A New Convenient Synthesis of 3-Amino-4-hydroxycoumarin Derivatives[1]

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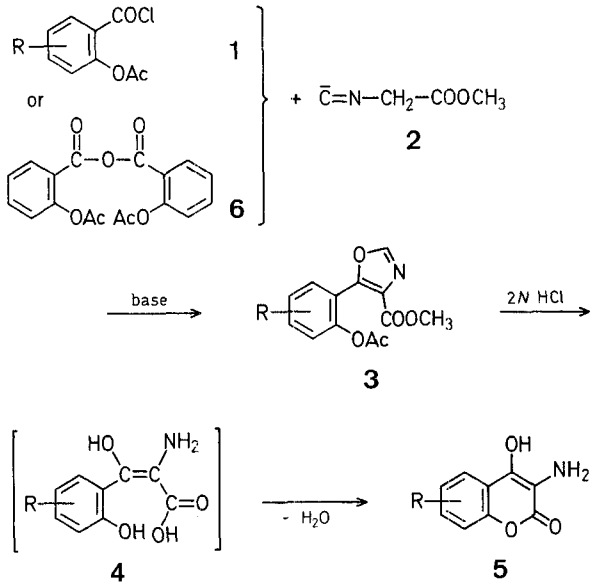
3-Amino-4-hydroxycoumarin derivatives are key intermediates for the synthesis of novobiocin and analogous compounds exhibiting strong antibacterial activity, and are pharmaceutically interesting compounds[2]. Several methods for the preparation of 3-amino-4-hydroxycoumarins have been reported. Of these, nitration[3] or azo-coupling reactions[4] of 4-hydroxycoumarin followed by reduction to the amino derivative have been employed frequently. However, these methods involve complicated procedures and thus are not advantageous for practical use.

In this paper, we wish to report a new convenient synthesis of 3-amino-4-hydroxycoumarin derivatives (**5**) using methyl isocyanoacetate. We have recently reported that the reaction of isocyano compounds with acyl halides or acid anhydrides affords α-amino-β-oxocarboxylic acids in good yields[5]. The reaction has now been extended to the preparation of the 3-aminocoumarin derivatives (**5**).



Methyl isocyanoacetate (**2**) reacts with 2-acetoxybenzoyl chlorides (**1**) in the presence of a base to give 5-(2-acetoxyphenyl)-4-methoxycarbonyl-1,3-oxazoles (**3**). Hydrolysis of compounds **3** with hydrochloric acid then affords the desired 3-amino-4-hydroxycoumarins **5** in fair to good yields (see Table, Method A). The reaction is assumed to proceed via the *O*-deacetylated intermediate **4**. 3-Amino-4-hydroxycoumarin hydrochloride (**5a**) thus obtained was spectroscopically identical with an authentic specimen[3].

The I.R. spectra of the hydrochlorides **5a** and **5f** showed the characteristic absorptions of the carbonyl group at 1710 cm^{-1} and of the C=C double bond near 1650 cm^{-1}. In the case of compounds **5b-e** which possess a free amino group, the C=C and C=O absorptions were shifted to lower ν-values due to intramolecular hydrogen bonding.

The reaction of **2** with *O*-acetylsalicylic anhydride (**6**) in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) also proceeded readily (Method B) to afford 5-(2-acetoxyphenyl)-4-methoxycarbonyl-1,3-oxazole (**3**, R = H), which was then hydrolyzed to give **5a** (identical with product **5a** prepared by Method A).

Preparation of 3-Amino-4-hydroxycoumarins (5); Typical Procedures:

Method A: 2-Acetoxybenzoylchloride (**1**, R = H; 3.97 g, 0.02 mol) dissolved in tetrahydrofuran (15 ml) was added dropwise to a stirred mixture of methyl isocyanoacetate (**2**; 1.98 g, 0.02 mol) and triethylamine (4.04 g, 0.04 mol) in tetrahydrofuran (45 ml) at 5–10°. Stirring was continued for 3 days at room temperature, the solvent was removed under reduced pressure, and the resultant residue was extracted with ethyl acetate. The extract was washed with water, 2% hydrochloric acid, and 10% sodium hydrogen carbonate solution, dried with magnesium sulfate, and evaporated in vacuo. *5-(2-Acetoxyphenyl)-4-methoxycarbonyl-1,3-oxazole* (**3**, R = H)[5] was obtained as a reddish oil; yield 4.0 g.

IR. (Film): ν_{max} = 3150, 1770, 1730, 1620, 1595 cm^{-1}.

The 1,3-oxazole **3**, R = H, was used without further purification. The compound (4.0 g) was dissolved in 2*N* methanolic hydrochloric acid (36 ml). The mixture was refluxed with stirring for 4 h, water

Table. Preparation of 3-Amino-4-hydroxycoumarins (**5**) by Method A

	R	m.p. (dec.)	Yield (%)	I.R. ν_{max} cm^{-1}	Elemental Analysis			
a	H[a]	215–220°	66	1710, 1652	calc.	C 50.60	H 3.77	N 6.59
					found	50.88	3.86	6.61
b	6-Cl	237–238°	45	1672, 1602	calc.[b]	C 52.52	H 3.30	N 3.82
					found	52.27	3.40	3.91
c	6-Br	280–285°	60	1690, 1605	calc.	C 42.21	H 2.36	N 5.47
					found	41.84	2.08	5.41
d	6-NO_2	248–250°	54	1670, 1600	calc.	C 48.66	H 2.70	N 12.61
					found	49.00	2.88	12.40
e	8-CH_3	220–225°	47	1665, 1602	calc.	C 62.82	H 4.75	N 7.33
					found	63.00	4.74	7.01
f	6,7-(CH=CH)$_2$—[c]	266–270°	55	1710, 1650	calc.	C 68.72	H 3.99	N 6.17
					found	69.01	3.91	6.00

[a] Hydrochloride.

[b] Elemental analysis of *6-chloro-4-hydroxy-3-tosylaminocoumarin*.

[c] 2-Amino-1-hydroxy-3-oxo-3*H*-naphtho[2,1-*b*]pyran (*3-Amino-4-hydroxy-6,7-benzocoumarin*) hydrochloride.

(30 ml) was then added, and the methanol was removed under reduced pressure. The residual aqueous solution was washed with ether, treated with activated charcoal, and neutralized with sodium hydrogen carbonate. The oily product was extracted with ethyl acetate, and hydrogen chloride gas was then bubbled into the extract with ice cooling. The solvent was removed and the crystalline residue washed with cold ethyl acetate. The ethyl acetate was removed by suction and the product recrystallized from ethanol/ethyl acetate as colorless needles; yield: 2.83 g (66%); m.p. 215–220° (dec.) (Ref.[3], m.p. 210–215°).

^{1}H-N.M.R. (DMSO-d_6): $\delta = 9.72$ (broad, 4H, NH_2·HCl, OH), 7.20–8.25 ppm (m, $4H_{arom}$).

Mass Spectrum: $m/e = 177$ ($M^+ - HCl$).

Method B: To a solution of methyl isocyanoacetate (**2**; 3.0 g, 0.03 mol) and DBU (4.5 g, 0.03 mol) in tetrahydrofuran (40 ml), a solution of acetylsalicylic anhydride (**6**; 10.3 g, 0.03 mol) in tetrahydrofuran (15 ml) was added dropwise, at room temperature with stirring. Stirring was continued for 12 h at room temperature and the mixture was then treated further as described under Method A; yield of *3-amino-4-hydroxycoumarin* (**5a**): 3.2 g (50%). The compound was spectroscopically concordant with **5a** prepared by the Method A.

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