**An Improved Synthetic Method of 1-Chloro-7-methoxy-9H-thioxanthen-9-one**

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**Abstract**

1-Chloro-7-methoxy-9H-thioxanthen-9-one (3) was prepared via cyclization of 2-chloro-6-(4-methoxyphenylthio)-benzonitrile (1) in a one pot, two step reaction with improved yield (60%) over the previous literature report.

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**Introduction**

Sulfur containing compounds have been the main focus for many years in our anticancer drug design research. (1) (2) Thioxanthenones, like lucanthone (Miracil D) (3–6) and hycanthone (Etrenol) (7–10) have been widely known as antischistosomal and anticancer agents. With the discovery of curative anticancer activities in animal models, this series of compounds, like WIN 33377, advanced into clinical trials. (11–14) In our endeavor to explore thioxanthenones as cancer specific cytotoxins, 1-chloro-9H-thioxanthones with or without 7-methoxyl group were synthesized as the early intermediates for our target compounds. The synthesis of 1-chloro-7-methoxy-9H-thioxanthone (3) was initially completed by a published method using CF₃SO₃H both as solvent and catalyst. Repeated attempts, however, gave only around 10% yield, which is much lower than the reported 53%. (10) Interestingly, the synthesis of 1-chloro-9H-thioxanthone performed also in our laboratory according to the method described for 1-chloro-7-methoxy-9H-thioxanthone (3) (10) gave 70% yield, which was comparable to or better the reported procedure (15) using polyphosphoric acid both as solvent and catalyst. After many attempts for the synthesis of 1-chloro-7-methoxy-9H-thioxanthone (3) through this reported method, it seemed that some critical condition might have been omitted in their procedure description. A new revised synthetic procedure was explored to improve the yield.
**Results and Discussion**

The crude product of compound (3) obtained through the published method (10) was analyzed by TLC using EtOAc:Hexane (1:9) as a mobile phase. There was a substantial amount of undesired byproduct, which might have resulted from intermolecular reactions among 2-chloro-6-((4-methoxyphenylthio))-benzonitrile (1). It was thought that the yield could be improved either by using a suitable neutral solvent to lower the nitrile concentration or using a weaker acid to dilute the strong acid CF₃SO₃H to decrease the acid strength. After a number of attempts using different combinations of methods, optimal conditions were obtained, which consisted of using methylene chloride as solvent, CF₃SO₃H as catalyst, and allowing the reaction to run for 4 days at room temperature (Sch. 1). This afforded the desired product (3) in 60% yield.

![Scheme 1](image)

**Experimental Section**

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and were uncorrected. ¹H NMR spectra were recorded on a Bruker, 400 MHz instrument with tetramethylsilane as internal standard. Chemical shifts are reported as values (ppm) downfield from tetramethylsilane. NMR abbreviations were used as follows: s (singlet), d (doublet), m (multiplet). IR spectra were recorded on FT-IR (Perkin Elmer Spectrum 1000) instrument. Silica GF plates (Analtech) were used for TLC (250 µm, 2.5 × 10 cm). Silica Gel (40 µm, Baker) was used for flash column chromatography. All organic reagents and solvents were reagent grade and purchased from commercial vendors.

**1-Chloro-7-methoxy-9H-thioxanthen-9-one (3).** Two grams of 2-chloro-6-((4-methoxyphenylthio))-benzonitrile (1) was dissolved in 50 mL of CH₂Cl₂. Four milliliters of CF₃SO₃H was added to the above solution at room temperature. The color of the solution changed from colorless to brown, then to dark brown after all the CF₃SO₃H was added. The reaction mixture was stirred for four days at room temperature. Upon the addition of 200 mL of distilled water, the original solvent CH₂Cl₂ was distilled off from the mixture. The resulting cloudy aqueous suspension mixture was subsequently allowed to reflux for 5 h. The solid was collected by filtration, washed with water and dried. The crude product was purified on a silica gel column using EtOAc:Hexane 1:9 as eluent to give 1.21 g (60%) of pure product (3): m.p. 133–134.5°C (lit. (10) m.p. 132–133°C); TLC Rf 0.30 in EtOAc:hexane 1:9; ¹H NMR (CDCl₃) 3.90 (s, 3H, OCH₃), 6.85 (s, 1H, ArH), 6.98 (d, 1H, ArH, J = 9.6 Hz), 7.35–7.45 (m, 3H, ArH), 8.38 (d, 1H, ArH, J = 7.6 Hz). IR (KBr) 1643.62, 1595.78, 1580.13, 1488.43, 1432.12, 1297.80, 1230.80, 1068.51, 1028.99, 852.25, 805.90, 779.16, 785.97, 659.96 cm⁻¹.


