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Lian Ee Khoo [a]

[a] National Institute of Education, School of Science Nanyang Technological University, 469 Bukit Timah Road , Singapore, 259756, SINGAPORE

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SYNTHESIS OF SUBSTITUTED 3-AMINOCOUMARINS FROM ETHYL N-2-HYDROXYARYLIDENEGLYCINATES

Lian Ee Khoo

National Institute of Education, School of Science
Nanyang Technological University,
469 Bukit Timah Road, Singapore 259756 SINGAPORE
E-mail: khoole@nievax.nie.ac.sg

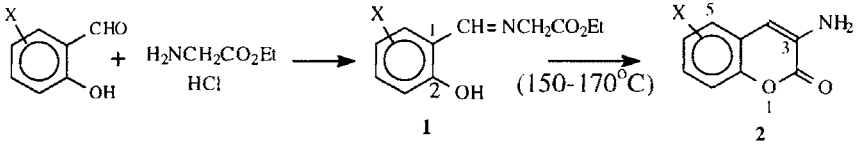
ABSTRACT

3-Aminocoumarin and its derivatives are prepared by a thermal (150-170°C) conversion reaction on the corresponding ethyl N-2-hydroxyarylidene-glycinates,[2-$HOC_6H_3(X)CH{=}NCH_2CO_2C_2H_5$; X = H, 5-Br, 5-OH, 5-$NO_2$, 3-OMe, 4-OMe, and 5,6-benzo], which are synthesized by condensing ethyl glycinate hydrochloride with substituted salicylaldehyde.

A claim[1] that 3-aminocoumarin can be prepared directly from salicylaldehyde and glycine has not been confirmed.[2] Thus, the amine is usually obtained by acid catalysed hydrolysis of the N-acetyl derivative which may be prepared by heating a mixture of N-acetylglycine, salicylaldehyde, and pyridine.[3,4] It has also been reported[5] that 3-aminocoumarin can be prepared by heating the magnesium chelates of salicylaldehyde with ethyl glycinate. However, these methods are either acid or base catalysed reactions and are not suitable

for preparing substituted 3-aminocoumarin which requires a starting material which is sensitive to basic or acidic reagent.

As a continuation to our studies on proton-transfer process of Mannich bases[6] and the complexation of organotin compounds[7] with zwitterionic Schiff bases, we recently had occasion to seek a simple method for the preparation of substituted 3-aminocoumarin. We now report that derivatives of 3-aminocoumarin can be synthesized by employing a thermal conversion reaction on substituted ethyl N-2-hydroxyarylideneglycinates, **1**, which were prepared by condensing ethyl glycinate hydrochloride with the appropriate salicylaldehye (Scheme 1).



1a X = H
1b X = 5-Br
1c X = 5-OH
1d X = 5-NO_2
1e X = 3-OMe
1f X = 4-OMe
1g X = 5,6-benzo

2a X = H
2b X = 6-Br
2c X = 6-OH
2d X = 6-NO_2
2e X = 8-OMe
2f X = 7-OMe
2g X = 5,6-benzo

Scheme 1

Accordingly, ethyl N-2-hydroxyarylideneglycinates, (**1a – 1g**), were obtained in good yields when ethyl glycinate hydrochloride was condensed with the appropriate substituted salicylaldehyde. Subsequent thermal decomposition at 150-170°C on the derivatives of **1** afforded the corresponding 3-amino-coumarins, (**2a – 2g**), [Scheme 1]. These compounds, **1** and **2**, have been characterised and their analytical and spectral data are shown in Tables 1 and 2 respectively.

Table 1. The physical properties and spectral data of ethyl N-2-hydroxyarylideneglycinates, **1a - 1g**.

Product Yield (%)	mp (°C) [lit. mp]	CHN analyses found (calculated) C H N	IR C=O; C=N; OH; (KBr, cm^{-1})	^{1}H NMR CH=NCH$_2$CO$_2$CH$_2$CH$_3$ *s(br)*	*s*	*s*	*q*	*t*	Ar *m*	other protons (δ ppm)
1a* (80)	37-39 [39][8]	63.08; 6.22; 6.36 (63.74);(6.34);(6.86)	1740;1615	12.9	8.4;	4.3	4.2;	1.3	6.7-7.5	-
1b (65)	95-96	46.19; 4.11; 5.12 (46.17);(4.22);(4.90)	1725;1625	12.5	8.6;	4.4	4.6;	1.3	6.8-7.6	-
1c (62)	144-146	58.92; 5.82; 6.53 (59.19); (5.88); (6.28)	1725;1635	12.2	8.5;	4.5	4.2;	1.2	6.8-7.6;	3.4 (δOH)
1d (93)	136-138	52.35; 4.65; 11.41 (52.38);(4.80);(11.11)	1740;1630	13.0	8.5;	4.5	4.3;	1.3	8.2-8.4	-
1e (70)	44 - 45	60.79; 6.26; 6.04 (60.75);(6.37);(5.90)	1730;1625	13.5	8.4;	4.4	4.2;	1.3	6.8-7.1	3.9 (δOCH$_3$)
1f (65)	76-78	60.24; 6.35; 6.18 (60.75);(6.37);(5.90)	1742;1618	10.2	8.2;	4.3	4.3;	1.3	7.1-8.2	3.9 (δ OCH$_3$)
1g* (55)	100-102 [103][8]	69.89; 5.73; 5.64 (70.02);(5.88);(5.44)	1755;1635	12.0	9.3;	4.7	4.5;	1.4	7.3-8.4	-

* Also characterised by comparison with reported melting point. At room temperature, **1a** slowly decomposes to **2a.**

s=singlet; *t*=triplet; *q*=quartet; *m*=multiplet; *(br)*=broad

Table 2. The physical properties and spectral data of derivatives of 3-aminocoumarins, **2a– 2g**.

Product Yield (%)	mp (°C) [lit. mp]	CHN-analyses found (calculated) C H N	IR C=O	IR NH_2	^{1}H NMR 4-H *s*	^{1}H NMR NH_2 *s (br)*	^{1}H NMR Ar *m*	^{1}H NMR other protons (δ ppm)
2a* (80)	135-137 [136][5]	66.95; 4.30; 8.75 (67.07);(4.38):(8.69)	1700	3300;3410	6.8	4.4	7.1-7.3	-
2b (60)	196-198	45.19; 2.51; 6.06 (45.02);(2.52);(5.84)	1700	3340;3420	6.6	4.4	7.1-7.4	-
2c (50)	214-216	60.34; 3.78; 7.64 (61.02);(3.98);(7.91)	1680	3360;3480	6.8	5.5	6.7-7.2	9.4 (δOH)
2d* (45)	201-202 [209][9]	52.04; 2.70;13.32 (52.43);(2.93);(13.59)	1715	3400;3480	6.7	4.6	7.2-8.3	-
2e (65)	124 - 126	63.11; 4.97; 7.13 (62.82);(4.75);(7.33)	1705	3380;3460	6.7	4.4	6.9-7.3	3.9 (δ OCH_3)
2f (65)	140-141	62.69; 4.99; 7.33 (62.82);(4.75);(7.33)	1706	3419;3324	7.1	3.9	6.8-7.3	3.8 (δ OCH_3)
2g (65)	156-158	73.50; 4.07; 6.55 (73.92) (4.03)(6.63)	1690	3330;3440	7.5	4.4	7.3-8.3	-

* Also characterised by comparison of reported melting point.
s=singlet; *m*=multiplet; *(br)*=broad

EXPERIMENTAL:

All the melting points determined on a Griffin melting point apparatus are uncorrected. Elemental CHN-analyses were performed in-house on a LECO CHNS-932 microanalyser. The proton NMR spectra (20 ~30 scans) were recorded on a JEOL FX90 MHz spectrometer at a temperature of 24°C. Depending on the solubility of the sample, **1** or **2**, $CDCl_3$ and/or DMSO-d_6 with TMS as the internal standard were used. The IR spectra for derivatives of **1** and **2**, prepared as KBr discs on NaCl windows, were measured on a Perkin-Elmer Model 1725 FT-IR spectrometer in the 4000 – 400 cm^{-1} frequency range. The IR spectrum was acquired after two to five scans.

ETHYL N-2-HYDROXYARYLIDENEGLYCINATES, (**1a** – **1g**).

To a stirred, cooled solution of ethyl glycinate hydrochloride (28g, 0.2moles) in diethyl ether (400mL) was bubbled in gaseous ammonia for 1 hr. After filtering off the ammonium chloride, the filtrate was allowed to warm to room temperature and the excess ammonia was driven off by bubbling nitrogen into the filtrate. The appropriate substituted salicylaldehyde (0.2 moles) in 50mL of diethyl ether was gradually added to the ethyl glycinate solution (200mL). The reaction mixture after refluxing for1 hour was cooled and then concentrated to *ca* 100mL before adding to it 100mL of petroleum ether (60-80°C). The mixture was allowed to cool in the freezer overnight.
The solid products were filtered and after recrystallisation using petroleum ether: diethyl ether (1:1), were identified to be ethyl N-2-hydroxyarylidene-glycinates, (**1a** - **1g**). The relevant spectroscopic data and CHN-analyses results of **1a** – **1g** are recorded in Table 1.

DERIVATIVES OF 3-AMINOCOUMARINS, (**2a** – **2g**).

A 25mL round bottom flask containing ethyl N-2-hydroxyarylideneglycinates