Coumarins represent an important group of natural products and a common part of various drugs and fluororescent dyestuffs. Herein, we present the synthesis of a coumarin that can serve as a key starting material in the design and synthesis of bioorthogonally applicable fluorogenic dyes. The synthesis of 7-azido-3-formylcoumarin started from 7-diallylaminocoumarin. This allyl protected aminocoumarin is otherwise hard to obtain by conventional methods but was conveniently accessed in good yields by a sequential, Wittig-reaction–UV isomerization process. This sequential approach was studied in more details and applied for the synthesis of a series of substituted coumarins even in one-pot.

**INTRODUCTION**

The coumarin (2H-chromen-2-one, benzopyran) framework is an important building block of naturally occurring compounds [1]. Its derivatives find broad range of applications, and its core structure can be recognized in many antibiotics, anticoagulants (e.g., warfarin) [2], antipsoriatic and anti-inflammatory agents, and anti-HIV drugs, for example, as inhibitors of HIV’s reverse transcriptase [3]. Moreover, the beneficial photophysical properties of coumarins raise this framework to one of the most frequently used building blocks in fluorescent dyes [4]. Over the years, we and others reported on the development of fluorogenic scaffolds based on several fluorescent cores, including coumarin [5]. The fluorescence of fluorogenic coumarins can be quenched by several means, for example, by photoinduced electron transfer [5a], twisted intramolecular charge transfer [5b], energy transfer [5c], or by moieties that suppress fluorescence by opening non-radiative relaxation pathways by biasing vibrational release of energy [5d]. Azide derived fluorogenic frames are of special importance as they can be applied in bioorthogonal labeling schemes due to the two-in-one feature of this small, biologically inert, yet highly energetic function being a bioorthogonal handle and a quencher moiety at the same time [6]. The excitation and emission wavelengths of coumarin based dyes can be easily shifted towards the biologically more advantageous red regime by extension of the conjugated system as part of polymethine chains. For this, 3-formylcoumarin scaffolds serve as a convenient precursor that can be condensed with species harboring carbon-nucleophiles to render polymethine frames (Fig. 1) [7]. Substituents on the coumarin frame substantially affect the overall spectroscopic features, and this is especially profound at the seventh position. Our ongoing project aims at designing and synthesizing azide quenched, bioorthogonally applicable fluorogenic probes, and we wanted to study 7-azidocoumarin based fluorogenic species. As discussed earlier, the azide group can act as a quencher of fluorescence and a bioorthogonal functional group at the same time. Previously, we have reported on a series of azide-quenched, bioorthogonally applicable fluorogenic species [5d,7a], however, until now, we were not able to access 7-azidocoumarin-based dye precursors that could have served as starting materials for such fluorogenic species. Introduction of the azide group is possible at different stages of synthetic routes mostly by a diazotization/azide substitution sequence of corresponding amines. However, the harsh conditions of diazotization often limit the possible functional groups. Direct condensation of 7-azido-3-formylcoumarin as a key precursor with carbon-nucleophiles would greatly simplify access to fluorogenic species, not to mention that it could also offer library based screen for fluorogenic species by modular approach. Thus, we aimed to synthesize 7-azido-3-formylcoumarin. There are several means for the formation of coumarin scaffolds, such as the Perkin reaction [8]. Besides Perkin condensation, other named reactions such as the Knoevenagel condensation [9] or the von Pechmann reaction [10] are also well known for
the synthesis of coumarins. Alternative means to build the coumarin frame are also reported, including, for example, condensation of salicylaldehydes with acetic acid derivatives [11], the Baylis-Hillman reaction [12], or oxidative cyclization of Z-cinnamic acids [13]. Pd-catalyzed reactions were also applied in various ways, for example, Heck-type coupling [14], ring closing of aryl alkyanoate [15], or acrylate [16] derivatives through C–H activation. A very recent paper reports on the synthesis of coumarins by mimicking the natural biosynthetic pathway where the coumarin scaffold is obtained from aryl-E-cinnamates under photoirradiation in the presence of riboflavin as photocatalyst [17]. We sought for routes involving suitably protected aminocoumarins as precursors for further transformations in order to access the target compound. While these synthetic routines are well credited, each has certain limitations. For example, routes starting from phenols or salicylaldehydes require electron-rich substituents. Furthermore, these methods are not universal in terms of substituents to be installed at different positions of the coumarin scaffold, not to mention that the applied – and sometimes very harsh – conditions have limited functional group tolerance. Although strategies exist for the introduction of substituents onto the coumarin core, the substrate scope of these routines usually has narrow range. Unfortunately, the previously listed reactions either did not work or gave only very poor yields when attempted to reach our aims.

We needed a synthetic route that uses mild conditions therefore investigated a sequential Wittig reaction followed by photoisomerization starting from salicylaldehydes in order to access coumarin derivatives as starting materials for our further aims. o-Hydroxy-Z-cinnamates are known to undergo spontaneous lactonization reaction giving rise to coumarins [18]. During the Wittig reaction, however, both Z and E isomers are formed, and mechanistic studies showed that the isomeric ratio depends both on the type of the ylide and the transition state of the formed intermediate [19]. E-cinnamates are not capable of ring closure via lactone formation but can be isomerized to their respective Z-forms either thermally or upon UV irradiation in an equilibrium process. Spontaneous lactonization shifts the equilibrium and, as a consequence, irrespective of the original E/Z ratio, all cinnamates are converted into coumarins. Similar approaches exist in the literature, however, they either resulted in low yields or were not exploited for the synthesis of protected coumarins [20].

RESULTS AND DISCUSSION

We wished to study the proposed reaction sequence in more details before devising a route to access the target compound. We chose 4-methoxy-2-hydroxy-benzaldehyde (1d) and two easily accessible ylides, that is, methyl(triphenylphosphoranylidene)acetate and methyl 2-(triphenylphosphoranylidene)propanoate as model compounds. In both cases, the Wittig-reaction resulted in a mixture of Z/E cinnamates. The reaction mixtures were analyzed in order to assess the obtained Z/E ratios. NMR studies indicated the presence of 77% E-cinnamate in case of 2d together with 23% 7-methoxycoumarin (4d, see Data S1 for NMR spectra). Formation of the latter product supported that Z-cinnamates undergo spontaneous ring-closing lactonization to give the respective coumarin scaffold. In case of the reaction between 1d and methyl 2-(triphenylphosphoranylidene)propanoate, similar analysis indicated nearly the sole presence (i.e., >95%) of the E-cinnamate (3d, see Data S1 for NMR spectra). Following purification, the reaction products were subjected to UV irradiation, and coumarins 4d and 5d were obtained in 69% and 63% yields, respectively.
Next, we wanted to test the scope and limitations of this synthetic route without the intermediate purification step. To this end, we have chosen a set of salicylaldehydes bearing various substituents. Synthesis of coumarins were carried out in the following manner: salicylaldehydes (1a–j) were mixed with the ylids overnight in methylene chloride at room temperature. Full conversions (>95%) were reached according to thin layer chromatography (tlc) analysis. Methylene chloride was removed, and without any purification, the obtained cinnamate–coumarin mixtures were dissolved in methanol in a quartz reaction flask and irradiated with low pressure mercury lamps until full consumption of the cinnamates as indicated by t.l.c. (Scheme 1). The coumarin products were then purified by column chromatography (SiO2). With the exception of 4-iodo-2-hydroxy benzaldehyde, where iodine elimination occurred (ca. 60% of the coumarins were deiodonated by gas chromatography-mass spectrometry analysis, not listed earlier), all substrates gave moderate to excellent yields (Fig. 2). Derivatives bearing substituents only at position 7 (1d, f, g, i, and j) generally gave higher isolated yields. Sterically demanding julolidine derivative (4h and 5h) and 6,7-dimethoxy coumarin (4e and 5e) were obtained in lower yields.

Regarding the necessary irradiation time, compounds with strongly electron donating groups (4f–g) required shorter times for full conversion. Although we did not determine Z/E ratios for each cinnamate, we suspect that the time required for full conversion is strongly dependent on the ratio of the primarily obtained cinnamate isomers, thus, the coumarin formed spontaneously during the Wittig reaction. Furthermore, it was observed that in case of R2 = Me, less time was necessary than for the corresponding R2 = H products. We also were curious whether the two steps could be driven in a one-pot manner without intermediate solvent exchange. To this end, we chose 4-hydroxy salicylaldehyde (1f) and reacted with both ylides in MeOH in a quartz flask. Following full conversion, the mixture was directly exposed to UV light for 4–9 h. Following work-up, target coumarins were isolated in good and excellent yields (74% and 97% for 4f and 5f, respectively).

Following these pre-studies, we have devised a synthetic path aiming at synthesizing of 7-azido-3-formylcoumarin (11), starting from 4-diallylamino salicylaldehyde (Scheme 2). Wittig reaction and subsequent UV-mediated coumarin formation resulted 4j in good yields (attempt for the synthesis of 4j by Knoevenagel condensation resulted very poor yields). 7-Diallylaminocoumarin was then subjected to Vilsmeyer–Haack formylation to result in 7-diallylamino-3-formylcoumarin, 6, in 80% yield. Subsequent reduction of the formyl group was effected by treatment with NaBH4 to obtain 7 in 49% yield. Formation of silyl protected derivative, 8, was necessary due to the very low solubility of amine-alcohol derivative. Pd-mediated removal of the allyl protecting groups gave 9 in good yield. Diazotization of 9 and removal of the triisopropylsilyl group provided 10 in

![Scheme 1](image1.png)

**Scheme 1.** Synthesis of substituted coumarins via the Wittig–UV irradiation sequence. (i) CH2Cl2, room temperature, 16 h, (ii) MeOH, irradiation, 40–50°C, 4–40 h, 25–97%.

![Figure 2](image2.png)

**Figure 2.** Prepared coumarins with the necessary irradiation time to reach full conversion and isolated yields. *Wittig reaction was carried out in MeOH, followed by irradiation (one pot).*
85% yield. Finally, oxidation of 10 with Dess–Martin periodane gave target compound 11 in 96% yield (Scheme 2).

CONCLUSION

In conclusion, we have applied a mild synthetic route suitable for the synthesis of problematic coumarin derivatives that are hard to access by conventional methods. The functional group tolerance of the method allows access to variously substituted coumarins, including protected amines that can be useful starting materials for bioconjugatable fluorogenic coumarin dyes and halogenated scaffolds offering further derivatization steps, for example, through cross-coupling reactions. With the key precursor in hand, we plan to extend the conjugated system using a set of C-nucleophilic modules in order to screen for new, bioorthogonally applicable fluorogenic compounds with biologically relevant spectral properties and high fluorogenicity. This work is underway in our laboratory, and results will be presented in due course.

EXPERIMENTAL

Unless otherwise indicated, starting materials were obtained from commercial suppliers (Sigma-Aldrich, Fluka, Merck, Alfa Aesar, Reanal, Molar Chemicals, Romil, TCI Chemicals) and used without further purification. Analytical thin-layer chromatography (TLC) was performed on silica gel 60 F254 precoated aluminium TLC plates from Merck. ZEOprep 60 silica gel (0.060–0.200 mm) was used for column chromatography from Zeochem. Flash column chromatography was performed on a Teledyne Isco CombiFlash® Rf + automated flash chromatography apparatus using silica gel (0.025–0.040 mm) from Zeochem. Visualization of TLC samples was performed with a 254/365 nm UV. NMR spectra were recorded on a Bruker Avance 250 MHz or a Varian Inova 500 MHz spectrometer. Chemical shifts (δ) are given in parts per million (ppm) using solvent signals as the reference. Coupling constants (J) are reported in Hertz (Hz). Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of a doublet), and brs (broad singlet). High resolution mass spectrometric measurements were performed using a Q-TOF Premier mass spectrometer (Waters Corporation, Milford, MA, USA) in positive electrospray ionization mode. The UV reactor was equipped with 9 × 10 W low pressure mercury lamps surrounding the quartz flask in a cylinder with a diameter of 23 cm. The quartz flask was at around 6–7 cm from the UV lamps. The solution was stirred with magnetic stirrer, and the temperature was around 40–50°C due to the irradiation.

**Synthetic procedures.**

**Typical two-step Wittig–UV sequential procedure.** The solution of 0.75–1.50 mmol (1.0 eq.) salicylaldehyde and 1.05 eq. ylide in 20 cm³ CH₂Cl₂ were stirred overnight at room temperature (r.t.). CH₂Cl₂ were stirred overnight at room temperature (r.t.). Solvent was removed under reduced pressure, and the residue was dissolved in 15–20 cm³ MeOH and then irradiated by UV light until full conversion of the cinnamates (monitored by TLC). The solvent was stirred with magnetic stirrer, and the temperature was around 40–50°C due to the irradiation.

**One-pot synthesis of coumarins.** A solution of the salicylaldehyde (0.50 mmol, 1.00 eq.) and the appropriate ylide (0.55 mmol, 1.1 eq.) in 10 mL MeOH in a quartz flask was stirred at r.t. for until full consumption of the starting material. The reaction mixture was then subsequently irradiated with UV light until full conversion (monitored by TLC). Following evaporation of the solvent, the product was purified by column chromatography.

**Synthesis of 3-formyl-7-azidocoumarin.** 3-Formyl-7-diallylamino coumarin (6). POCl₃ (2.5 cm³) was added dropwise to N,N-dimethylformamide (3.4 cm³) at 0°C under N₂ atmosphere. After 10-min stirring, the mixture was allowed to warm to r.t., and 2 cm³ CHCl₃ was added followed by 7-diallylamino coumarin, 4j (1.07 g, 4.43 mmol) in dimethylformamide (3 cm³). The reaction mixture was stirred for 4 h at 60°C then cooled...
to r.t. The mixture was poured onto ~100 g of crushed ice, and the pH was set to ~6 using cc.NaOH solution. The mixture was extracted with CH2Cl2 (3 × 100 cm³). The combined organic layers were washed with 150 cm³ brine and dried over MgSO4. The solution was filtered, and the solvent was removed in vacuo. The crude product was purified by flash column chromatography (SiO2, hexanes/EtOAc, EtOAc: 0 → 10 v/v) to give 6 as bright orange crystals (0.96 g, 80%). m.p.: 114–117°C. δH(500 MHz; CDCl3) 7.55 (1H, s), 7.23 (1H, d, 3 J 8.7), 6.58 (1H, dd, 3 J 8.7, 4 J 2.3), 6.52 (1H, d, 4 J 2.1), 5.87–5.76 (2H, m), 5.19 (2H, d, 3 J 11.0), 5.15 (2H, d, 3 J 17.8), 4.52 (2H, s), 3.97–3.94 (4H, m), 2.97 (1H, br s). δC(126 MHz; CDCl3) 162.6, 155.7, 151.5, 139.7, 132.5, 128.7, 121.3, 116.9, 109.7, 109.2, 98.4, 61.4, 53.0. HRMS (ESI) [M + Na]+ calcd. for [C16H16NO3Na]+: 294.1105, found: 294.1104.

3-Hydroxymethyl-7-diallylaminocoumarin (8). 3-Hydroxy-7-diallylaminocoumarin (7) (249 mg, 0.92 mmol, 1.0 eq.) and imidazole (186 mg, 2.73 mmol, 3.0 eq.) were dissolved in 10 cm³ CH3Cl2. Chlorotrisopropylsilane (353 mg, 1.83 mmol, 2.0 eq.) was added slowly at 0°C, and then the reaction mixture was allowed to warm up to r.t. and stirred for 16 h. The mixture was filtered through Celite pad, and then the solvent was removed in vacuo. Product was purified by flash column chromatography (SiO2, hexanes/EtOAc, EtOAc: 0 → 10 v/v) to provide 8 as a colorless oil (367 mg, 93%). Rf = 0.47 (hexanes/EtOAc 5:1 v/v). IR (neat) v = 3056, 2935, 1768, 1601, 1562, 1261, 1126 cm⁻¹. δH(500 MHz; CDCl3) 7.71 (1H, s), 7.26 (1H, d, 3 J 8.8), 6.58 (1H, dd, 3 J 8.7, 4 J 2.3), 6.55 (1H, d, 4 J 2.0), 5.89–5.74 (2H, m), 5.22–5.10 (4H, m), 4.67 (2 H, s), 3.95 (4H, d, 3 J 4.5), 1.22–1.14 (3H, m), 1.09 and 1.08 (18H, 2 × s). δC(126 MHz; CDCl3) 161.5, 155.2, 151.1, 137.5, 132.7, 128.4, 122.4, 116.7, 109.7, 109.5, 98.5, 60.4, 53.1, 18.1, 12.1. HRMS (ESI) [M + Na]+ calcd. for [C25H37NO3SiNa]+: 450.2435, found: 450.2442.

3-((Triisopropylsilyl)oxy)methyl-7-aminocoumarin (9). 3-((Triisopropylsilyl)oxy)methyl-7-diallylaminocoumarin, 8 (200 mg, 0.47 mmol, 1.0 eq.), 1,3-dimethylbarbituric acid (438 mg, 2.81 mmol, 6.0 eq.), and Pd(PPh3)4 (14 mg, 0.012 mmol, 0.025 eq.) were dissolved in 4 cm³ tetrahydrofuran, and TBAF.3H2O (367 mg, 93%). The crude product was purified by flash column chromatography (SiO2, hexanes/EtOAc, EtOAc: 0 → 30 v/v) to result 9 as a yellowish-white powder (133 mg, 82%). m.p.: 146–151°C. Rf = 0.60 (hexanes/ EtOAc 1:1 v/v). IR (neat) v = 3478, 3370, 3244, 2943, 2866, 1682, 1599, 1402, 1251, 1132 cm⁻¹. δH(500 MHz; CDCl3) 7.72 (1H, s), 7.24 (1H, d, 3 J 8.4), 6.64 (1H, s), 6.55 (1H, d, 3 J 8.2), 4.66 (2H, s), 4.23 (2H, brs). 1H, 1.22–1.12 (3H, m), 1.09 and 1.07 (18H, 2 × s). δC(126 MHz; CDCl3) 161.4, 155.0, 150.0, 137.7, 128.9, 123.1, 112.1, 111.1, 100.8, 18.1, 12.1. HRMS (ESI) [M + Na]+ calcd. for [C19H29NO3SiNa]+: 370.1809, found: 370.1809.
then, CH₂Cl₂ (25 cm³) was added and the organic phase was washed with water (1 × 5 cm³), dried over MgSO₄, filtered, and concentrated in vacuo. Product was purified by flash column chromatography (SiO₂, hexanes/EtOAc, EtOAc%: 0 → 33 v/v) to provide 9 as an off-white powder (122 mg, 85%). R₁ = 0.50 (hexanes/EtOAc 1:1 v/v). IR (neat) ν = 3431 br, 3082, 2937, 2102, 1682, 1595, 1553, 1427, 1267, 1171 cm⁻¹. δ (1H, s), 1H, d, 2H). δ (126 MHz; CDCl₃) 187.6, 159.9, 157.0, 147.8, 145.0, 132.4, 120.5, 116.8, 115.4, 107.3. HRMS (ESI) [M + Na]⁺ calcd. for [C₁₀H₇N₃O₃Na⁺]: 240.0380, found: 240.0385.

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REFERENCES AND NOTES


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