A CONVENIENT SYNTHESIS OF 3-ARYL COUMARINS

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Abstract - A new, convenient, one-step synthesis of 3-aryl coumarins from 2-fluorobenzaldehyde and aryl acetic acids is reported.

Since coumarins occur widely in plant sources,[2] there exists considerable interest in synthetic approaches to this heterocylic system. Several general and direct synthetic routes have been extensively studied.[3,4] The more important methods for coumarin synthesis include the Pechmann reaction[5] between a phenol and a ß-keto ester, the Knoevenagel reaction[6] and Perkin reactions[7] between an o-hydroxybenzaldehyde and an active methylene compound. All of these major methods presumably involve incorporation of a phenolic oxygen as the ring-oxygen in the coumarin product since they formally involve ring closure of 2-hydroxycinnamic acids or related intermediates. We have successfully used a modified Perkin condensation to synthesize a large number of α-(2-thienyl)-4-substituted cinnamic acids.[8-11] However, it was found, in connection with another study, that during the attempted preparation of α-(2-thienyl)-2-fluorocinnamic acid from the reaction of o-fluorobenzaldehyde and 2-thiophene acetic acid in the presence of triethylamine in acetic anhydride that 3-(2-thienyl)coumarin (1) is formed. That the reaction product was the coumarin 1 was demonstrated by its ms data, ^{13}C, ^{17}O and ^{1}H nmr data, ir data, elemental analysis and the melting point of the compound was in agreement with the literature value.[12] The ^{17}O nmr spectroscopic data with signals at 348 and 219 ppm were particularly useful in the characterization of 1 as a coumarin.[13] In expanding upon this discovery, it has been found that the sequence outlined in Scheme I is general for aryl acetic acids. Table I contains a listing of the 3-aryl coumarins which have been prepared by this method.

Scheme I

Table I. 3-Aryl Coumarins

Compound No	3-Substituent
1	2-thienyl
2	3-thienyl
3	phenyl
4	4-chlorophenyl
5	4-methylphenyl

We assume that this reaction proceeds through substituted 2-fluorocinnamic acids. The coumarins can conceivably be formed from the substituted 2-fluorocinnamic acid by an elimination/addition mechanism (benzyne) or by a direct nucleophilic displacement reaction involving the carboxylate ion. While we have not yet carried out detailed mechanistic studies, we note that when 2-bromobenzaldehyde and 2-thiophene acetic were allowed to react, a mixture of the coumarin **1** and α-(2-thienyl)-2-bromocinnamic acid was formed. The expected acrylic acid was the major product and the coumarin 1 was formed in low yield from this reaction. It is well known[14] that fluoride is displaced more rapidly than bromide in nucleophilic displacement reactions whereas bromoaromatic compounds more rapidly form benzynes. Consequently, the observation for the reaction with 2-bromobenzaldehyde is consistent with a nucleophilic displacement mechanism.

This approach should be general and applicable to the synthesis of a number of heterocyclic systems. The scope of the reaction is under investigation.

EXPERIMENTAL

All melting points were recorded on a Thomas-Hoover Unimelt apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlab, Atlanta, Georgia. The nmr spectra were recorded in deuteriochloroform, unless otherwise indicated, with Varian VXR 400, JEOL GX-270 or Varian EM 360L spectrophotometers.

General Procedure for 3-Aryl Coumarins. A mixture of o-fluorobenzaldehyde (1 mmole), aryl acetic acid (1 mmole), 3.2 ml of acetic anhydride and 1.6 ml of distilled triethylamine was refluxed for 8 h. The reaction mixture was allowed to cool and was poured into water and was extracted with diethyl ether. The organic phase was washed with water, 5% aqueous sodium hydroxide, and again with water until neutral pH was obtained. The organic layer was separated and dried over sodium sulfate. Removal of the ether under reduced pressure gave the 3-aryl coumarin. Recrystallization was from ethanol which gave crystalline compounds as summarized below.

1: mp 167-168°C; lit.[12] mp 167-8°C; yield 47% ms:M^+, 228. Anal. Calcd. for $C_{13}H_8O_2S$: C, 68.40; H, 3.53. Found: C, 68.42; H, 3.61. ^{17}O nmr (CH_3CN) δ 348 (C=O), 219 (-O-); ^{13}C nmr δ 158.9, 152.4, 135.8, 135.1, 130.9, 127.5, 127.4, 127.3, 126.9, 124.4, 121.7, 119.2, 116.1. ^1H nmr δ 8.01 (1H, s), 7.81 (1H, q), 7.54 (1H, q), 7.50 (1H, q), 7.42 (1H, q), 7.36 (1H, d), 7.30 (1H, m), 7.13 (1H, q).

2: mp 174-175°C; yield 36%, Anal. Calcd. for $C_{13}H_8O_2S$: C, 68.40; H, 3.53. Found: C, 68.37; H, 3.57. ^{17}O nmr (CH_3CN) δ 348 (C=O); 219 (-O-); ^{13}C nmr δ 159.3, 152.4, 136.6, 134.0, 130.6, 127.3, 125.8, 125.5, 125.1, 124.0, 122.3, 119.1, 115.8. ^1H nmr δ 8.1 (1H, s), 7.88 (1H, s) 7.2-7.6 (6H, m).

3: mp 139-140°C; lit mp[12] 139-140°C, yield 35%, ^{17}O nmr (CH_3CN) δ 348 (C=O), 218 (-O-); ^{13}C nmr δ 159.9, 153.2, 139.3, 134.4, 130.9, 128.4, 128.2, 128.0, 127.5, 124.1, 119.4, 116.0. ^1H nmr

δ ^{1}H nmr δ, 7.77 (1H, s), 7.68 (2H, d), 7.2-7.5 (7H, m).

4: mp 184-185°C; yield 27%, Anal. Calcd. for $C_{15}H_9ClO_2$: C, 70.19; H, 3.53. Found: C, 70.13; H, 3.58. ^{13}C nmr δ, 159.7, 153.2, 139.3, 134.6, 132.8, 131.2, 129.4, 128.3, 127.6, 124.2, 119.2, 116.3. ^{1}H nmr δ, 7.8 (1H, s), 7.65 (2H, d), 7.54 (3H, m), 7.3-7.43 (3H, m).

5: mp 157-158°C; yield 30%, Anal. Calcd. for $C_{16}H_{12}O_2$: C, 81.33; H, 5.12. Found: C, 81.27; H, 5.17. ^{17}O nmr (CH_3CN) δ, 353 (C=O), 221 (-O-); ^{13}C nmr δ, 160.0, 153.1, 138.6, 138.5, 131.6, 130.7, 128.8, 128.1, 127.4, 124.0, 119.5, 116.1, 21.0. ^{1}H nmr δ, 7.8 (1H, s), 7.6 (2H, d), 7.5 (2H, d), 7.2-7.4 (4H, m).

α-(2-Thienyl)-2-bromocinnamic Acid.

A mixture of 2-bromobenzaldehyde (0.1 mole), 2-thiophene acetic acid (0.1 mole), 16 ml of distilled triethylamine and 32 ml of acetic anhydride was refluxed for 12 h. The mixture was poured into ca. 1000 ml of water and made alkaline with potassium hydroxide followed by being boiled with charcoal for ca. 1 h., the charcoal was removed by filtration. The filtrate was cooled to approximately 5°C and was acidified with concentrated hydrochloric acid to approximately pH 4 and a brown sticky precipitate was obtained. The solid was filtered and recrystallized from cyclohexane which gave a pale yellow crystalline compound 13.5 g, (45%) mp 107-108°C. Anal. Calcd. for $C_{13}H_9BrO_2S$: C, 50.50; H, 2.93. Found: C, 50.41; H, 2.96. The acidic filtrate was diluted with water and another solid was obtained. Recrystallization from ethanol gave a yellow crystalline compound 2.3 g (10%) mp 167-168°C which had physical properties identical with those of **1**.

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