Synthesis of Unsymmetrically Substituted Benzils *via* the Friedel–Crafts Reaction of Arenes with α -Chloro- α -(methylthio)acetophenones

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Lewis acid-promoted reactions of arenes with α -chloro- α -(methylthio)acetophenones 6–8 gave the Friedel–Crafts reaction products 9, which were then treated with 3 molar eq of cupric chloride in aqueous acetone to afford the unsymmetrically substituted benzils 10.

Keywords Friedel–Crafts reaction; benzil; cupric chloride; α -chlorosulfide; Lewis acid; oxidation; β -ketosulfide; α -diketone; chlorination

In a series of papers,¹⁾ we have shown that the α -chlorosulfides **1** having an electron-withdrawing group (EWG) such as an ethoxycarbonyl group react with arenes in the presence of Lewis acid to give the Friedel–Crafts (F–C) reaction products **2** in excellent yields. In an extension of these reactions, we have now examined the F–C reactions of arenes with a range of α -chloro- α -(methylthio)acetophenones **6–8**. The present paper describes a new convenient synthesis of the unsymmetrically substituted benzils **10** by oxidation of the F–C reaction products **9** with cupric chloride.

The requisite α -chlorosulfides **6–8** were prepared by treatment of the corresponding sulfides **3–5** with *N*-chlorosuccinimide (NCS). When a benzene solution of **6** was treated with a stoichiometric amount of stannic chloride (SnCl_4) at room temperature, the F–C reaction product **9a** ($\text{R}^1 = \text{R}^2 = \text{H}$) was obtained in 75% yield. Similarly the chloride **7** reacted with benzene to afford **9d** ($\text{R}^1 = 4\text{-MeO}$, $\text{R}^2 = \text{H}$) in 69% yield. The reactions of **6–8** with an equimolar amount of electron-rich arenes such as veratrole or 1,3-benzodioxole were performed by using dichloromethane as a solvent to give the corresponding F–C reaction products. The results are summarized in Table I. In the cases of the reactions with 1,3-benzodioxole, the use of SnCl_4 as a Lewis acid sometimes led to the formation of

by-products, so that a milder reagent, titanium tetrachloride (TiCl_4), was employed.

Recently, Caubere *et al.*²⁾ reported that the α -methylthio

Chart 1

TABLE I. F–C Reaction of Arenes with **6–8** and Oxidation of **9** with CuCl_2

R ¹	R ²	F–C reaction of arenes with 6–8				Oxidation of 9	
		Lewis acid	Temp./time (min)	Products		Products	
				No.	Yield (%)	No.	Yield (%)
		SnCl_4	r.t./40	9a	75	10a	99
		SnCl_4	r.t./90	9b	57	10b	83
		TiCl_4	r.t./90	9c	76	10c	90
		SnCl_4	r.t./60	9d	69	10d	70
		SnCl_4	0 °C/60	9e	86	10e	73
		TiCl_4	0 °C/90	9f	93	10f	79
		TiCl_4	r.t./90	9g	62	10g	98

ketones **11**, on treatment with 2 molar eq of cupric chloride (CuCl_2) and 4 molar eq of cupric oxide (CuO) in 1% aqueous acetone, gave directly the α -diketones **13** in good yields. This reaction was suggested to proceed *via* the α -chloro- α -methylthio ketones **12** as intermediates, since CuCl_2 is known to chlorinate the α -position of simple ketones.³⁾ They also found that CuCl_2 alone, in a stoichiometric amount or in excess (a molar ratio was not given), led to a mixture of the starting sulfide **11** and the α -diketone **13**. Actually treatment of the β -ketosulfide **9a** ($\text{R}^1 = \text{R}^2 = \text{H}$) with combined CuCl_2 (2 eq) and CuO (4 eq) gave benzil (**10a**; $\text{R}^1 = \text{R}^2 = \text{H}$) quantitatively, whereas 1 or 2 molar eq of CuCl_2 alone resulted in the formation of a mixture of **9a** and **10a** in a ratio of 1:0.6 or 1:2.4,

Chart 2

Chart 3

respectively. We found, however, that the oxidation of **9a** to **10a** was effected smoothly with 3 molar eq of CuCl_2 alone. Thus, heating of a homogeneous solution of **9a** and CuCl_2 (3 mol eq) in 10% aqueous acetone under reflux for 1 h gave **10a** quantitatively. Similar treatment of the F-C products **9b–g** gave the corresponding unsymmetrically substituted benzils **10b–g** in excellent yields.⁴⁾ The results are summarized in Table I.

Oxidation of **9** to **10** may proceed according to the stoichiometry shown in Chart 3. Thus, the β -ketosulfide **9** is chlorinated with 2 molar eq of CuCl_2 (probably *via* a radical process)⁵⁾ to give the α -chlorosulfide **14**, which is then hydrolyzed with the aid of an additional CuCl_2 giving the benzil **10**: the resultant methyl mercaptan might be oxidized with CuCl_2 to give dimethyl disulfide.

Finally, in order to test the applicability of this method to the synthesis of other α -dicarbonyl compounds, we

Chart 4

TABLE II. Physical Properties and Spectral Data for Compounds **9b–g** and **10b–g**

Compd. No.	mp ($^{\circ}\text{C}$) ^{a)} (lit. mp)	Analysis (%)		Formula	IR cm^{-1} ^{b)}	¹ H-NMR (CDCl_3 , δ)
		Calcd	Found			
		C	H			
9b	Oil	67.52 (67.27)	6.00 (6.15)	$\text{C}_{17}\text{H}_{18}\text{O}_3\text{S}$	1685	2.04 (3H, s), 3.83, 3.85 (3H $\times$ 2, s $\times$ 2), 5.46 (1H, s), 6.7–7.1 (3H, m), 7.2–7.6 (3H, m), 7.85–8.1 (2H, m)
9c	Oil	286.0662 ^{c)} (286.0643)		$\text{C}_{16}\text{H}_{14}\text{O}_3\text{S}$	1690	2.04 (3H, s), 5.40 (1H, s), 5.88 (2H, s), 6.6–7.1 (3H, m), 7.3–7.6 (3H, m), 7.85–8.1 (2H, m)
9d	Oil	70.56 (70.25)	5.92 (6.26)	$\text{C}_{16}\text{H}_{16}\text{O}_2\text{S}$	1680	2.03 (3H, s), 3.75 (3H, s), 5.46 (1H, s), 6.85 (2H, d, $J=9$ Hz), 7.1–7.65 (5H, m), 7.97 (2H, d, $J=9$ Hz)
9e	Oil	332.1081 ^{c)} (332.1063)		$\text{C}_{18}\text{H}_{20}\text{O}_4\text{S}$	1680	2.04 (3H, s), 3.77, 3.80, 3.83 (3H $\times$ 3, s $\times$ 3), 5.44 (1H, s), 6.65–7.1 (5H, m), 7.95 (2H, d, $J=9$ Hz)
9f	Oil	316.0769 ^{c)} (316.0781)		$\text{C}_{17}\text{H}_{16}\text{O}_4\text{S}$	1680	2.04 (3H, s), 3.83 (3H, s), 5.40 (1H, s), 5.93 (2H, s), 6.65–7.1 (5H, m), 7.98 (2H, d, $J=9$ Hz)
9g	Oil	346.0874 ^{c)} (346.0887)		$\text{C}_{18}\text{H}_{18}\text{O}_5\text{S}$	1680	2.03 (3H, s), 3.86 (6H, s), 5.39 (1H, s), 5.89 (2H, s), 6.6–7.05 (4H, m), 7.45–7.7 (2H, m)
10b	111–113 (111–113) ^{d)}				1665	3.93 (6H, s), 6.87 (1H, d, $J=9$ Hz), 7.3–7.7 (5H, m), 7.8–8.1 (2H, m)
10c	104–106	70.86 (70.51)	3.96 (4.00)	$\text{C}_{15}\text{H}_{10}\text{O}_4$	1665	6.00 (2H, s), 6.80 (1H, d, $J=9$ Hz), 7.25–7.65 (5H, m), 7.8–8.1 (2H, m)
10d	59–60 (62–63) ^{d)}				1665	3.83 (3H, s), 6.92 (2H, d, $J=9$ Hz), 7.2–7.7 (3H, m), 7.75–8.1 (4H, m)
10e	121–123 (123–124) ^{d)}				1660	3.88 (3H, s), 3.93 (6H, s), 6.90 (1H, d, $J=8$ Hz), 6.97 (2H, d, $J=9$ Hz), 7.3–7.7 (2H, m), 7.95 (2H, d, $J=9$ Hz)
10f	109–111	67.60 (67.39)	4.25 (4.31)	$\text{C}_{16}\text{H}_{12}\text{O}_5$	1660	3.86 (3H, s), 6.04 (2H, s), 6.7–7.1 (3H, m), 7.35–7.6 (2H, m), 7.90 (2H, d, $J=9$ Hz)
10g	152–153	64.97 (64.79)	4.49 (4.53)	$\text{C}_{17}\text{H}_{14}\text{O}_6$	1660	3.95 (6H, s), 6.05 (2H, s), 6.7–7.0 (2H, m), 7.3–7.65 (4H, m)

a) Benzils **10** were recrystallized from ethanol except for **10b** (from methanol). b) Measured in CCl_4 for **9b–g** and in CHCl_3 for **10b–g**. c) High-resolution MS (M^+). d) Ref. 9 for **10b**, ref. 4a for **10d**, and ref. 10 for **10e**.

treated the α -methylthio carbonyl compounds **15a–c** with 3 molar eq of CuCl_2 . The oxidation of **15a** occurred smoothly to give the α -diketone **16a** in 91% yield, whereas the reactions of **15b–c** with CuCl_2 were very sluggish, and prolonged heating of the mixture afforded a complex mixture of products. On the other hand, the 3-(methylthio)-oxindole **17** gave *N*-methylisatin (**18**) in 89% yield. These results suggest that the chlorination of α -methylthio carbonyl compounds with CuCl_2 proceeds *via* their enol forms.

Experimental

Melting points are uncorrected. Infrared (IR) spectra were recorded with a JASCO A-100 spectrophotometer. Proton nuclear magnetic resonance ($^1\text{H-NMR}$) spectra were determined with a JEOL JNM-PMX 60 (60 MHz) spectrometer using tetramethylsilane as an internal standard. High-resolution mass spectra (MS) were obtained with a Hitachi M-80 instrument at 20 eV. Column chromatography was performed on Silica gel 60 PF₂₅₄ (Merck) under pressure.

General Procedure for the Preparation of α -Chlorosulfides 6–8 *N*-Chlorosuccinimide (0.68 g, 5 mmol) was added to a stirred solution of **3**,⁶⁾ **4**,⁶⁾ or **5**⁶⁾ (5 mmol) in CCl_4 (50 ml) at 0 °C and the stirring was continued at room temperature for 24 h. The precipitated succinimide was filtered off and the filtrate was concentrated *in vacuo* to give quantitatively the chlorosulfides **6**, **7**, and **8**, respectively, which, without further purification, were used immediately in the next step or stored in a refrigerator.

General Procedure for the Preparation of α -Methylthio Ketones 9a–g Method A: SnCl_4 (261 mg, 1 mmol) was added to a stirred solution of **6** or **7** (1 mmol) in benzene (3 ml) at 10 °C and the stirring was continued at room temperature for 40–60 min. Water (10 ml) was added to the reaction mixture and the organic layer was separated. The aqueous layer was further extracted with benzene and the combined organic layers were dried. The solvent was removed by evaporation and the residue was chromatographed on silica gel (hexane:ethyl acetate=7:3) to give **9a**⁷⁾ (75%) and **9d** (69%), each as an oil. The physical data of **9d** are listed in Table II.

Method B: The Lewis acid (1 mmol) indicated in Table I was added to a stirred solution of **6–8** (1 mmol) and an arene such as veratrole or 1,3-benzodioxole (1 mmol) in CH_2Cl_2 (15 ml) at 0 °C and stirring was continued at the temperature indicated in Table I for 60–90 min. The reaction was quenched by the addition of water (10 ml) and the mixture was worked up to give the F–C reaction products **9b**, **c**, **e–g**, whose yields and physical data are listed in Tables I and II, respectively.

Benzil (10a): General Procedure for the Preparation of Unsymmetrically Substituted Benzils Cupric chloride dihydrate (303 mg, 1.78 mmol) was added to a solution of **9a** (153 mg, 0.59 mmol) in acetone (3.6 ml) and water (0.4 ml) and the mixture was heated under reflux for 1 h. After completion of the reaction (the green color of cupric ion faded), the reaction mixture was diluted with benzene (20 ml) and dried over MgSO_4 (3 g). The inorganic materials were removed by filtration, the filtrate was concentrated *in vacuo*, and the residue was chromatographed on silica gel (hexane:ethyl acetate=9:1) to give **10a** (123 mg, 99%), mp 91–92 °C (from ethanol)

(lit.^{4a)} mp 94–95 °C). IR $\nu_{\text{max}}^{\text{CCl}_4}$ cm^{-1} : 1675. $^1\text{H-NMR}$ (CDCl_3) δ : 7.2–7.7 (6H, m), 7.85–8.15 (4H, m). The yields and physical data of unsymmetrically substituted benzils **10b–g** are listed in Tables I and II, respectively.

1-Phenyl-1,2-propanedione (16a) Using a procedure similar to that described for the preparation of **10a**, 1-methylthio-1-phenyl-2-propanone (**15**)^{1b)} (204 mg, 1.13 mmol) was treated with $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ (579 mg, 3.39 mmol) to give **16a** (153 mg, 91%) as an oil, whose spectral data were identical to those of an authentic sample purchased from Wako Pure Chemical Industries, Ltd. IR $\nu_{\text{max}}^{\text{CCl}_4}$ cm^{-1} : 1710, 1670. $^1\text{H-NMR}$ (CDCl_3) δ : 1.50 (3H, s), 7.3–7.9 (3H, m), 7.9–8.2 (2H, m).

1-Methyl-1H-indole-2,3-dione (18) Using a procedure similar to that described for the preparation of **10a**, 1-methyl-3-(methylthio)oxindole (**17**)^{1d)} (100 mg, 0.52 mmol) was treated with $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ (265 mg, 1.55 mmol) to give **18** (75 mg, 89%), mp 128–129.5 °C (from ethanol), (lit.⁸⁾ mp 131–113 °C). IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 1730. $^1\text{H-NMR}$ (CDCl_3) δ : 3.25 (3H, s), 6.8–7.3 (2H, m), 7.45–7.8 (2H, m).

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