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Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 11 Jul 2007.

To cite this article: Matthew C. Davis (2007) Improvements in the Synthesis of a Coumaromethacrylate Dye, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 37:14, 2383-2389, DOI: 10.1080/00397910701410996

To link to this article: http://dx.doi.org/10.1080/00397910701410996

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Synthetic Communications®, 37: 2383–2389, 2007

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910701410996

Improvements in the Synthesis of a Coumaromethacrylate Dye

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Abstract: A new method to prepare a coumaromethacrylate dye has been devised. The older three-step route was shortened to a one-pot, solvent-free step.

Keywords: coumarin, methacrylate, one pot, solvent-free

A new research initiative required a steady supply of the coumaromethacrylate dye (**4**) that was first prepared here in the early 1990s.[1,2] The original synthesis was devised and carried out by Dr. Ronald A. Henry (Scheme 1). After carrying out the three-step preparation as described, there appeared to be opportunities for improvement.

Since 4-diethylamino-2-hydroxybenzaldehyde (**1**) continues to be commercially available, it remained the starting material. Recent research in solvent-free reactions showed that the 3-methoxycarbonylcoumarin (**2**) might be made as shown in Scheme 2.[3,4] Mixing **1**, dimethyl malonate, and piperidine gave a sticky mixture that could not be stirred efficiently. The formation of **2** was also slow at room temperature. However, running the reaction at 80°C gave a mixture that could be magnetically stirred. Using 0.3 molar equivalents of piperidine, the reaction was typically complete in 1 to 2 h. No chromatography was necessary with this solvent-free

Received in the USA December 8, 2006
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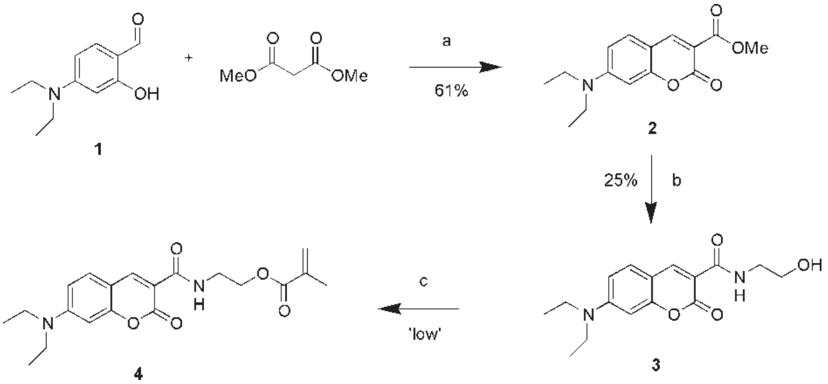

Scheme 1. Original method to prepare the coumaromethacrylate monomer. Reagents and conditions: a) MeOH, piperidine, rt; b) $H_2NCH_2CH_2OH$, PhH, reflux; c) DCC, DMAP, methacrylic acid, CH_2Cl_2.

procedure. The product was indeed a solid and was recrystallizable from methyl *tert*-butyl ether, providing **2** in 70% yield.

The previously obtained low yield of ethanolamide (**3**) by reaction of **2** with ethanolamine in refluxing benzene was confirmed. Complete consumption of the ester could not be achieved without the concomitant increase in polar impurity. A second molecule of ethanolamine may have been condensing upon **3** and opening the coumarin ring. After recrystallization from toluene, the product appeared to be pure **3** by nuclear magnetic resonance (NMR) spectroscopy, but its melting point of 115°C was noticeably lower than 126°C, reported by Henry. Most likely, a small amount of ethanolamine was contaminating the product, which is removed by the polar solvent system. Recrystallizing crude **3** from a mixture of water and ethanol raised the melting point sufficiently, although the product became a hemihydrate.

It was a surprise to find that reaction between **2** and ethanolamine without solvent gave **3** in good yield without the polar impurity seen when the reaction

$$\begin{tikzcd} 1 \arrow[r, "a", "70\%"'] \arrow[dr, "a{,}b"', "65\%"] & 2 \arrow[d, "b"] \\ 4 & 3 \arrow[l, "c"', "62\%"] \end{tikzcd}$$

Scheme 2. Reagents and conditions: a) dimethyl malonate, piperidine, 80°C; b) H_2 NCH_2CH_2OH, 80°C; c) methacrylic anhydride, DMAP, THF.

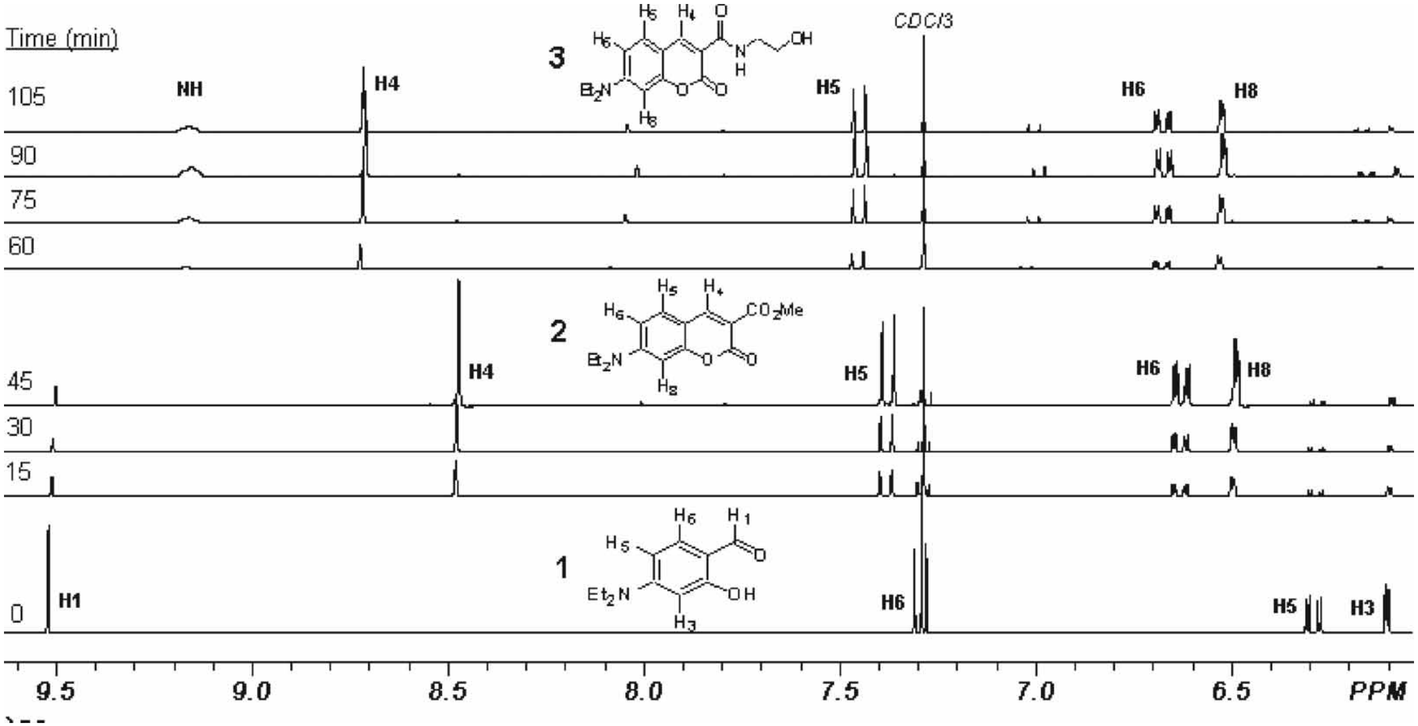

Figure 1. Proton NMR progress in the one-pot conversion of **1** into **3** as described in the Experimental section. For clarity, the region between 9.6 and 6 ppm is shown. The reaction was sampled at 15-min intervals by dissolving an aliquot in $CDCl_3$. At 1 min, piperidine was added to the mixture. At 46 min, ethanolamine was added to the reaction.

was conducted in benzene. These reaction conditions were not studied further since the prospect of transforming **1** directly into **3** as a one-pot procedure appeared (Scheme 2). To this end, a 140-mmol- scale reaction was monitored by proton NMR. After 1 h, the formation of **2** peaked, and ethanolamine was added. After another hour of heating, all **2** was consumed and formation of **3** was complete (Figure 1). The recrystallization solvent (water/ethanol) was added to the reaction mixture while hot and **3** precipitated shortly thereafter. The overall yield of the one-pot procedure to make **3** was 65% and required no chromatography.

The methacrylate ester (**4**) was previously made using the coupling reagent dicyclohexylcarbodiimide and methacrylic acid. This procedure resulted in residual *N*,*N*'-dicyclohexylurea and **3**, contaminating the product and necessitating silica-gel chromatography for purification. Instead, the esterification could be performed with fresh methacryloyl chloride in methylene chloride in the presence of 4-dimethylaminopyridine base. However, there was a close running impurity by thin-layer chromatography (TLC) with similar proton NMR as the product. No attempts were made to isolate and identify the by-product. Following the example set by Vensteenkiste et al.,[5] reaction of **3** with a slight excess of methacrylic anhydride in tetrahydrofuran in the presence of 4-dimethylaminopyridine eliminated the impurity. Simply pouring the reaction mixture into water gave **4** in high yield. The product could be recrystallized from ethanol in analytically pure form with a yield of 62%.

In conclusion, a new process for the preparation of the coumaromethacrylate **4** has been developed. A solvent-free, one-pot reaction was found to rapidly furnish the coumaroethanolamide **3** in good yield. Methacrylation of the ethanolamide (**3**) was achieved with methacrylic anhydride. No chromatography was necessary at any stage of the synthesis. The overall yield of the two-step process was 40%.

EXPERIMENTAL

Melting points were collected on an electrothermal capillary melting-point apparatus and are not corrected. All NMR data were collected on a Bruker Avance II 300-MHz spectrometer (^{1}H at 300 MHz, ^{13}C at 75 MHz). NMR data (FIDs) were processed using NUTS software from Acorn NMR (Livermore, CA), and spectra are referenced to tetramethylsilane. The following reagents were purchased from Sigma-Aldrich (Milwaukee) and used as received: methacrylic anhydride 94% (inhibited with 2000 ppm topanol A), 4-diethylamino-2-hydroxybenzaldehyde 98%, 4-methoxyphenol ReagentPlus® 99%, dimethyl malonate 98%, ethanolamine ReagentPlus® >99%, 4-(dimethylamino)pyridine (DMAP) 99%, piperidine ReagentPlus® 99%. Elemental analyses were performed by Atlantic Microlab, Inc. (Norcross, GA).

3-Methoxycarbonyl-7-(diethylamino)coumarin (2)

A 500-mL, round-bottomed flask equipped with magnetic stirbar was charged with 25 g of 4-diethylamino-2-hydroxybenzaldehyde (**1**, 0.13 mol) and 18.7 g of dimethyl malonate (0.14 mol, 1.1 equiv). The mixture was set to stir in a 70°C oil bath. After a few minutes, all the solids had dissolved, and 3.3 g of piperidine in one portion (0.04 mol, 0.3 equiv) were added. The mixture immediately became yellow-orange in color, and MeOH was seen collecting on the headspace of the flask. Analysis by ^{1}H NMR showed complete consumption of the aldehyde in 2.5 h. The oil bath was removed, and after cooling to rt, the mixture was partitioned between 50 mL of H_2O and 200 mL of $CHCl_3$. While stirring, 2.2 mL of glacial HOAc (0.04 mol) were added to neutralize the piperidine. The organic layer was separated and washed again with 50 mL of H_2O followed by 100 mL of brine. The organic layer was dried for 30 min over 10 g of anhydrous $MgSO_4$ and filtered. The organic layer was treated with 2 g Darco® G-60 for 30 min and filtered through a pad of diatomaceous earth on a coarse glass frit. The solvent was rotary evaporated, leaving an orange-colored oil. After storage under vacuum, the oil solidified into a yellow solid (33.9 g, 96%). The crude was recrystallized from methyl *tert*-butyl ether to give 25.1 g of the title compound **2** as a bright yellow, crystalline powder (70%). Mp 70–72°C. δ_H ($CDCl_3$): 8.48 (s, 1H), 7.38 (d, $J = 9.0$ Hz, 1H), 6.63 (dd, $J = 9.1$ and 2.4 Hz, 1H), 6.48 (d, $J = 2.6$ Hz, 1H), 3.93 (s, 3H), 3.47 (q, $J = 7.2$ Hz, 4H), 1.25 (t, $J = 7.2$ Hz, 6H); δ_C ($CDCl_3$): 165.11, 158.67, 158.47, 153.11, 149.78, 131.27, 109.76, 108.59, 107.84, 96.79, 52.45, 45.26, 12.55. Elemental analysis calculated for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.57; H, 6.22; N, 5.14.

3-*N*-(2-Hydroxyethyl)carboxamido-7-(diethylamino)coumarin hemi-hydrate (3)

A 250-mL, round-bottomed flask equipped with magnetic stirbar was charged with 25 g of 4-diethylaminosalicylaldehyde (**1**, 0.129 mol) and 20.4 g of dimethyl malonate (17.7 mL, 0.16 mol, 1.2 equiv). The mixture was stirred in an 80°C oil bath, and all the solids dissolved. In one portion, 3.83 mL of piperidine (3.29 g, 0.039 mol, 0.3 equiv) were added to the mixture. The color immediately became yellow-orange, and methanol was seen to condense in the headspace of the flask. The reaction was monitored by ^{1}H NMR of aliquots from the reaction dissolved in $CDCl_3$. After 1 h, all the aldehyde was consumed, and, in one portion, 11.57 g ethanolamine (11.34 mL, 0.19 mol, 1.47 equiv) were added to the reaction. Again, methanol is seen to condense in the headspace of the flask. The reaction was monitored as done previously. After 1 h, a mixture of 60 mL of H_2O and 40 mL of EtOH was added to the mixture. The reaction mixture dissolved in the solvent, and then the oil bath was removed. After 10 min, a yellow crystalline solid precipitated, and stirring stopped. Another 40 mL of the solvent mixture was added, and the solid was broken up. The product was collected on a coarse-porosity glass frit. It was not possible to rinse the solid thoroughly on the frit, so the crude was recrystallized from a mixture of 60 mL of H_2O and 40 mL of EtOH. After filtering on a coarse-porosity glass frit, the small, bright yellow flakes were dried overnight (10 Torr, 60°C) to remove residual H_2O. The mass of product was 26.3 g, representing a 65% yield (calculated on anhydrous product). Mp 121–123°C (lit.[1] 126–127 C). δ_H ($CDCl_3$): 9.14 (t, $J = 6$ Hz, 1H), 8.68 (s, 1H), 7.42 (d, $J = 9.4$ Hz, 1H), 6.65 (dd, $J = 9.0$ and 2.5 Hz, 1H), 6.49 (d, $J = 2.4$ Hz, 1H), 3.83 (t, $J = 5.1$ Hz, 2H), 3.62 (q, $J = 4.9$ Hz, 2H), 3.46 (q, $J = 7.1$ Hz, 4H), 2.03 (bs, 1H), 1.25 (t, $J = 7.1$ Hz, 6H); δ_C ($CDCl_3$): 165.07, 162.94, 157.95, 152.96, 148.53, 131.48, 110.29, 109.96, 108.58, 96.80, 63.15, 45.33, 43.29, 12.65. Elemental analysis calculated for $C_{16}H_{20}N_2O_4{\cdot}1/2\ H_2O$: C, 61.34; H, 6.71; N, 8.94. Found: C, 61.64; H, 6.70; N, 8.94.

3-*N*-(2-Methacryloxyethyl)carboxamido-7-(diethylamino)coumarin (4)

The product is light sensitive; all operations were performed under cloth or foil covers to avoid exposure to light as far as possible.

A two-necked, 500-mL, round-bottomed flask equipped with magnetic stirbar was charged with 26.3 g of compound **3** (0.084 mol), 21.47 g of DMAP (0.176 mol, 2 equiv), 20 mg of 4-methoxyphenol, and 250 mL of THF (anhydrous, inhibitor free). An N_2 bubbler was equipped to one neck, and a 10-mL pressure-equalizing addition funnel was equipped to the second neck. The mixture was stirred in a warm H_2O bath until complete dissolution. The mixture was cooled in an ice bath, and the addition funnel was charged with 19.55 mL of methacrylic anhydride (20.33 g, 0.132 mol, 1.5 equiv). The addition was made dropwise over 5 min. After 30 min, TLC showed complete consumption of **3**. The reaction mixture was poured into 750 mL of vigorously stirred, cold H_2O. A pale yellow solid precipitated, and after 20 min, the solid was collected on a coarse-porosity glass frit. The solid was broken up and rinsed on the frit twice with 150-mL portions of cold H_2O. The solid was air dried under vacuum on the frit for 2 h to obtain 40.5 g of crude product. The crude contained some H_2O but was otherwise more than 95% by ^1H NMR. The yellow solid was recrystallized from 400 mL of EtOH to give 19.9 g of the title compound **4** as a pale yellow powder (62%). Mp 138–140°C (lit.[1] 143–144°C). δ_H ($CDCl_3$): 9.08 (t, $J = 4.9$ Hz, 1H), 8.71 (s, 1H), 7.45 (d, $J = 9.2$ Hz, 1H), 6.65 (dd, $J = 8.9$ and 2.6 Hz, 1H), 6.49 (d, $J = 2.4$ Hz, 1H), 6.19 (pent, $J = 1.2$ Hz, 1H), 5.59 (pent, $J = 1.6$ Hz, 1H), 4.32 (t, $J = 5.6$ Hz, 2H), 3.77 (q, $J = 5.8$ Hz, 2H), 3.46 (q, $J = 7.2$ Hz, 4H), 1.98 (m, $J \approx 1.2$ Hz, 3H), 1.24 (t, $J = 7.2$ Hz, 6H); δ_C ($CDCl_3$): 167.49, 163.62, 162.98, 157.92, 152.86, 148.44, 136.27, 131.40, 126.26, 110.25, 110.22, 108.59, 96.80, 63.60, 45.30, 38.65, 18.51, 12.62. Elemental analysis calculated for $C_{20}H_{24}N_2O_5$: C, 64.5; H, 6.50; N, 7.52. Found: C, 64.29; H, 6.51; N, 7.46.

ACKNOWLEDGMENTS

The generous financial support by the Army Research Laboratory is gratefully acknowledged. Thanks to Dr. Geoffrey A. Lindsay (NAWCWD) for advice and encouragement throughout the course of this research. Thanks to Andrew P. Chafin (NAWCWD) for suggestions and corrections during the preparation of this manuscript. Thanks to Chrissy Everett (NAWCWD) for assistance in purchasing reagents and obtaining combustion analysis.

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