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Short Note

5-Chloro-6-oxo-6*H*-xantheno[4,3-*d*]thiazole-2-carbonitrile

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Abstract: Xanthones and benzothiazoles are important classes of heterocyclic compounds with versatile biological activities. Herein, we describe a straightforward and scalable synthesis of 5-chloro-6-oxo-6*H*-xantheno[4,3-*d*]thiazole-2-carbonitrile, a thiazole-fused xanthone, via a six-step approach, using Appel's salt for the synthesis of the thiazole ring. The thiazole-fused xanthone was fully characterized employing ^{1}H and ^{13}C NMR spectra, using direct and long-range heteronuclear correlation experiments (HMBC and HMQC).

Keywords: xanthone; thiazole; imidazole

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Citation: Paraskevas, K.; Iliopoulos-Tsoutsouvas, C.; Georgiou, E.A.; Kostakis, I.K. 5-Chloro-6-oxo-6*H*-xantheno[4,3-*d*]thiazole-2-carbonitrile. *Molbank* **2022**, *2022*, M1489. https://doi.org/10.3390/M1489

Academic Editor: Fawaz Aldabbagh

Received: 11 October 2022
Accepted: 7 November 2022
Published: 10 November 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

1. Introduction

Many compounds based on the tricyclic planar chromophore framework, fully or partially consisting of anthraquinone [1], xanthone [2], or acridine [3,4], show interesting cytostatic and antitumor properties. In addition, benzothiazole moiety is present in various natural or synthetic compounds possessing beneficial biological activities [5–7] such as anticancer [8], anti-viral [9], etc. (Figure 1).

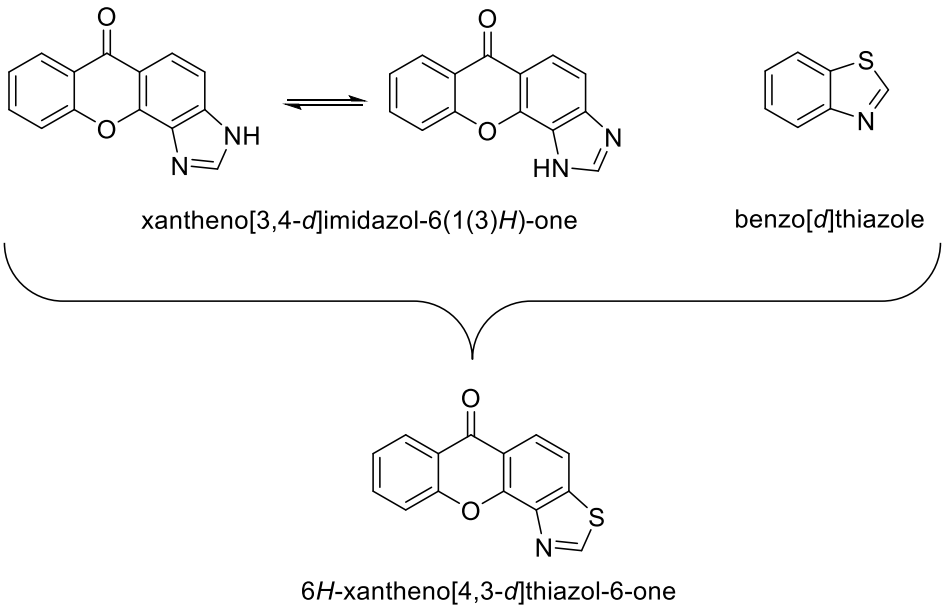


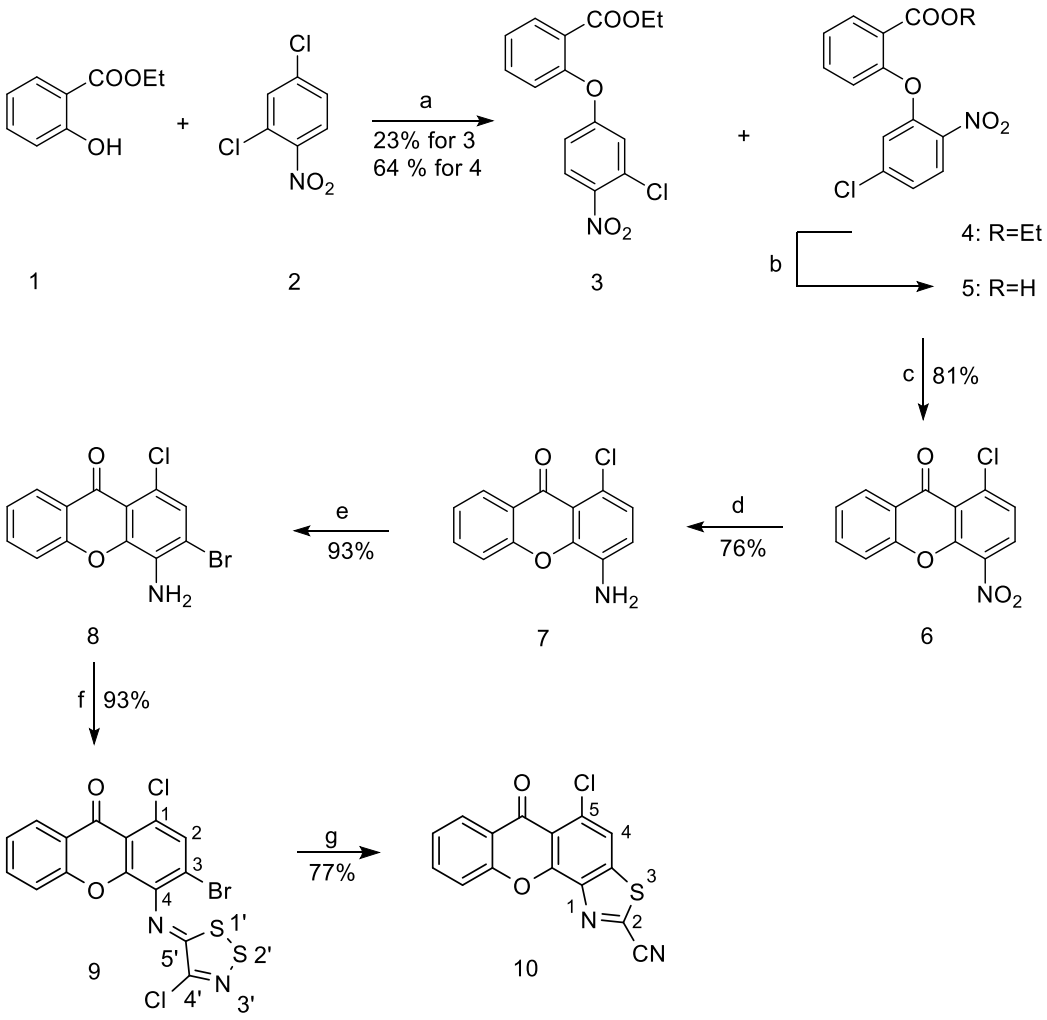
Figure 1. Benzothiazole- and imidazole-fused xanthones of interest. Tautomerism of xantheno[3,4-d]imidazol-6(1(3)*H*)-one.

We have been involved in the design, synthesis, and cytotoxic activity evaluation of a series of amino-substituted xanthones with a fused imidazole moiety [10]. These compounds have shown promising antiproliferative activity against human breast cancer cells. While exploring the structure–activity relationships of this class of compounds, we

have found that imidazole tautomerism is crucial for improving antiproliferative activity. Prompted by the considerations mentioned above, we decided to examine these two scaffolds further, and we herein describe the design of 5-chloro-6-oxo-6*H*-xantheno[4,3-*d*]thiazole-2-carbonitrile. In this compound, the imidazole ring of xantheno[3,4-*d*]imidazol-6(1(3)*H*)-one derivative has been replaced by the thiazole ring in order to have a better insight into the structure–activity relationships.

2. Results and Discussion

The synthetic procedure is depicted in Scheme 1. Our efforts focused on the development of a reliable and scalable procedure for the synthesis of xantheno[3,4-*d*]imidazol-6(1(3)*H*)-one, using simple starting materials and classic chemistry reactions; thus, several analogs could be obtained.



Scheme 1. Reagents and conditions: (**a**) Cu_2O, K_2CO_3, DMF dry, 110 °C, 8h; (**b**) 40% NaOH; (**c**) PPA, 110 °C; (**d**) $SnCl_2 \cdot 2H_2O$; (**e**) Br_2, CH_3COOH, 80 °C; (**f**) Appel's salt, pyridine, RT; (**g**) CuI, pyridine, 160 °C.

Commercially available ethyl salicylate (**1**) was used as a starting material which, upon treatment with 2,4-dichloronitrobenzene (**2**), resulted in a mixture of isomeric esters **3** and **4** (23% and 64%, respectively), which were separated by column chromatography [11]. Each ester was identified by ^{1}H NMR and ^{13}C NMR spectra, using both direct and long-range heteronuclear correlation experiments (HMQC and HMBC). The structural identification was based on the observation that C-1′ of compound **3** exhibits a ^2J coupling with two aromatic protons (i.e., H-2′ and H-6′) whilst C-1′ of compound **4** exhibits a ^2J coupling only with H-6′ (Scheme S1, Supplementary Material). Ester **4** was then saponified under mild

conditions, and the resulting carboxylic acid was cyclized to the corresponding xanthone **6** upon treatment with PPA. Reduction of the nitro derivative **6** to the aniline **7**, followed by bromination upon treatment with Br_2 in acetic acid, resulted in the bromoxanthone **8**. The next step concerns the preparation of 5-chloro-6-oxo-6*H*-xantheno[4,3-*d*]thiazole-2-carbonitrile **(10).** For this purpose, **8** was reacted with Appel's salt [12–14] to provide the *N*-arylimino-1,2,3-dithiazole **9,** which was heated at 160 °C, using CuI as a catalyst, with Start E Milestone MW apparatus.

Imino compound **9** and thiazole compound **10** were isolated in pure forms by column chromatography. Their structure was unambiguously established by ^{1}H and ^{13}C NMR spectra, using both direct and long-range heteronuclear correlation experiments (HMBC and HMQC). Structural discrimination of the two compounds resulted from the characteristic chemical shifts of H-2 and H-4, respectively, in the ^{1}H NMR spectra. More specifically, ^{1}H NMR spectra of compound **10** showed a typical singlet at 8.40 ppm assigned to H-4, while in the case of compound **9**, H-2 is shifted upfield by 0.48 ppm to 7.92 ppm. This may be attributed to the dithiazole group attached to the xanthone moiety. The characteristic signal of nitrile group at 112.89 ppm is also observed in the ^{13}C NMR spectrum of compound **10**, whilst, in the case of compound **9,** we observe two peaks at 147.05 ppm and 165.65 ppm for C-5′ and C-4′, respectively. The HRMS of **10** was also obtained to further confirm the proposed structure determined by NMR spectra.

2.1. General

All commercially available reagents and solvents were purchased from Alfa Aesar (Ward Hill, Massachusetts, MA, USA) and used without any further purification. Melting points were determined on Büchi apparatus and were uncorrected. ^{1}H NMR spectra and 2-D spectra were recorded on a Bruker Avance 400 instrument, whereas ^{13}C NMR spectra were recorded on a Bruker AC 200 spectrometer (Bruker BioSpin GmbH—Rheinstetten, Germany). Spectra were obtained with samples dissolved in $CDCl_3$ or DMSO-*d6* and were referenced to TMS (d scale). Assignments of ^{1}H and ^{13}C NMR signals were unambiguously achieved with the help of D/H exchange and 2D techniques: COSY, NOESY, HMQC, and HMBC experiments. Flash chromatography was performed on Merck silica gel (40–63 μm) with the indicated solvent system using gradients of increasing polarity in most cases (Merck KGaA—Darmstadt, Germany). The reactions were monitored by analytical thin-layer chromatography (Merck pre-coated silica gel 60 F254 TLC plates, 0.25-mm layer thickness). Mass spectra were recorded on a UPLC Triple TOF-MS ((UPLC: Acquity of Waters (Milford, MA 01757, USA), SCIEX Triple TOF-MS 5600+ (Framingham, MA 01701, USA)).

2.1.1. Synthesis of Ethyl 2-(5-Chloro-2-nitrophenoxy)benzoate (**4**)

A suspension of ethyl salicylate (33.37 g, 201 mmol, **1**), 2,4-dichloronitrobenzene (38.4 g, 200 mmol, **2**), K_2CO_3 (27.74 g, 201 mmol), and Cu_2O (2.85 g, 20.1 mmol) in dry DMF (50 mL) was heated at 110 °C for 8 h, under an argon atmosphere. After completion of the reaction, the mixture was vacuum evaporated, the residue was dissolved in CH_2Cl_2, and the filtrate was concentrated in vacuo. The residue was dissolved in CH_2Cl_2, washed with water, dried (Na_2SO_4), and evaporated to dryness. Flash chromatography on silica gel using a mixture of cyclohexane/EtOAc 100:5 as the eluent provided the title compounds **3** and **4** (23% and 64%, respectively).

Data of ethyl 2-(3-chloro-4-nitrophenoxy)benzoate (**3**): Mp 76–78 °C (Et_2O-n-hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.17 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 4.25 (q, *J* = 7.1 Hz, 2H, CH_2CH_3), 6.96 (d, *J* = 2.0 Hz, 1H, H-2′), 6.84 (dd, *J* = 9.1 Hz, 2.0 Hz, 1H, H-6′), 7.16 (d, *J* = 8.0 Hz, 1H, H-3), 7.41 (dt, *J* = 8.0 Hz, 1.1Hz, 1H, H-4), 7.63 (dt, *J* = 8.0 Hz, 1.1 Hz, 1H, H-5), 7.98 (d, *J* = 9.1 Hz, 1H, H-5′), 8.06 (dd, *J* = 8.0 Hz, 1H, H-6); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 14.15 (CH_2CH_3), 61.45 (CH_2CH_3), 114.85 (C-6′), 118.85 (C-2′), 123.32 (C-3), 124.46 (C-1), 126.45 (C-4), 128.01 (C-5′), 129.74 (C-4′), 132.62 (C-6), 134.43 (C-5), 141.63 (C-3′), 152.86 (C-2), 162.16 (C-1′), 164.54 (CO).

Data of ethyl 2-(5-chloro-2-nitrophenoxy)benzoate (**4**): Mp. 87–89 °C (Et_2O-*n*-hexane); $_1$H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.16 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 4.23 (q, *J* = 7.2 Hz, 2H, CH_2CH_3), 6.71 (d, *J* = 2.0 Hz, 1H, H-6′), 7.11 (dd, *J* = 8.9 Hz, 2.0 Hz, 1H, H-4′), 7.18 (d, *J* = 8.1 Hz, 1H, H-3), 7.41 (dt, *J* = 8.1 Hz, 1.0 Hz, 1H, H-4), 7.63 (dt, *J* = 8.1 Hz, 1.0 Hz, 1H, H-5), 7.96 (d, *J* = 8.9 Hz, 1H, H-3′), 8.03 (dd, *J* = 8.1 Hz, 1H, H-6); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 13.81 (CH_2CH_3), 61.42 (CH_2CH_3), 117.65 (C-6′), 122.21 (C-4′), 122.95 (C-3), 124.16 (C-1), 126.25 (C-5), 126.92 (C-2), 132.72 (C-6), 134.34 (C-4), 138.13 (C-2′), 140.20 (C-5′), 152.76 (C-1′, C-2), 164.45 (CO).

2.1.2. Synthesis of 1-Chloro-4-nitro-9H-xanthen-9-one (**6**)

A cold 40% NaOH solution (2 mL) was added dropwise to a suspension of **4** (1.29 g, 4 mmol) in ethanol (10 mL), and the resulting mixture was stirred at room temperature. for 30 min. After completion of the reaction, the solution was poured into ice water and acidified with 18% HCl solution (pH~2). The resulting 2-(5-chloro-2-nitrophenyloxy)benzoic acid (**5**) was filtered, air-dried, and dissolved in hot polyphosphoric acid. The mixture was heated at 110 °C for 1h, and upon cooling, it was poured into ice water. The precipitate formed was filtered, air-dried, and purified by column chromatography (silica gel) using a mixture of CH_2Cl_2/cyclohexane 1:4–3:1 as the eluent, to afford 0.89 g (81%) of the title compound **6** [10]. Mp. 270 °C (EtOH). ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm) 7.53 (td, *J* = 8.1 Hz, 1.0 Hz, 1H, H-7), 7.62 (d, *J* = 8.1 Hz, 1H, H-5), 7.66 (d, *J* = 8.1Hz, 1H, H-2), 7.90 (dt, *J* = 8.1 Hz, 1.0 Hz, 1H, H-6), 8.14 (d, *J* = 8.1 Hz, 1 Hz, 1H, H-8), 8.43 (d, *J* = 8.1 Hz, 1H, H-3); ^{13}C NMR (DMSO-d_6, 50 MHz) δ (ppm) 118.35 (C-5), 120.44 (C-9a), 122.14 (C-8a), 125.76 (C-7), 126.67 (C-8), 126.74 (C-2), 130.42 (C-3), 136.51 (C-4), 136.61 (C-6), 138.87 (C-1), 150.07 (C-4a), 154.27 (C-10a), 174.29 (C-9).

2.1.3. Synthesis of 4-Amino-1-chloro-9H-xanthen-9-one (**7**)

$SnCl_2{\cdot}2H_2O$ (1.23 g, 5.46 mmol) was added to a suspension of 1-chloro-4-nitro-9*H*-xanthen-9-one (1 g, 3.64 mmol, **6**) in HCl 36% (30 mL) at 0 °C, and the resulting mixture was stirred at 60 °C for 1 hr. After completion of the reaction, the mixture was allowed to cool down and poured into water. After basification (pH = 8–9) by the addition of 5% aqueous Na_2CO_3, the mixture was extracted with CH_2Cl_2 (3 × 30 mL), the combined organic solvents washed successively with water, dried (Na_2SO_4), and evaporated to dryness. Flash chromatography on silica gel using a mixture of CH_2Cl_2 /EtOAc 6:1-4:1 as the eluent provided 0.68 g (76%) of the title compound **18**. Mp. 219–221 °C (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.34 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.73 (td, *J* = 8.0, 1.5 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.42 (t, *J* = 8.0, 1H), 7.19 (d, *J* = 8.0 Hz, 1H, H-2), 6.98 (d, *J* = 8.0 Hz, 1H, H-3), 4.28 (s, D_2O exch., 2H, NH_2); ^{13}C NMR (151 MHz, $CDCl_3$) δ (ppm) 176.17 (C-9), 154.68 (C-10a), 145.71 (C-4a), 135.05 (C-4), 134.58 (C-6), 127.21 (C-8), 126.61 (C-2), 124.31 (C-7), 122.54 (C-8a), 121.82 (C-1), 118.90 (C-9a), 118.16 (C-3), 117.25 (C-5).

2.1.4. Synthesis of 4-Amino-3-bromo-1-chloro-9H-xanthen-9-one (**8**)

A suspension of 4-amino-1-chloro-9*H*-xanthen-9-one (1.5 g, 6.11 mmol, **7**) and bromine (0.6 mL, 6.3 mmol) in glacial acetic acid (10 mL) was irradiated for 8 min with Start E Milestone apparatus. The irradiation was programmed to obtain 80 °C. After completion of the reaction, the mixture was poured into ice water and washed with CH_2Cl_2 (3 × 40 mL). The combined organic phase was washed successively with 5% Na_2CO_3 solution, 5% $Na_2S_2O_3$ solution, and water, dried (Na_2SO_4), and evaporated to dryness. Flash chromatography on silica gel using a mixture of cyclohexane/EtOAc 6:1-2:1 as the eluent provided 1.85 g (93%) of the title compound **8**. Mp 204–207 °C (EtOAc); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.12 (d, *J* = 7.9 Hz, 1H, H-8), 7.88 (t, *J* = 7.9Hz, 1H, H-6), 7.76 (d, *J* = 7.9 Hz, 1H, H-5), 7.51 (s, 1H, H-2), 7.47 (t, *J* = 7.9 Hz, 1H, H-7), 6.07 (s, D_2O exch., 2H, NH_2); ^{13}C NMR (151 MHz, DMSO-d_6) δ (ppm) 174.96 (C-9), 154.34 (C-10a), 144.43 (C-4a), 135.95 (C-4), 135.23 (C-6), 128.76 (C-2), 125.92 (C-8), 124.64 (C-7), 121.44 (C-1, C-8a), 118.05 (C-5), 116.88 (C-9a), 109.09 (C-3).

2.1.5. Synthesis of 3-Bromo-1-chloro-4-((4-chloro-5H-1,2,3-dithiazol-5-ylidene)amino)-9H-xanthen-9-one (**9**)

4,5-dichloro-1,2,3-dithiazolium chloride (3.8 g, 18 a mmol, Appel's salt) and pyridine (7.4 mL, 35 mmol) were added to a solution of 4-amino-3-bromo-1-chloro-9*H*-xanthen-9-one (5.55 g, 17 mmol, **8**) in anh. CH_2Cl_2 at room temperature. The resulting solution was stirred at room temperature for 2 days. After completion of the reaction, the solution was successively washed with water, dried (Na_2SO_4), and evaporated to dryness. The residue was purified by column chromatography (silica gel) using a mixture of cyclohexane/EtOAc 4:1–2:1 as the eluent to provide 8.5 g (93%) of the title compound **9**. Mp. 241.7–243 °C (EtOAc); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.13 (dd, *J* = 7.9, 1.5 Hz, 1H, H-8), 7.92 (s, 1H, H-2), 7.86 (td, *J* = 7.9, 1.5 Hz, 1H, H-6), 7.59 (d, *J* = 7.9 Hz, 1H, H-5), 7.48 (t, *J* = 7.9 Hz, 1H, H-7). ^{13}C NMR (151 MHz, DMSO-d_6) δ (ppm) 174.93 (C-9), 165.65 (C-5′), 154.46 (C-10a), 147.05 (C-4′), 145.94 (C-4a), 138.97 (C-4), 136.09 (C-6), 130.16 (C-2), 129.22 (C-3), 126.49 (C-8), 125.57 (C-7), 122.14 (C-8a), 119.29 (C-1), 118.86 (C-9a), 118.54 (C-5).

2.1.6. Synthesis of 5-Chloro-6-oxo-6H-xantheno[4,3-d]thiazole-2-carbonitrile (**10**)

A suspension of compound **9** (1.5 g, 3.26 mmol) and CuI (1.26 g, 6.6 mmol) in dry pyridine (10 mL) was irradiated for 2 min with Start E Milestone apparatus. The irradiation was programmed to obtain 160 °C. After completion of the reaction, the mixture was vacuum evaporated, the residue was dissolved in CH_2Cl_2, filtered through a Celite pad, and the filtrate was evaporated to dryness. Flash chromatography on silica gel using a mixture of cyclohexane/EtOAc 8:1 as the eluent provided 0.78 g (77%) of the title compound **10**. Mp. 275 °C (EtOAc); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.40 (s, 1H, H-4), 8.18 (d, *J* = 7.9 Hz, 1H, H-7), 7.92 (t, *J* = 7.9 Hz, 1H, H-9), 7.80 (d, *J* = 7.9 Hz, 1H, H-10), 7.56 (t, *J* = 7.9 Hz, 1H, H-8). ^{13}C NMR (151 MHz, DMSO-d_6) δ (ppm) 174.04 (C-6), 153.93 (C-10a), 151.33 (C-11a), 141.32 (C-2), 140.70 (C-4a), 138.79 (C-5), 135.67 (C-9), 132.06 (C-11b), 126.10 (C-7), 125.46 (C-8), 122.26 (C-6a), 120.23 (C-4), 118.00 (C-10), 116.10 (C-5a), 112.89 (CN). HRMS (ESI) calculated for $C_{15}H_5ClN_2O_2S + H^+$ [M + H$^+$]: 312.9833. Found: 312.9822.

3. Conclusions

5-chloro-6-oxo-6*H*-xantheno[4,3-*d*]thiazole-2-carbonitrile, a thiazole-fused xanthone, was synthesized. The methodology described herein comprises six steps, with a 26% overall yield. The methodology described herein is straightforward and scalable; thus, it could be used to synthesize several analogs of this scaffold.

Supplementary Materials: The following material is available online. Scheme S1: Structural Discrimination of compounds **3** and **4**; Figure S1: ^{1}H NMR spectrum of compound **4**; Figure S2: HMBC spectrum of compound **4**; Figure S3: HMQC spectrum of compound **4**; Figure S4: ^{1}H NMR spectrum of compound **8**; Figure S5: ^{1}H NMR spectrum of compound **9**; Figure S6: ^{1}H NMR spectrum of compound **10**; Figure S7: ^{13}C NMR spectrum of compound **8**; Figure S8: ^{13}C NMR spectrum of compound **9**; Figure S9: ^{13}C NMR spectrum of compound **10**; Figure S10: HMBC spectrum of compound **10**; Figure S11: HMQC spectrum of compound **10**; Figure S12: COSY spectrum of compound **10**.

Author Contributions: Design, conception, and writing, I.K.K.; synthesis, structure elucidation, and NMR studies, K.P., C.I.-T. and E.A.G. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study are available in this article.

Conflicts of Interest: The authors declare no conflict of interest.

Sample Availability: Samples of the compounds are available from the authors.

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