Communication

Efficient Synthesis of a 2-Decyl-tetradecyl Substituted 7-Bromophenothiazine-3-carbaldehyde Building Block for Functional Dyes

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Abstract: (1) Polyfunctional molecules are versatile building blocks for efficient syntheses of novel phenothiazine-based materials with promising electronic properties. A prerequisite is a facile, high yielding access to these building blocks that bear solubilizing moieties and functional groups for orthogonal transformation. (2) Here, an efficient, improved two-step protocol for accessing a solubilizing 2-decyl-tetradecyl functionalized phenothiazine, i.e., an *N*-alkylated 7-bromophenothiazine-3-carbaldehyde, by Vilsmeier–Haack formylation and NBS (*N*-bromo succinimide) bromination is reported. (3) The sequence proceeds with higher yields and in shorter reaction times than the standard access employing bromination with elementary bromine. In addition, the work-up procedure essentially uses absorptive filtration on a plug of silica with the eluent.

Keywords: building blocks; chromophores; electrophores; fluorophores; 10*H*-phenothiazine; solar cell dyes

1. Introduction

Bifunctional phenothiazine derivatives are important building blocks in the synthesis of functional chromophores, such as in dye sensitized solar cells (DSSC) [1–4]. For instance, *N*-alkylated 7-bromophenothiazine-3-carbaldehydes can be readily transformed via various cross-coupling reactions, such as Suzuki–Miyaura coupling [4–15], Beller cyanation [16], Sonogashira coupling [17–22], Buchwald–Hartwig, and Ullmann arylaminations [23–28] into 7-functionalized phenothiazine aldehydes. Furthermore, the aldehyde functionality can be efficiently reacted in Knoevenagel condensations to produce phenothiazinyl merocyanine dyes [1–4]. Furthermore, 7-bromophenothiazine-3-carbaldehydes are excellent substrates in diversity-oriented SuKnoCon (<u>Su</u>zuki-coupling, <u>Kno</u>evenagel <u>con</u>densation) synthesis of donor–donor–acceptor (Do–Do–Acc) system as dyes for DSSCs in the sense of a consecutive multicomponent reaction (MCR) in a one-pot fashion using arylboronic acids/arylboronates and methylene active components as reactants [1–3]. Here, we exemplarily communicate the two-step synthesis of 7-bromo-10-(2-decyltetradecyl)-10*H*-phenothiazine-3-carbaldehyde, which is a favorable, solubilizing, and nonaggregating building block for unsymmetrically substituted phenothiazine materials.

2. Materials and Methods

2.1. General Considerations and Instrumentation

10-(2-Decyl-tetradecyl)-10*H*-phenothiazine (1) was prepared according to the procedure described in [2]. Chloroform (for HPLC ≥ 99.8%; Merck KGaA, Darmstadt, Germany), DMF (Analytical reagent grade ≥ 99.8%; Fisher Scientific GmbH, Schwerte, Germany), phosphorus oxychloride (99%; Acros Organics, Geel, Belgium), and *N*-bromo succinimide (99%; Sigma Aldrich Chemie GmbH, Taufkirchen, Germany) were purchased and used without further purifications. Dried dichloromethane was taken from the MBraun solvent

drying system MB-SPS-800. Reaction progress was monitored by thin layer chromatography (TLC) on silica gel 60 with a F254 fluorescence indicator on aluminum sheets from Macherey-Nagel and UV irradiation at excitation wavelengths of 254 nm and 365 nm. The crude products were adsorbed on Celite® 545 (0.02–0.10 mm) from Carl Roth GmbH prior to chromatographic purification. Purification was then carried out by preparative flash column chromatography at a pressure of approx. 1 bar on silica gel 60 (0.040–0.063 nm) from Macherey-Nagel as a stationary phase and distilled *n*-hexane and diethyl ether mixtures as eluents. The substances were analyzed by mass spectrometry and NMR spectroscopy at the Center for Molecular and Structural Analytics at Heinrich Heine University Düsseldorf (CeMSA@HHU). The MALDI-TOF mass spectra were recorded on the UltrafleXtreme (Bruker Daltronics) and NMR spectra (^{1}H-, ^{13}C{^{1}H}- und DEPT-135 spectra) on a Bruker Avance III 300 NMR spectrometer. Deuterated acetone (δ_H 2.05, δ_C 29.84) was used as a solvent to record the NMR spectra. IR measurements were performed on Shimadzu IRAffinity 1 (ATR).

2.2. 10-(2-Decyl-tetradecyl)-10H-phenothiazine-3-carbaldehyde (2)

In a sintered, dry screw-cap *Schlenk* tube with magnetic stir bar under nitrogen atmosphere *N*,*N*-dimethylformamide (2.10 mL, 27.1 mmol, 2.40 equiv) was cooled to 0 °C (water-ice bath) for 15 min. Phosphorus oxychloride (1.70 mL, 18.2 mmol, 1.60 equiv) was added dropwise to the precooled DMF and the mixture was then stirred at 0 °C for an additional 15 min until a colorless, viscous fluid had formed (Vilsmeier reagent). *N*-Alkyl phenothiazine **1** (6.05 g, 11.3 mmol, 1.00 equiv) was dissolved in chloroform (11.3 mL), added to the freshly prepared solution of the Vilsmeier reagent, and stirred at 70 °C for 15 h. After cooling to room temperature, the reaction mixture was carefully (cooling with water-ice bath) diluted with deionized water (22.6 mL, 2.00 mL/mmol) and neutralized with a saturated sodium carbonate solution. After separating the organic layer in a separating funnel, the aqueous layer was extracted with dichloromethane (3 × 50 mL). The combined organic layers were dried (anhydrous magnesium sulfate), filtered, and the evaporated crude product was adsorbed on Celite® 545. After purification by flash chromatography on silica gel (30:1 *n*-hexane/diethyl ether), phenothiazine carbaldehyde **2** (5.74 g, 10.2 mmol, 90%) was obtained as a bright yellow oil after drying overnight under vacuo. R_f (*n*-hexane/diethyl ether 30:1): 0.38. ^{1}H NMR (300 MHz, acetone-*d₆*): δ 0.89 (t, ^3J = 6.6 Hz, 6 H), 1.20–1.43 (m, 40 H), 1.95–2.04 (m, 1 H), 3.96 (d, ^3J = 7.2 Hz, 2 H), 7.03 (ddd, ^3J = 7.7, 7.2 Hz, ^4J = 1.2 Hz, 1 H), 7.13 (dd, ^3J = 8.3 Hz, ^4J = 1.2 Hz, 1 H), 7.20 (d, ^3J = 8.5 Hz, 1 H), 7.20 (dd, ^3J = 7.7 Hz, ^4J = 1.6 Hz, 1 H), 7.25 (ddd, ^3J = 8.3, 7.2 Hz, ^4J = 1.6 Hz, 1 H), 7.64 (d, ^4J = 1.9 Hz, 1 H), 7.75 (dd, ^3J = 8.4 Hz, ^4J = 1.9 Hz, 1 H), 9.8 (s, 1 H). ^{13}C{^{1}H} NMR (75 MHz, acetone-*d₆*): δ 14.4 (CH$_3$), 23.4 (CH$_2$), 26.9 (CH$_2$), 30.1 (CH$_2$), 30.2 (CH$_2$), 30.3 (CH$_2$), 30.39 (CH$_2$), 30.4 (CH$_2$), 30.43 (CH$_2$), 30.6 (CH$_2$), 32.2 (CH$_2$), 32.7 (CH$_2$), 35.60 (CH), 52.6 (CH$_2$), 117.0 (CH), 118.0 (CH), 124.5 (CH), 125.6(C$_{quat}$), 126.8 (C$_{quat}$), 128.4 (CH), 128.6 (CH), 128.8 (CH), 130.7 (CH), 132.7 (C$_{quat}$), 145.2 (C$_{quat}$), 152.3 (C$_{quat}$), 190.4 (CH). IR: $\tilde{v}$ [cm^{-1}] = 2953 (m), 2920 (s), 2851 (s), 2718 (w), 1688 (s), 1597 (m), 1574 (m), 1558 (m), 1491 (w), 1460 (s), 1445 (m), 1416 (w), 1371 (m), 1339 (m), 1308 (m), 1287 (m), 1250 (m), 1196 (s), 1163 (w), 1150 (w), 1134 (w), 1101 (w), 1042 (w), 1001 (w), 920 (w), 897 (w), 883 (w), 853 (w), 814 (m), 745 (s), 719 (m), 691 (m), 640 (w), 606 (w). MS (MALDI-TOF): *m/z* = 563 ([M]$^+$). Anal. calcd. for C$_{37}$H$_{57}$NOS (563.4): C 78.81, H 10.19, N 2.48, S 5.69; found: C 78.64, H 10.26, N 2.42, S 5.68.

2.3. 7-Bromo-10-(2-decyl-tetradecyl)-10H-phenothiazine-3-carbaldehyde (3)

In a sintered screw-cap *Schlenk* tube with magnetic stir bar, phenothiazine carbaldehyde **2** (2.22 g, 3.95 mmol, 1.00 equiv) was dissolved in dry dichloromethane (39.5 mL) and *N*-bromo succinimide (0.77 g, 4.34 mmol, 1.10 equiv) was added portion wise. The reaction mixture was stirred at 50 °C for 15 h (be careful: the vessel is under pressure). After cooling to room temperature, the solvent was removed under reduced pressure and the crude product was adsorbed onto Celite® 545. Product **3** was purified by absorptive

filtration on silica gel (*n*-hexane/diethyl ether 30:1), dried overnight under vacuo, and obtained as bright yellow oil (2.48 g, 3.90 mmol, 98%). R_f (30:1 *n*-hexane/diethyl ether): 0.14. ^{1}H NMR (300 MHz, acetone-d_6): δ 0.84–0.92 (m, 6 H), 1.17–1.42 (m, 40 H), 1.92–2.02 (m, 1 H), 3.91 (d, [3]J = 7.2 Hz, 2 H), 7.02 (d, [3]J = 8.7 Hz, 1 H), 7.18 (d, [3]J = 8.5 Hz, 1 H), 7.29 (d, [4]J = 2.3 Hz, 1 H), 7.35 (dd, [3]J = 8.7 Hz, [4]J = 2.3 Hz, 1 H), 7.62 (d, [4]J = 1.9 Hz, 1 H), 7.74 (dd, [3]J = 8.5 Hz, [4]J = 1.9 Hz, 1 H), 9.85 (s, 1 H). ^{13}C{^{1}H} NMR (75 MHz, acetone-d_6): δ 14.4 (CH$_3$), 23.4 (CH$_2$), 26.7 (CH$_2$), 30.3 (CH$_2$), 30.4 (CH$_2$), 30.43 (CH$_2$), 31.9 (CH$_2$), 32.7 (CH$_2$), 35.3 (CH), 52.5 (CH$_2$), 116.1 (C$_{quat}$), 117.2 (CH), 119.4 (CH), 125.9 (C$_{quat}$), 127.9 (C$_{quat}$), 128.9 (CH), 130.3 (CH), 130.8 (CH), 131.2 (CH), 132.8 (C$_{quat}$), 144.5 (C$_{quat}$), 151.6 (C$_{quat}$), 190.3 (CH). MS (MALDI-TOF): m/z = 643 ([M^{81}Br]$^+$). IR: $\tilde{\nu}$ [cm^{-1}] = 2920 (m), 2851 (m), 2722 (w), 1690 (m), 1593 (m), 1555 (m), 1491 (w), 1456 (s), 1414 (w), 1393 (w), 1377 (w), 1335 (w), 1304 (w), 1269 (w), 1196 (m), 1155 (w), 1103 (w), 1082 (w), 1042 (w), 918 (w), 897 (w), 868 (w), 812 (m), 774 (w), 741 (w), 714 (w), 698 (w), 687 (w), 656 (w), 617 (w). Anal. calcd. for C$_{37}$H$_{56}$BrNOS (642.3): C 69.13, H 8.78, N 2.18, S 4.99; found: C 68.81, H 8.46, N 2.24, S 5.14.

3. Results and Discussion

Starting from the *N*-alkylated phenothiazine **1** reaction with the in situ generated Vilsmeier reagent in chloroform furnishes carbaldehyde **2** by Vilsmeier–Haack formylation (Figure 1) [28]. In comparison to the protocol described in the literature, here the phenothiazine carbaldehyde **2** was obtained in a shorter reaction time and with significantly better yields around 90% [2]. The dropwise addition of substrate **1** to the in situ generated formylation agent from DMF and POCl$_3$ ensures rapid initiation of the formylation, which then proceeds in a closed vessel at an oil bath temperature of 70 °C, i.e., 10 degrees higher than the boiling point of chloroform. The reaction reproducibly gives yields around 90% after purification. The regioselective formylation rationalizes by the stronger *para*-directing effect of the alkyl-substituted nitrogen atom. Indeed, the ^{1}H NMR spectrum in the aromatic region is very well resolved and the single set of aromatic protons with the expected splitting pattern accounts for a single isomer of the *para*-formylated product **2**.
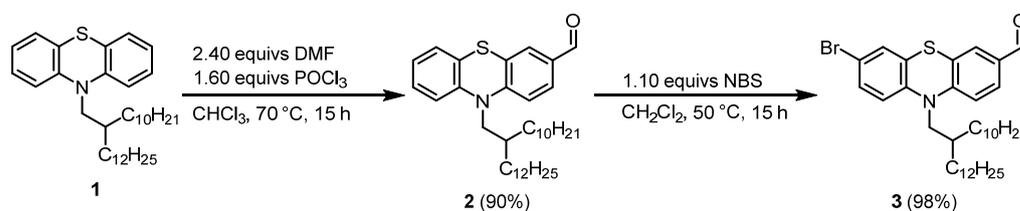
Figure 1. Synthesis of 7-bromo-10-(2-decyl-tetradecyl)-10*H*-phenothiazine-3-carbaldehyde (**3**) in a two-step sequence of Vilsmeier–Haack formylation and NBS bromination.

Bromination of phenothiazine carbaldehyde **2** proceeded in dichloromethane in a closed vessel at 50 °C (10 degrees above the boiling point of dichloromethane) with *N*-bromo succinimide (NBS) [29] to give 7-bromophenothiazine-3-carbaldehyde **3** with an excellent yield of 98%. The ^{1}H NMR spectrum in the aromatic region is again well resolved and the expected splitting pattern accounts for selective bromination *para* to the nitrogen atom, now on the other benzo ring. It is noteworthy to mention that for the isolation and purification of the crude products, a simple adsorptive filtration through a plug of silica gel is sufficient to furnish, after drying in high vacuum, the compounds **2** and **3** essentially analytically pure. Compared to the established protocol, the combined yield of both steps has been increased from 51 to 88%, with a concomitant reduction in the total reaction time from 60 to 30 h.

4. Conclusions

The two-step formylation–bromination process provides improved access to an *N*-alkyl 7-bromophenothiazine-3-carbaldehyde in shorter reaction times and very high yield. This polyfunctional phenothiazine building block is broadly used in forming phenothiazine-

based functional chromophores and can be likewise extended to alternate *N*-alkyl substituents.

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