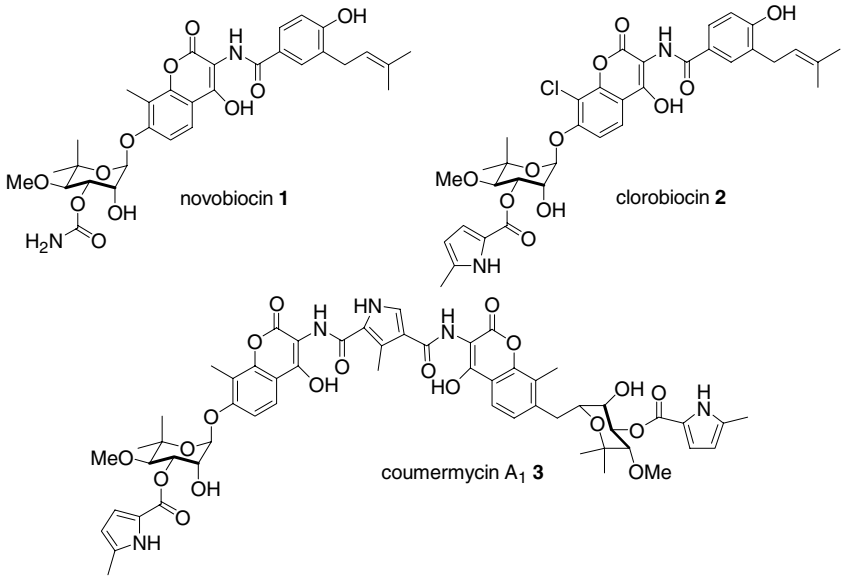


**Figure 1.** Natural antibiotics containing 3-aminocoumarin.

*Keywords*: Salicylaldehydes; 3-Acetamidocoumarins; 3-Aminocoumarins.
* Corresponding author. Tel.: +1 709 737 8406; fax: +1 709 737 3702; e-mail: gbodwell@mun.ca

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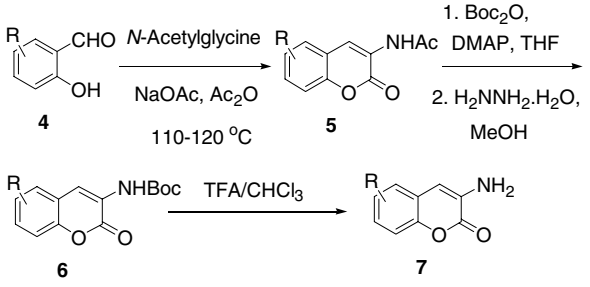
experienced by us and others.[11] The final step of these syntheses is typically the hydrolysis of a 3-acetamidocoumarin, which can result in the formation of a 3-hydroxycoumarin, both under acidic and basic conditions.[12] Herein, we report an efficient and convenient synthesis of 3-aminocoumarin and several derivatives bearing a substituent on the carbocyclic ring.

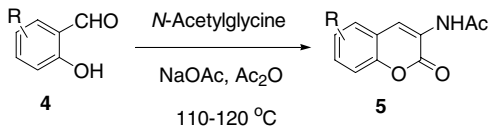
For the parent 3-aminocoumarin (**7a**), the synthesis commenced with the conversion of commercially available (or easily prepared from salicylaldehyde and *N*-acetylglycine[13]) 3-acetamidocoumarin (**5a**) to Boc-protected 3-aminocoumarin (**6a**) using the method of Burk and Allen[14] in 94% yield. This one-pot procedure, which was originally developed for amino acids, involves an acylation–deacylation sequence in which an *N*-acetyl compound is reacted with di-*t*-butyl dicarbonate in the presence of DMAP to give an imide, followed by reaction with hydrazine hydrate to remove the acetyl group. The resulting *t*-butyl carbamate (**6a**) could then be easily deprotected to give 3-aminocoumarin (**7a**) in high yield (99%) under anhydrous conditions through the action of 15% TFA/$CHCl_3$ (Scheme 1). In our hands, this method has proved to be very reproducible and we have prepared up to 15 g of 3-aminocoumarin in a single run.

For the synthesis of substituted 3-aminocoumarins, suitably substituted 3-acetamidocoumarins (**5**) were required. Being commercially unavailable, it was envisaged that these compounds could be prepared from the corresponding salicylaldehyde and *N*-acetylglycine.[13] Since the yield for parent 3-acetamidocoumarin (**5a**) is low (27%) using this method, efforts were made to optimize the reaction conditions for the conversion of salicylaldehyde (**4a**) into compound **5a**. After varying reaction time, temperature, number of equivalents of *N*-acetylglycine and sodium acetate, it was found that the use of 4.0 equiv of sodium acetate and 1.0 equiv of *N*-acetylglycine at 110–120 °C for 3.5 h gave the best yield (46%) for the parent 3-acetamidocoumarin (**5a**). Employing the same reaction conditions for a series of substituted salicylaldehydes (commercially available or easily prepared by known formylation protocols[15]) afforded the corresponding 3-acetamidocoumarins (**5b–i**) (Table 1). The yields for these reactions were variable. Poor yields were obtained when an electron-donating group was situated *para* to the aldehyde function of the starting salicylaldehyde (Table 1, entries 6 and 8). Otherwise, the yields ranged from 40% to 69%. When




**Scheme 1.** General synthesis of 3-aminocoumarins **7**.

**Table 1.** Condensation of salicylaldehydes with *N*-acetylglycine




| Entry | R | Product | Yield[a] (%) |
|---|---|---|---|
| 1 | H | **5a** | 46 |
| 2 | 6-Br | **5b** | 69 |
| 3 | 6-Me | **5c** | 42 |
| 4 | 6-$NO_2$ | **5d** | 69 |
| 5 | 6-OMe | **5e** | 40 |
| 6 | 7-OMe | **5f** | 20 |
| 7 | 8-OMe | **5g** | 69 |
| 8 | 7-OAc | **5h** | 21[b] |
| 9 | 5,6-Benzo | **5i** | 63 |

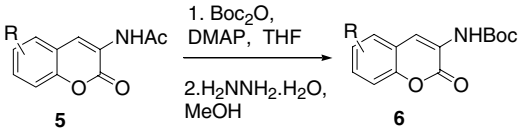
[a] Isolated yield, >95% purity by $^1$H NMR analysis.
[b] 4-$HOC_6H_4CHO$ was the starting material in this reaction. The hydroxyl group undergoes acetylation under the reaction conditions.

the starting material was 4-hydroxysalicylaldehyde (Table 1, entry 8), O-acylation took place, giving 7-acetoxy-3-acetamidocoumarin (**5h**) as the product.

The next step involved conversion of the acetamide to a *t*-butyl carbamate. Burk and Allen's one-pot protocol was then employed to afford the Boc-protected 3-aminocoumarins (**6b–i**) (Table 2). Under these conditions, the acetoxy group in compound **5h** was converted back to a hydroxy group (Table 2, entry 8). For the most part, the yields were high. As above, the yields of the products with donor groups at the 7-position (Table 2, entries 6 and 8) were comparatively low.

Removal of the Boc-group using 15% TFA/$CHCl_3$ then afforded the 3-aminocoumarins (**7b–i**) in generally very good yields (58–96%) (Table 3). In no case was any 3-hydroxycoumarin detected. Clearly, the use of a *t*-butoxycarbonyl protecting group is crucial because it can be removed under anhydrous conditions. The optimal reaction times for preparing the desired 3-amino-

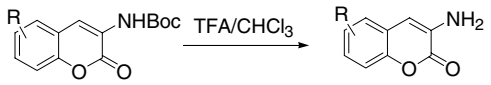
**Table 2.** Conversion of 3-acetamidocoumarins (**5**) into Boc-protected 3-aminocoumarins (**6**)




| Entry | R | Product | Yield[a] (%) |
|---|---|---|---|
| 1 | H | **6a** | 94 |
| 2 | 6-Br | **6b** | 87 |
| 3 | 6-Me | **6c**[b] | 90 |
| 4 | 6-$NO_2$ | **6d** | 93 |
| 5 | 6-OMe | **6e**[b] | 93 |
| 6 | 7-OMe | **6f**[b] | 58 |
| 7 | 8-OMe | **6g**[b] | 92 |
| 8 | 7-OH | **6h**[b] | 50 |
| 9 | 5,6-Benzo | **6i**[b] | 95 |

[a] Isolated yield, >95% purity by $^1$H NMR analysis.
[b] New compound. See Ref. 16.

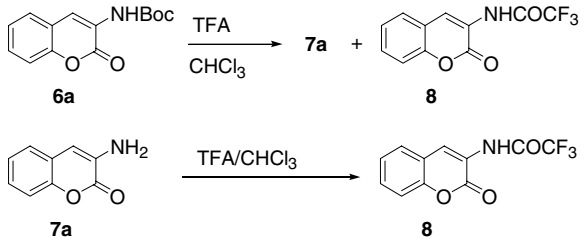
**Table 3.** Removal of the Boc group




6 7

| Entry | R | Product | Yield[a] (%) |
|---|---|---|---|
| 1 | H | **7a** | 99 |
| 2 | 6-Br | **7b** | 67 |
| 3 | 6-Me | **7c** | 96 |
| 4 | 6-$NO_2$ | **7d** | 89 |
| 5 | 6-OMe | **7e** | 95 |
| 6 | 7-OMe | **7f** | 58[b] |
| 7 | 8-OMe | **7g** | 80 |
| 8 | 7-OH | **7h** | 96 |
| 9 | 5,6-Benzo | **7i** | 65 |

[a] Isolated yield, >95% purity by $^1$H NMR analysis.
[b] 37% **6f** recovered after 3 h.




**Scheme 2.** Formation of 3-trifluoroacetamidocoumarin **8**.

coumarins were found to be generally between 3 and 4.5 h at room temperature. Longer reaction times resulted in a decrease in the yields of desired 3-aminocoumarins and the formation of the corresponding 3-trifluoroacetamidocoumarin (**8**) (Scheme 2). For the parent system, 3-trifluoroacetamidocoumarin (**8a**)[17] was isolated in 14% yield after a reaction time of 31 h. Yields as high as 35–45% were obtained for substrates **6d** and **6e** when the reaction was run for 27 h. Evidently, the 3-aminocoumarin, once formed, is acylated by the solvent. Indeed, stirring pure 3-aminocoumarin (**7a**) in 15%. TFA/$CHCl_3$ at room temperature resulted in the slow formation of compound **8a** (tlc analysis). After stirring for 7 days, roughly equivalent amounts of compounds **7a** and **8a** were present in solution (tlc analysis) and, after a further day's reaction at reflux, trifluoroacetamidocoumarin (**8a**) was isolated in 68% yield.

In conclusion, we have developed a hydrolysis-free method for the synthesis of 3-aminocoumarins. It can be used to prepare multigram quantities of various 3-aminocoumarins and does not result in the formation of any 3-hydroxycoumarins.

## Acknowledgments

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## Supplementary data

Experimental procedures, characterization data and $^1$H and $^{13}$C NMR spectra for individual compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.05.088.

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16. Compound **6c**: Mp = 133–134 °C; $\delta_H$ ($CDCl_3$, 500 MHz) = 8.22 (s, 1H), 7.40 (s, 1H), 7.24 (m, 1H), 7.20 (m, 2H), 2.39 (s, 3H), 1.53 (s, 9H) ppm; $\delta_C$ ($CDCl_3$, 125 MHz) = 159.0, 152.7, 147.9, 134.9, 130.2, 127.4, 124.7, 120.6, 120.0, 116.2, 81.8, 28.4, 21.1 ppm; IR $\nu$ = 3407 (m), 1717 (m), 1707 (m), 1632 (s), 1616 (s), 1581 (s), 1510 (m) $cm^{-1}$; MS *m/z* (%) = 175 (100, $M^+$); HRMS calcd for $C_{15}H_{17}NO_4$ 275.1158, found 275.1149. Compound **6e**: Mp = 164–165 °C (EtOAc/hexanes); $\delta_H$ ($CDCl_3$, 500 MHz) = 8.24 (s, 1H), 7.42 (s, 1H), 7.23 (d, $J$ = 9.0 Hz, 1H), 6.97 (dd, $J$ = 9.2, 2.6 Hz, 1H), 6.90 (d, $J$ = 2.7 Hz, 1H), 3.83 (s, 3H), 1.54 (s, 9H) ppm; $\delta_C$ ($CDCl_3$, 125 MHz) = 158.9, 156.8, 152.7, 144.2, 125.2, 120.8, 120.4, 117.5, 116.8, 109.8, 82.0, 56.0, 28.4 ppm; IR $\nu$ = 3416 (m), 1729 (s), 1693 (b), 1583 (s) $cm^{-1}$; MS *m/z* (%) = $M^+$ not obs., 191 (100); HRMS calcd for $C_{15}H_{17}NO_5$ 291.1107, found 291.1101. Compound **6f**: Mp = 117–118 °C (EtOAc/hexanes); $\delta_H$ ($CDCl_3$, 500 MHz) = 8.23 (s, 1H), 7.35 (d, $J$ = 8.7 Hz, 1H), 7.29 (s, 1H), 6.86 (dd, $J$ = 8.6, 2.6 Hz, 1H), 6.81 (d, $J$ = 1.8 Hz, 1H), 3.85 (s, 3H), 1.53 (s, 9H) ppm; $\delta_C$ ($CDCl_3$, 125 MHz) = 161.0, 159.1, 152.8, 151.2, 128.3, 122.4, 121.4, 113.5, 113.2, 100.9, 81.7, 55.9, 28.4 ppm; IR $\nu$ = 3318 (m), 1726 (m), 1699 (s), 1631 (m), 1613 (s), 1575 (m), 1524 (s) $cm^{-1}$; MS *m/z* (%) = $M^+$ not obs., 191 (100); HRMS calcd for $C_{15}H_{17}NO_5$ 291.1107, found 291.1099. Compound **6g**: Mp = 97–99 °C (EtOAc/hexanes); $\delta_H$ ($CDCl_3$, 500 MHz) = 8.25 (s, 1H), 7.43 (s, 1H), 7.22–7.19 (m, 1H), 7.04 (d, $J$ = 7.0 Hz, 1H), 6.97 (d, $J$ = 8.1 Hz, 1H), 3.96 (s, 3H), 1.53 (s, 9H) ppm; $\delta_C$ ($CDCl_3$, 125 MHz) = 158.3, 152.7, 147.2, 139.2, 125.1, 125.1, 121.0, 120.6, 119.1, 111.3, 81.9, 56.4, 28.4 ppm; IR $\nu$ = 3318 (m), 1729 (s), 1703 (s), 1580 (m), 1532 (m) $cm^{-1}$; MS *m/z* (%) = $M^+$ not obs., 191 (100); HRMS calcd for $C_{15}H_{17}NO_5$ 291.1107, found 291.1110. Compound **6h**: Mp = 177–178 °C ($CH_2Cl_2$/hexanes); $\delta_H$ ($CDCl_3$, 500 MHz) = 8.24 (s, 1H), 7.32 (d, $J$ = 7.8 Hz, 1H), 7.27 (s, 1H), 6.88 (d, $J$ = 1.5 Hz, 1H), 6.83 (dd, $J$ = 8.2, 2.6 Hz, 1H), 6.42 (s, 1H), 1.53 (s, 9H) ppm; $\delta_C$ ($CDCl_3$, 125 MHz) = 159.6, 157.8, 152.9, 151.1, 128.7, 122.4, 122.0, 114.3, 113.4, 103.2, 82.0, 28.4 ppm; IR $\nu$ = 3317 (m), 17039 (s), 1681 (s), 1633 (s), 1608 (s), 1535 (s), 1512 (s) $cm^{-1}$; MS *m/z* (%) = $M^+$ not obs., 177 (100); HRMS calcd for $C_{14}H_{15}NO_5$ 277.0950, found 277.0951. Compound **6i**: Mp = 192–194 °C (EtOAc/hexanes); $\delta_H$ ($CDCl_3$, 500 MHz) = 9.10 (s, 1H), 8.35 (d, $J$ = 7.8 Hz, 1H), 7.90–7.85 (m, 2H), 7.65–7.64 (m, 1H), 7.58–7.55 (m, 1H), 7.49 (s, 1H), 7.44 (d, $J$ = 9.4 Hz, 1H), 1.59 (s, 9H) ppm; $\delta_C$ ($CDCl_3$, 125 MHz) = 158.8, 152.8, 148.3, 130.9, 130.3, 129.2, 129.0, 127.8, 126.3, 124.8, 122.6, 116.8, 116.6, 114.6, 82.0, 28.5; IR $\nu$ = 3316 (m), 1701 (s), 1575 (s), 1522 (s) $cm^{-1}$; MS *m/z* (%) = $M^+$ not obs., 211 (100); HRMS calcd for $C_{18}H_{17}NO_4$ = 311.1158, found = 311.1149.
17. Compound **8a**: Mp = 132–133 °C (EtOAc/hexanes); $\delta_H$ ($CDCl_3$, 500 MHz) = 8.81 (s, 1H), 8.70 (s, 1H), 7.59–7.54 (m, 2H), 7.40–7.36 (m, 2H) ppm; $\delta_C$ ($CDCl_3$, 125 MHz) = 158.1, 155.7 (q, $J_{C-F}$ = 39.1 Hz), 150.7, 131.3, 128.5, 126.5, 125.8, 122.2, 119.0, 116.9, 115.3 (q, $J_{C-F}$ = 288.4 Hz) ppm; IR $\nu$ = 3298 (m), 1735 (m), 1694 (s), 1626 (b), 1607 (s), 1555 (s) $cm^{-1}$; HRMS calcd for $C_{11}H_6F_3NO_3$ 257.0300, found 257.0298.