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New Method for the Preparation of Dibenzo[*b,f*][1,4]thiazepines

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ABSTRACT: *The S-amination of 9*H*-thioxanthen-9-ol (***2a***) and 9-substituted derivatives* **2b–e** *(Me (***b***), Et (***c***), ^{i}Pr (***d***), Ph (***e***)) with O-mesitylenesulfonylhydroxylamine (MSH) was carried out. The expected product, 10-amino-9-hydroxy-9-isopropyl-9*H*-thioxanthenium mesitylenesulfonate (***3d***), was obtained in 78% yield from the corresponding thioxanthen-9-ol* **2d**. *However, in the case of* **2a–c** *and* **2e** *the reaction led instead to dibenzo[*b, f*][1,4]thiazepines* **6a–c** *and* **6e** *in moderate yields.* © 2004 Wiley Periodicals, Inc. Heteroatom Chem 15:246–250, 2004; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20010

INTRODUCTION

The chemistry of 10,11-dihydrodibenzo[*b, f*][1,4]-thiazepine and its derivatives has been widely investigated because of their interesting biological activities [1]. However, only a few methods are available for the synthesis of dibenzo[*b,f*][1,4]thiazepines. Among them the Bischler–Napieralski type cyclization of 2-formylaminophenyl phenyl sulfide has been widely used in organic synthesis [2,3].

Quite recently, we have found that a heterocyclic fluoro-λ^6-sulfanenitrile bearing an SN triple bond, 5-fluoro-10,10-dihydro-5λ^6,10λ^6-thianthren-5-nitrile, is obtained from the reaction of 10,10-dioxo-5*H*-5λ^4,10λ^6-thianthrene-5-ylideneamine with Selectfluor™ (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2,2,2]octane bis(tetrafluoroborate)) [4]. This reaction is presumably a candidate for the preparation of various fluoro-λ^6-sulfanenitriles because the conversion of cyclic-*N*-bromosulfimide with the fluoride anion to the corresponding λ^6-sulfanenitriles is difficult. In a further extension of these studies, we examined the preparation of *S*-aminated thioxanthen-9-ols **2a–e** as a precursor of fluoro-λ^6-sulfanenitriles. While the reaction of 9-isopropyl-9*H*-thioxanthen-9-ol (**2d**) with MSH gave the expected corresponding *S*-aminothioxanthenium salts **3d**, in the case of 9*H*-thioxanthen-9-ol (**2a**) and 9-methyl-, -ethyl-, and –phenyl-9*H*-thioxanthen-9-ols **2b–c** and **2e** it led instead to the corresponding dibenzo[*b, f*][1,4]thiazepines **6a–c** and **6e**. We report here on a rather unusual, new type reaction of 9*H*-thioxanthen-9-ol **2** with MSH.

RESULTS AND DISCUSSION

9*H*-Thioxanthen-9-ol (**2a**) and 9-substituted 9*H*-thioxanthen-9-ols **2b–e** were prepared according to the following procedure (Scheme 1). 9*H*-Thioxanthen-9-ol (**2a**) was prepared according to the reported literature method [5]. 9-Substituted 9*H*-thioxanthen-9-ols **2b–e** were prepared by the reaction of thioxanthen-9-one (**1**) with alkyl and phenyl Grignard reagents in ether under reflux conditions [5–7]. It is known that the isolation of 9-substituted

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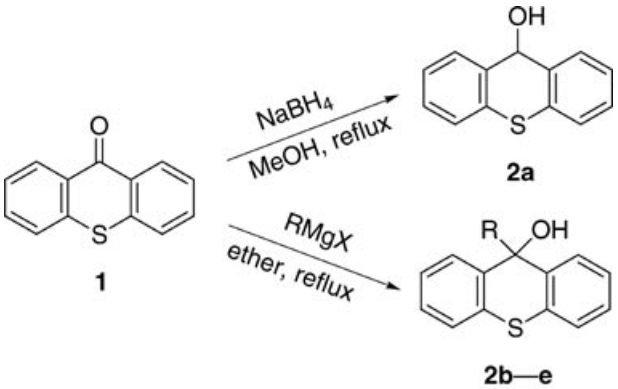
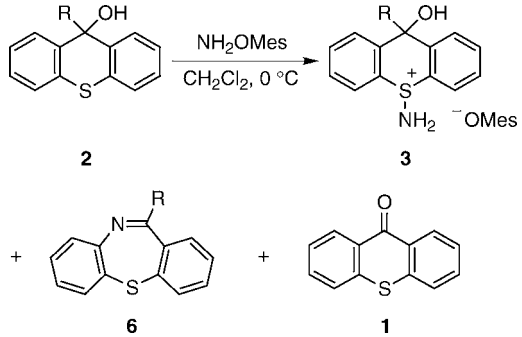


SCHEME 1

alcohols is generally unsuccessful [7,8], but 9-methyl and 9-isopropyl-thioxanthen-9-ols **2b** and **2d** could be obtained in 84% and 95% purity, respectively, and 9-ethyl- and 9-phenyl-thioxanthen-9-ols **2c** and **2e** could be isolated in 88% and 65% yields, respectively, by recrystallization from the reaction mixtures.

The reaction of **2** with *O*-mesitylenesulfonylhydroxylamine (MSH) was carried out in CH_2Cl_2 at 0°C (Table 1) [9]. In the reaction of **2d**, the expected S-aminated product, 10-amino-9-hydroxy-9-isopropyl-9*H*-thioxanthenium mesitylenesulfonate (**3d**) was obtained in 78% yield as a single isomer. This S-aminated compound **3d** is not hydrolyzed under

TABLE 1 Reaction of 2 with MSH

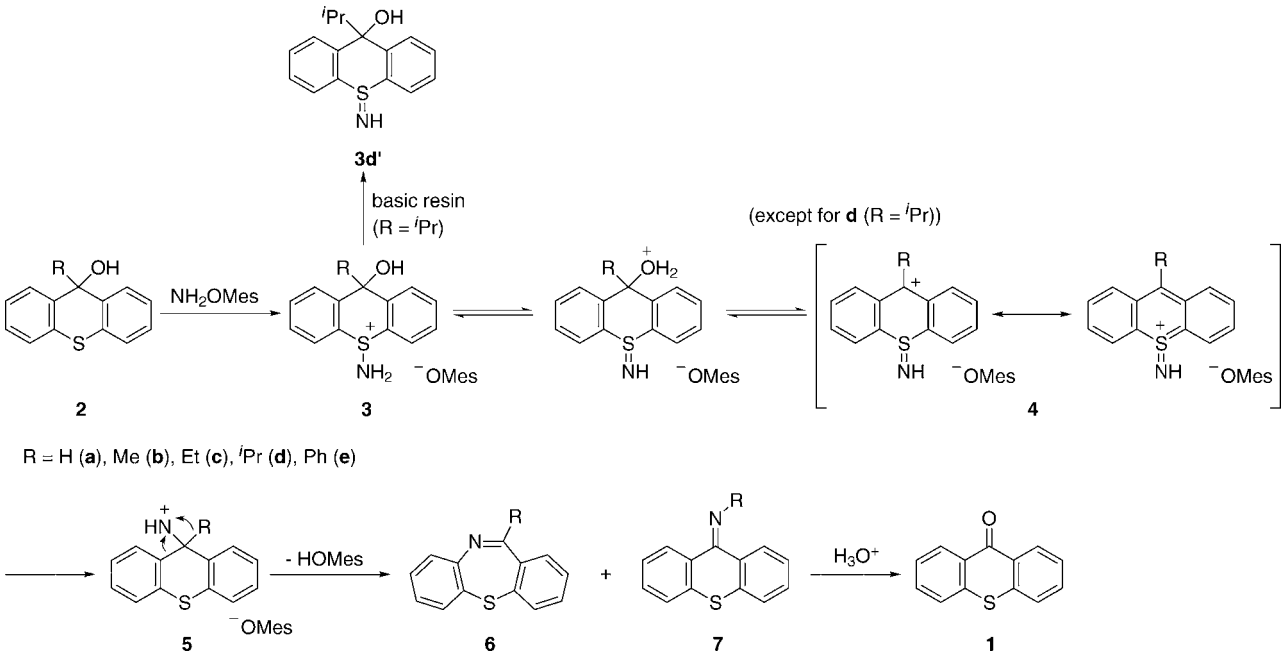


		Yield (%)		
2	*R*	**3**	**6**	**1**
a	H	–[a]	43[b]	38[b]
b	Me	–[a]	21[b]	12[b]
c	Et	–[a]	58[b]	26[b]
d	^{i}Pr	78[b]	–[a]	trace
e	Ph	–[a]	57[b]	37[b]

[a]Not detected.
[b]Isolated yield.

either acidic or alkaline conditions. Upon refluxing in benzene contained concentrated hydrochloric acid or 60% perchloric acid for 24 h, compound **3d** was almost recovered (recovery: 96%) and treatment of **3d** with a basic resin (IRA-410/OH^- form) gave the corresponding sulfimide **3d′** (see Scheme 2). On the other hand, the reactions of **2a–c** and **2e** gave the corresponding dibenzo[*b, f*][1,4]thiazepines **6a–c** and **6e** in moderate yields instead of S-aminated thioxanthenium salts **3a–c** and **3e**, together with thioxanthen-9-one (**1**) (Table 1). Since in the reaction of **2e** aniline was obtained in 31% yield, thioxanthen-9-one (**1**) should be formed by hydrolysis of thioxanthen-9-ylidene-amine **7** (see Scheme 2) [10].

The formation of dibenzo[*b, f*][1,4]thiazepines **6a–c** and **6e** is unusual and unexpected. A plausible mechanism for the formation of **6a–c** and **6e** from the thioxanthen-9-ols **2a–c** and **2e** is proposed in Scheme 2. In the first step, it is reasonable to assume that thioxanthen-9-ols **2a–c** and **2e** are aminated by MSH to give the corresponding S-aminated thioxanthene-9-ols **3a–c** and **3e**. The resulting **3a–c** and **3e** then may undergo dehydration to form the corresponding imino thioxanthylium cations, **4a–c** and **4e**, followed by intra- or intermolecular migration of the imine nitrogen to the 9-carbon atom affording the intermediates, nitrenium ions **5a–c** and **5e**. The driving force for such migration may be responsible for the formation of imino thioxanthylium cations **4**. It is well known that thioxanthene-9-ols react with sulfuric acid or perchloric acid to produce the corresponding thioxanthylium cations [5,6,11]. Tamura et al. have reported that thioxanthene *N*-(*p*-toluenesulfonyl)sulfimide and 9-substituted thioxanthene *N*-(*p*-toluenesulfonyl)sulfimide undergo rearrangement to 9-*N*-(*p*-toluenesulfonamido)thioxanthene [12]. They suggested that this rearrangement is explained in terms of the intermediacy of the thioxanthylium cations. However, as mentioned above, treatment of S-aminated compound **3d** with hydrochloric acid or perchloric acid resulted in almost recovery of the starting material, and 11-isopropyl-dibenzo[*b, f*][1,4]thiazepine (**6d**) was not obtained even in trace amounts. This can be explained by assuming the nonbonded interaction between the 9-isopropyl group and two *peri*-hydrogen atoms to prevent transformation of the imino thioxanthylium cation. Finally, the intermediates **5a–c** and **5e** possibly rearrange to the corresponding dibenzo[*b, f*][1,4]thiazepines **6a–c** and **6e** [13]. A similar result has been reported that the thermolysis and photolysis of 9-aryl-azidothioxanthen undergo rearrangement to



SCHEME 2

form 11-aryl-dibenzo[*b, f*][1,4]thiazepine and arylthioxanthen-9-ylidene-amine [10,14].

EXPERIMENTAL

General

All reagents and solvents were obtained commercially and were further purified by general methods when necessary. Infrared spectra (IR) were recorded on a Horiba FT-710 spectrometer. NMR spectra were obtained on a JEOL-JNM 400 NMR spectrameter and calibrated by using tetramethylsilane (TMS) as an internal reference. Chemical shifts (δ) were measured in parts per million, and coupling constants (J values) were in hertz (Hz). Mass spectra were recorded on a JEOL-JMS 700 mass spectrometer. Melting point was measured on a Yanaco Mp-J3 melting point apparatus. Elemental analyses were performed on a Yanaco MT-5 CHN CORDER.

*Synthesis of 9H-Thioxanthen-9-ol (**2a**)*

To a well stirred suspension of 1 g, 4.7 mmol of thioxanthene-9-one (**1**) in 30 ml of MeOH was added 0.7 g, 18.5 mmol (3.9 equiv) of $NaBH_4$. The suspension was heated to refluxing temperature and monitored by TLC. When the reaction was complete (within 5 h), the solution was quenched with 20 ml of dilute hydrochloric acid (5%) and extracted with diethyl ether (5 × 40 ml). After drying over anhydrous sodium sulfate and removal of the solvent, the residue was recrystallized from *n*-hexane to give a 94% yield of **2a**; mp 104–105°C (Ref [5] 104–105°C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.57 (d, J = 7.2 Hz, 1H), 7.26–7.34 (m, 4H), 7.49 (d, J = 7.6 Hz, 2H), 7.62 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$)δ 72.1, 126.7, 126.9, 127.2, 127.6, 132.0, 136.4; IR (KBr) 3299 cm^{-1}(OH), 2881 cm^{-1} (CH); MS (*m/z*) 214 (M^+).

*General Procedure for Syntheses of 9-Substituted 9H-Thioxanthen-9-ols (**2b–e**)*

To a well stirred solution of 1.5 g, 7.1 mmol of thioxanthene-9-one (**1**) in 20 ml of dry diethyl ether was added 3 equiv of the corresponding Grignard reagents in anhydrous state. The solution was heated to refluxing temperature to react for 24 h. After treatment with a solution of NH_4Cl (6 g) in ice water (about 30 ml), the solvent was evaporated and the aqueous solution was extracted with chloroform (3 × 30 ml). The extract was dried over anhydrous magnesium sulfate and the solvent was evaporated. The compounds **2b–e** could not be isolated by silica-gel column chromatography. But the compounds **2c** and **2e** could be isolated by recrystallization from the reaction mixtures [5–7].

*9-Methyl-9H-thioxanthen-9-ol (**2b**)*

The crude product contained as impurity a small amount of 9-methylene-9*H*-thioxanthene and could

not be isolated by recrystallization [6,7a,7c]; Yield 84% (determined by ^{1}H NMR); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53 (s, 3H), 7.22–7.41 (m, 6H), 7.88 (dd, J_1 = 6.2 Hz, J_2 = 1.6 Hz, 2H); IR (coat) 3424 cm^{-1}(OH), 2965 cm^{-1} (CH); MS (*m/z*) 228 (M^+).

*9-Ethyl-9H-thioxanthen-9-ol (**2c**)*

Yield 88%; mp 72°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.69 (t, J = 7.4 Hz, 3H), 1.83 (q, J = 7.4, Hz, 2H), 7.23 (dt, J_1 = 7.4 Hz, J_2 = 1.2 Hz, 2H), 7.29–7.33 (m, 2H), 7.38–7.40 (m, 2H), 7.80–7.83 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.0, 31.3, 75.6, 125.5, 126.26, 126.33, 127.1, 130.1, 140.2; IR (KBr) 3430 cm^{-1}(OH), 2969, 2932, 2887 cm^{-1} (CH); MS (*m/z*) 242 (M^+); Anal. Calcd for $C_{15}H_{14}OS$: C, 74.34, H, 5.82; Found: C, 74.51, H, 5.87.

*9-Isopropyl-9H-thioxanthen-9-ol (**2d**)*

The crude product contained as impurity of thioxanthene-9-one [7a]. Thioxanthene-9-one (**1**) was removed partly by recrystallizing from acetone to obtain **2d** in 95% purity. Yield 80% (determined by ^{1}H NMR); ^{1}H NMR (400 MHz, $CDCl_3$)δ 0.70 (d, J = 6.8 Hz, 6H), 2.40 (sept, J = 6.8 Hz, 1H), 7.23 (dt, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 2H), 7.30 (dt, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 2H), 7.41 (dd, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 2H), 7.78 (dd, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 2H); IR (coat) 3436 cm^{-1}(OH), 2965, 2933, 2872 cm^{-1} (CH); MS (*m/z*) 256 (M^+).

*9-Phenyl-9H-thioxanthen-9-ol (**2e**)*

Yield 65%; mp 108°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97–7.00 (m, 2H), 7.15–7.19 (m, 3H), 7.26–7.31 (m, 2H), 7.36–7.44 (m, 4H), 8.03 (dd, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 2H); ^{13}C NMR (100 MHz, CD_3CN) δ 77.3, 127.3, 127.5, 127.6, 127.9, 128.3, 128.4, 128.8, 132.0, 141.5, 144.9; IR (KBr) 3303 cm^{-1}(OH); MS (*m/z*) 290 (M^+) [5–7].

*Reaction of 9H-thioxanthen-9-ols **2** with MSH*

To a solution of 9*H*-thioxanthen-9-ols **2** (300 mg) in 40 ml of CH_2Cl_2 at 0°C was added slowly 1.1 equiv of *O*-mesitylenesulfonylhydroxylamine (MSH) in 6 ml of CH_2Cl_2. The solution was warmed to room temperature and the reaction was monitored by TLC. When the reaction had been complete, the solution was evapolated, and then the residue was purified by recrystallization or silica-gel column chromatography.

*10-Amino-9-hydroxy-9-isopropyl-9H-thioxanthenium mesitylenesulfonate (**3d**)*

Yield 78%; mp 179°C; ^{1}H NMR (400 MHz, CD_3OD) δ 0.78 (d, J = 6.4 Hz, 6H), 1.74 (sept, J = 6.4 Hz, 1H), 2.23 (s, 3H), 2.62 (s, 6H), 6.86 (s, 2H), 7.73 (t, J = 8.0 Hz, 2H), 7.80 (t, J = 8.0 Hz, 2H), 8.05 (d, J = 8.0 Hz, 2H), 8.08 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 17.3, 20.8, 23.3, 40.9, 77.2, 125.9, 128.8, 128.9, 130.1, 131.7, 133.2, 138.3, 140.2, 140.9, 142.6; IR (KBr) 3030–3500 cm^{-1} (OH, NH_2); 2971, 2934, 2875 cm^{-1}(CH); Anal. Calcd for $C_{25}H_{29}NO_4S_2$: C, 63.67; H, 6.20; N, 2.79; Found: C, 63.38; H, 6.26; N, 3.04.

*Dibenzo[b,f][1,4]thiazepine (**6a**)*

Yield 43%; mp 115°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15–7.19 (m, 1H), 7.29–7.46 (m, 7H), 8.9 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$)δ 126.9, 127.2, 128.2, 128.8, 129.2, 129.4, 131.4, 131.6, 132.7, 137.2, 139.3, 148.5, 162.2; IR (KBr) 1628 cm^{-1} (C=N); MS (*m/z*) 211 (M^+); Anal. Calcd for $C_{13}H_9NS$: C, 73.90, H, 4.29, N, 6.63; Found: C, 73.52, H, 4.29, N, 6.28.

*11-Methyl-dibenzo[b,f][1,4]thiazepine (**6b**)*

Yield 21%; oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.66 (s, 3H), 7.05 (dt, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 1H), 7.18 (dd, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 1H), 7.24–7.34 (m, 3H), 7.39–7.47 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.5, 125.2, 125.4, 127.8, 128.3, 128.7, 129.0, 130.6, 131.8, 132.3, 139.3, 139.8, 148.6, 169.7; IR (coat) 2921 cm^{-1} (CH), 1628 cm^{-1} (C=N); HRMS Calcd for $C_{14}H_{11}NS$: 225.0612; Found 225.0580.

*11-Eethyl-dibenzo[b,f][1,4]thiazepine (**6c**)*

Yield 58%; mp 67–68°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, J = 7.6 Hz, 3H), 2.94 (dq, J_1 = 7.6 Hz, J_2 = 2.8 Hz, 2H), 7.03 (dt, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 1H), 7.18 (dd, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 1H), 7.23–7.28 (m, 1H), 7.31–7.49 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$)δ 11.5, 35.3, 125.2, 125.2, 127.5, 128.3, 128.7, 129.0, 130.4, 131.8, 132.3, 138.8, 140.5, 148.7, 174.0; IR (KBr) 2970, 2923, 2870 cm^{-1} (CH), 1633 cm^{-1} (C=N); MS (*m/z*) 239 (M^+); Anal. Calcd for $C_{15}H_{13}NS$: C, 75.27; H, 5.47; N, 5.85. Found: C, 74.98; H, 5.49; N, 5.52.

*11-Phenyl-dibenzo[b,f][1,4]thiazepine (**6e**) [2]*

Yield 57%; mp 117°C (Ref [2a] 118°C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06–7.10 (m, 1H), 7.19 (dd, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1H), 7.26–7.50 (m, 8H), 7.56 (dd, J_1 =

7.6 Hz, $J_2 = 0.8$ Hz, 1H), 7.79–7.82 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 125.5, 125.7, 127.7, 128.2, 128.6, 129.0, 129.7, 130.5, 130.6, 131.0, 132.0, 132.4, 137.4, 140.6, 141.0, 148.9, 168.4; IR (KBr) 1612 cm^{-1}(C=N); MS (*m*/*z*) 287 (M^+).

*Preparation of 10-Imino-9-isopropyl-9,10-dihydro-10-λ^4-thioxanthen-9-ol (**3d′**)*

A solution of **3d** (150 mg) in methanol was passed through a column of Amberlite IRA-410 ion-exchange resin (strong base, OH^- form) followed by evaporation of the solvent to give **3d′** (85 mg, 98%); mp 189°C (decomp); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80 (d, $J = 6.8$ Hz, 6H), 1.95 (sept, $J = 6.8$ Hz, 1H), 7.39–7.45 (m, 4H), 7.79–7.82 (m, 2H), 7.92–7.96 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 17.4, 37.7, 77.5, 124.7, 127.4, 128.8, 130.5, 140.2, 142.6; IR (KBr) 3403 cm^{-1}(OH), 3220 cm^{-1}(NH); 2968, 2933, 2872 cm^{-1} (CH); Anal. Calcd for $C_{16}H_{17}NOS$: C, 70.81; H, 6.31; N, 5.16; Found: C, 70.62; H, 6.36; N, 5.05.

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