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# Synthesis and molecular structure of 2-bromo-N-(4-(7-(diethylamino)-coumarin-3-yl)phenyl)propanamide: New coumarin-based fluorescent ATRP initiator

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ABSTRACT

The 2-bromo-N-(4-(7-(diethylamino)-coumarin-3-yl)phenyl)propanamide was synthesized and analyzed by NMR and FT-IR spectroscopies, high resolution mass-spectrometry and single crystal X-ray diffraction. The crystal structure belongs to the monoclinic system, $P2_{1/c}$ space group with a = 14.9120(7) Å, b = 11.3177(5) Å, c = 12.0106(5) Å, α = 90°, β = 94.758(2)°, γ = 90° and V = 2020.04(16) Å$^3$. Furthermore, it was shown to be an efficient fluorescent ATRP initiator in polymerizations of acrylates.


## 1. Introduction

Atom transfer radical polymerization (ATRP) is a versatile method for controlled living polymerizations [1–3], which allows polymers with controlled molecular weights and narrow dispersities to be prepared. It is catalytic process mediated by redox active transition metal complexes and initiated by different alkyl (pseudo)halides. As the initiator is incorporated in the α-chain end, various functionalized polymers can be prepared using functional initiators. Particular case are optical polymers based on different fluorescent dyes [4–11].

However, there are no examples of fluorescent coumarin-based ATRP initiators and only single example of non-fluorescent coumarin-based ATRP initiator [12].

Coumarins are heterocyclic compounds of considerable synthetic and pharmacological interest because of their biological activities [13]. At the same time they are widely used as fluorescent dyes [14] due to their large Stokes shifts, high fluorescent quantum yields, chemical stability and synthetic availability.

7-(Diethylamino)-3-(4-aminophenyl)coumarin **1** is the fluorescent dye of choice due to its usability, high quantum yield, easy synthesis and presence of highly reactive 4-aminophenyl moiety, which allows to bind it to a wide range of substrates [14,15].

Acylation of this amino-group with 2-bromopropionyl bromide allowed to obtain 2-bromo-N-(4-(7-(diethylamino)-coumarin-3-yl)phenyl)propanamide **2** as a new fluorescent ATRP initiator. Herein we describe its synthesis, characterization with NMR, FT–IR spectroscopy and high-resolution mass spectrometry, crystal structure determination and evaluation in the synthesis of fluorescent polymers via ATRP process.

## 2. Experimental

### 2.1. General

1,4-Dioxane and THF were purified by distillation over $CaH_2$, followed by passing through the column packed with molecular sieves 4 Å. Degassed solvents were stored over molecular sieves under an argon atmosphere in a refrigerator. Butyl acrylate (BA, Sigma Aldrich, ≥99%) and methyl acrylate (MA, Sigma Aldrich, 99%) were passed through a column packed with basic alumina to

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remove hydroquinone monomethyl ether immediately before use. 4-(Diethylamino)salicylaldehyde (Alfa Aesar, 99%), 4-nitro phenylacetonitrile (Alfa Aesar, 98%), piperidine (Alfa Aesar, 99%), tin(II)chloride dihydrate (Alfa Aesar, 98%), triethylamine (Sigma Aldrich, ≥99.5%), 2-bromopropionyl bromide (Alfa Aesar, 97%), copper(I) bromide (Sigma Aldrich, 98%), *N,N,N′,N″,N″*-pentamethyldiethylenetriamine (PMDETA, Sigma Aldrich, 99%) and hydrochloric acid (Alfa Aesar, 36.5–38.0%) were used as received.

NMR spectra were recorded using a Bruker AMX 300 spectrometer at 298 K. Chemical shifts are expressed in parts per million with residual solvent signals as internal reference ($^1$H, $^{13}$C NMR). IR spectra were recorded using a Thermo Fischer Nexus 6700 FTIR spectrometer in ATR mode. High-resolution mass spectra (HRMS) were measured on Waters GCT Premier CAB109 TOF detector in ESI mode.

The monomer conversion was determined by $^1$H NMR in $CDCl_3$ and the number-average molar mass ($M_n$) values and dispersities ($Đ$) of the polymer samples were obtained from size-exclusion chromatography (SEC) in THF as eluent. Prior to injection, samples were diluted to a concentration of 5 mg mL$^{-1}$ and filtered through 0.45 μm Nylon syringe filters.

The SEC analyses were conducted using a Waters 2414 refractive index detector, a mini DAWN TREOS Multi-Angle Light Scattering (MALS) detector (Wyatt Technology) equipped with a set of 2 columns (Shodex KF-802.5 and KF-804) at a flow rate of 1.0 mL min$^{-1}$ (35 °C). The column system was calibrated with narrow PSt standards, obtained from Polymer Laboratories, ranging from 580 to 164500 g mol$^{-1}$. Polystyrene calibration was applied with next Mark-Houwink-Sakurada (MHS) parameters: $K_{PSt} = 11.4 \times 10^{-5}$ dL g$^{-1}$ and $a_{PSt} = 0.716$ for polystyrene [16]; $K_{PMA} = 19.5 \times 10^{-5}$ dL g$^{-1}$ and $a_{PMA} = 0.660$ for poly(methyl acrylate) [17] and $K_{PBA} = 12.2 \times 10^{-5}$ dL g$^{-1}$ and $a_{PBA} = 0.700$ for poly(*n*-butyl acrylate) [18].

All the syntheses were carried out using standard Schlenk and high vacuum line techniques under an argon atmosphere.

### 2.2. Synthesis

*7-(Diethylamino)-3-(4-aminophenyl)coumarin* **1**: 4-(Diethylamino)salicylaldehyde (10 g, 51.75 mmol), 4-nitrophenylacetonitrile (8.4 g, 51.75 mmol) and piperidine (0.1 mL, 1 mmol) were stirred in 150 mL of EtOH at ambient temperature during 24 h. Then about 100 mL of solvent were removed by distillation under reduced pressure. An equivalent volume of concentrated HCl was added at once and the reaction mixture was refluxed during 15 min. After cooling to ambient temperature, $SnCl_2H_2O$ (50 g, 220 mmol) was added at once. The resulting mixture was refluxed for 1 h and then stirred at room temperature for 3 h. The obtained suspension was neutralized with NaOH and concentrated under reduced pressure. Remaining solid was extracted with boiling EtOAc. After concentration of the solution, precipitate of desired product appeared. Yield: 11 g (69%). Orange crystals. $^1$H NMR (300.13 MHz, $CDCl_3$, 298 K, Fig. S1): δ = 7.59 (s, 1H, 4-H, coumarin), 7.54–7.48 (m, $^3J_{H,H}$ = 8.7 Hz, 2H, 2-H, $C_4H_6$–$NH_2$), 7.27 (d, $^3J_{H,H}$ = 8.6 Hz, 1H, 5-H, coumarin), 6.74–6.69 (m, $^3J_{H,H}$ = 8.7 Hz, 2H, 3-H, $C_4H_6$–$NH_2$), 6.57 (dd, $^3J_{H,H}$ = 8.8, $^4J_{H,H}$ = 2.5 Hz, 1H, 6-H, coumarin), 6.52 (d, $^4J_{H,H}$ = 2.4 Hz, 1H, 8-H, coumarin), 4.04–3.40 (br, 2H, $NH_2$), 3.41 (q, $^3J_{H,H}$ = 7.1 Hz, 4H, $CH_2CH_3$), 1.20 (t, $^3J_{H,H}$ = 7.1 Hz, 6H, $CH_2CH_3$). $^{13}$C{$^1$H} NMR (75.47 MHz, $CDCl_3$, 298 K, Fig. S2): δ = 162.1, 155.9, 150.1, 146.3, 138.7, 129.4, 128.6, 126.0, 121.2, 114.9, 109.5, 108.9, 97.2, 44.9, 12.6. IR (Fig. S3): 1688 (C=O), 3444 ($NH_2$ asymm.), 3353 ($NH_2$ symm.) cm$^{-1}$. HRMS (ESI-TOF, Fig. S4): found − 309.1607, calculated for $C_{19}H_{21}N_2O_2$ − 309.1603.

*2-Bromo-N-(4-(7-(diethylamino)-coumarin-3-yl)phenyl)propanamide* **2**: 2-Bromopropionyl bromide (3.15 mL, 30 mmol) was added dropwise to the wigorously stirred solution of 7-(diethylamino)-3-(4-aminophenyl)coumarin (7.71 g, 25 mmol) and triethylamine (4.15 mL, 30 mmol) in 100 mL of dry THF at 0 °C (ice bath) and obtained mixture was stirred 3 h at ambient temperature. Obtained suspension was concentrated under reduced pressure and remaining solid was triturated with 200 mL of deionized water. Precipitate was collected by filtration, washed by aqueous ethanol and recrystallized from ethanol. Yield: 9.6 g (86%). Orange crystals. $^1$H NMR (300.13 MHz, DMSO-$d_6$, 298 K, Fig. S5): δ 10.42 (s, 1H, NH), 8.05 (s, 1H, 4-H, coumarin), 7.68 (q, $^3J_{H,H}$ = 9.0 Hz, 4H, $C_6H_4$), 7.50 (d, $^3J_{H,H}$ = 8.9 Hz, 1H, 5-H coumarin), 6.72 (dd, $^3J_{H,H}$ = 8.9, $^4J_{H,H}$ = 2.4 Hz, 1H, 6-H coumarin), 6.55 (d, $^3J_{H,H}$ = 2.2 Hz, 1H, 8-H coumarin), 4.73 (q, $^3J_{H,H}$ = 6.6 Hz, 1H, CHBr), 3.44 (q, $^3J_{H,H}$ = 7.0 Hz, 4H, $CH_2CH_3$), 1.77 (d, $^3J_{H,H}$ = 6.7 Hz, 3H, $CH_3CHBr$), 1.13 (t, $^3J_{H,H}$ = 7.0 Hz, 6H, $CH_3CH_2$). $^{13}$C{$^1$H} NMR (75.47 MHz, DMSO-$d_6$, 298 K, Fig. S6): δ = 167.4, 160.5, 155.7, 150.3, 140.4, 137.9, 130.9, 129.5, 128.4, 118.9, 118.3, 109.1, 108.5, 96.1, 44.5, 44.1, 21.4, 12.3. IR (Fig. S7): 1678 (C=O, amide), 1688 (C=O, coumarin), 3318 (NH) cm$^{-1}$. HRMS (ESI-TOF, Fig. S8): found − 445.0940, calculated for $C_{22}H_{24}BrN_2O_3$ − 445.0953.

### 2.3. Crystal structure determination

Diffraction measurements of single crystal of **2** were performed at 193(2) K on a Bruker-AXS SMART APEX II diffractometer equipped with a 30 W air-cooled microfocus source, using $Mo_{K\alpha}$ radiation (λ = 0.71073 Å). Phi- and omega- scans were used. The data were integrated with SAINT, and an empirical absorption correction with SADABS was applied [19]. The structures were solved by direct methods (SHELXS-97) and refined using the least-squares method on $F^2$ [20]. All non-H atoms were refined with anisotropic

**Table 1**
Crystallographic data for **2**.

| | | | |
|---|---|---|---|
| Chemical formula | $C_{22}H_{23}BrN_2O_3$ | Calculated density | 1.458 g cm$^{-3}$ |
| Formula weight | 443.33 | Crystal size | 0.18 × 0.16 × 0.04 mm |
| Temperature | 193(2) K | Θ range for data collection | 2.76°–26.40° |
| Wavelength | 0.71073 Å | Limiting indices | −18 ≤ h ≤ 18, −14 ≤ k ≤ 14, −15 ≤ l ≤ 14 |
| Crystal system | Monoclinic | Reflections collected/unique | 52591/4136 |
| Space group | $P2_1/c$ | R(int) | 0.0778 |
| Crystal color | Orange | Completeness to theta = 26.40 | 99.9% |
| a | 14.9120(7) Å | Number of refined parameters | 260 |
| b | 11.3177(5) Å | GOF on $F^2$ | 1.087 |
| c | 12.0106(5) Å | R [I > 2σ(I)] | 0.0476 |
| α | 90° | $wR^2$ | 0.1254 |
| β | 94.758(2)° | $\rho_{max}$ | 0.639 e Å$^{-3}$ |
| γ | 90° | $\rho_{min}$ | −0.794 e Å$^{-3}$ |
| Volume | 2020,04(16) Å$^3$ | μ | 2.060 mm$^{-1}$ |
| Z | 4 | F(000) | 912 |