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Coupling Reactions of 2-Aryl-1,3-dithiolane-S-oxides with MeMgI

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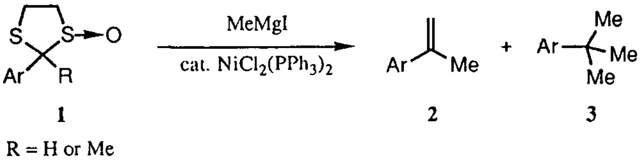
ABSTRACT

Reactions of 2-aryl-1,3-dithiolane-S-oxides **1** *with MeMgI in refluxing benzene-ether furnish a useful procedure for introducing the isopropenyl group. The reaction may proceed via a fragmentation-coupling process leading to the alkylative olefination product.*

INTRODUCTION

We recently reported a series of new synthetic applications of the dithioacetal functionality [1]. To illustrate, dithioacetals react with Grignard reagents in the presence of a catalytic amount of a nickel catalyst to give the corresponding olefins in good yields [2]. It has been reported that, upon treatment with Grignard reagents, sulfoxides which bear an α-hydrogen atom undergo a Pummerer-type rearrangement, the product of which, in turn, reacts with excess Grignard reagent to form a thioether [3]. Based on this strategy, we have recently found that 2-aryl-1,3-dithiolane-S-oxides **1** (R = H) undergo a tandem Pummerer type rearrangement and nickel-catalyzed cross-coupling reaction leading to the formation of the isopropenyl derivative **2** in addition to a small amount of **3** (Equation 1) [4]. Interestingly, the reactions of 2-aryl-2-methyl-1,3-dithiolane-S-oxides **1** (R = Me) under the same conditions also give a mixture of **2** and **3** [4]. The isolation of ethanedithiol as its dibenzyl thioether from both reactions suggests that this reaction proceeds via a dithioacetal intermediate **4**. It is well documented that an alkyllithium can promote fragmentation of the dithiolane moiety to give a mercaptan [5]. A recent report has shown that, upon treatment with a strong base such as LDA, 1,3-dithiolane-S-oxides furnish the corresponding thioketones via a similar process [6]. Since a thioketone can also react with the Grignard reagent [7], we felt that 1,3-dithiolane-S-oxides **1** may also undergo a similar fragmentation, a product of which may further react with the excess Grignard reagent leading to the olefinic products. We now report the reaction of **1** with Grignard reagents and also suggest a plausible mechanism.



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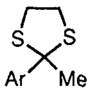

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RESULTS AND DISCUSSION

Treatment of 2-aryl-1,3-dithiolane-S-oxides **1a–d** with 5 equiv of MeMgI in refluxing benzene-ether for 16 hours followed by usual workup afforded a mixture of **2**, **3**, and **4**. When each 2-aryl-2-methyl-

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[†] Dedicated to Professor Yao-Zeng Huang on the occasion of his eightieth birthday.

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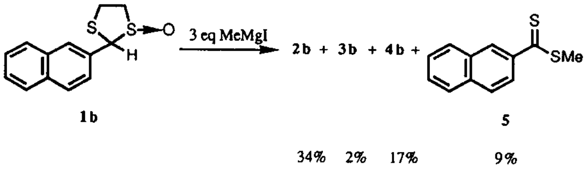
TABLE 1 Reactions of **1a–h** with MeMgI

Ar	*R*	*%Yield*		
1a 1-Naphthyl	H	**2a** 56	**3a** 2	**4a** 14
1b 2-Naphthyl	H	**2b** 57	**3b** 3	**4b** 17
1c 4-MeC_6H_4	H	**2c** 52	**3c** 4	**4c** 17
1d 4-$MeOC_6H_4$	H	**2d** 55	**3d** 6	**4d** 19
1e 1-Naphthyl	Me	**2a** 66	**3a** 1	
1f 2-Naphthyl	Me	**2b** 72	**3b** 2	
1g 4-MeC_6H_4	Me	**2c** 63	**3c** 3	
1h 4-$MeOC_6H_4$	Me	**2d** 68	**3d** 3	

1,3-dithiolane-S-oxide **1e–h** was allowed to react with 3 equiv of MeMgI under similar conditions, a styrene **2a–d** was obtained in moderate yield in addition to a small amount of a *tert*-butyl product **3a–d** respectively. The results are tabulated in Table 1.

The results of the present study and those of our previous work [4] suggest that 2-aryl-1,3-dithiolane-S-oxides **1a–d** react with the Grignard reagent in the presence or absence of the nickel catalyst to give the same products **2** and **3**. The isolation of **4** from the reactions of **1a–d** indicates that the Pummerer rearrangement, followed by the coupling process, occurred [4]. Furthermore, this observation provides direct evidence to show that the nickel-catalyzed reactions of **1a–d** proceed via intermediate **4** which undergoes the nickel-catalyzed cross-coupling reactions with Grignard reagents to give **2** and **3** [1a,2,4]. It is noted that no further reaction of **4** with MeMgI could occur in the absence of the nickel catalyst. Consequently, the reactions with the nickel catalyst and without the nickel catalyst may occur via different mechanisms.

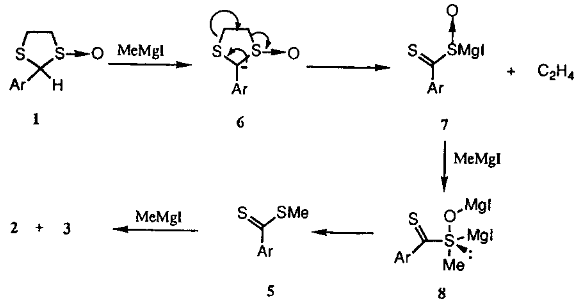
In order to verify the actual mode of the reaction, sulfoxide **1b** was treated with 3 equiv of MeMgI in benzene-ether under reflux conditions for 4 hours. In addition to the expected products, **2b**, **3b**, and **4b**, thioester **5** was obtained in 9% yield (Equation 2). It is worthy of note that the reaction of **5** with MeMgI afforded **2b** and **3b** in 68 and 4% yields, respectively (Equation 3).



(2)

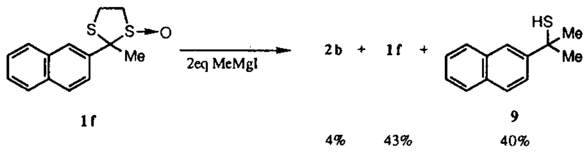
$$5 \xrightarrow[\text{3eq MeMgI}]{} \underset{68\%}{2b} + \underset{4\%}{3b} \qquad (3)$$

The formation of thioester **5** indicates that fragmentation of the anion **6** may occur (Equation 4) [8]. Indeed, the ethylene thus formed was trapped as 1,2-dibromoethane in 65% yield. The transformation of the sulfoxide intermediate **7** into thioester **5** may take place via **8** in a manner similar to that suggested in a related system [9,10].



(4)

Since there is no acidic proton at the C-2 position in **1e–h**, deprotonation with the Grignard reagent may occur at the C-4 position. Accordingly, when **1f** was treated with 2 equiv of MeMgI in refluxing benzene-ether for 2 hours and the reaction mixture was worked up as usual, in addition to **2b** and the recovered **1f**, thiol **9** was obtained in 40% yield (Equation 5). We have established that the reaction of **9** with MeMgI under our normal conditions afforded a 33:1 mixture of **2b** and **3b** in 68% yield. The sulfur moiety from the reactions of **1f** and **9** has been trapped as dibenzyl sulfide **10**. Based on these results, a plausible mechanism is proposed (Equation 6). Fragmentation of the anion **11** may lead to intermediate thione **12** which further reacts with MeMgI to give, via mercaptide anion **13**, a mixture of **2** and **3**.



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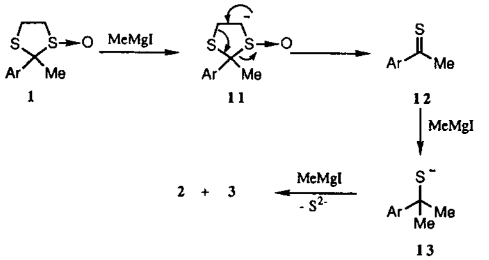

(6)

Since both **1a–d** and **1e–h** gave similar **2** to **3** ratios, the same intermediate **12** may be involved in both types of reaction. In other words, the reaction of **5** with MeMgI may lead to thione **12** which further reacts with the Grignard reagent to give **2** and **3**. It is well documented that the reaction of a thione with Grignard reagents can give C-alkylated and/or S-alkylated products, and only MeMgI yields products having the attacking nucleophile attached to the original thiocarbonyl carbon atom [7]. Indeed, when **1f** was treated with EtMgBr or Me_3SiCH_2MgCl, a complex mixture of products was obtained. These results are consistent with the involvement of a thione intermediate **12**. Nevertheless, the isolation of **3** from these reactions and from the reaction of thiol **9** with MeMgI is somewhat striking. Further investigation is required to elucidate the actual mode of the reaction leading to the formation of **3**.

In summary, our results have shown unambiguously that the reactions of 1,3-dithiolane-S-oxides with Grignard reagents proceed via two different pathways to give the same product(s). In the presence of the nickel catalyst, tandem Pummerer-type rearrangement and nickel-catalyzed alkylative olefination readily occur. In the absence of the nickel catalyst, deprotonation followed by a fragmentation-coupling process leading to the alkylative olefination product occurs.

EXPERIMENTAL

Melting and boiling points are uncorrected. ^1H NMR spectra were obtained on a Bruker AC200 (200 MHz) NMR spectrometer. Chemical shifts are reported in the δ scale using tetramethylsilane as the internal standard, and deuteriochloroform was used as the solvent. The ^{13}C NMR spectra were recorded on a Bruker AC200 spectrometer operating at 50 MHz using deuteriochloroform (δ 77.0) as the internal standard. Mass spectral data (MS) were obtained on a Finigan TSQ-16C mass spectrometer or a JEOL JMS-HX110 mass spectrometer. Preparative GC was operated on a Hitachi G-3000 gas chromatograph using a 30% SE30 stationary phase (6 ft).

General Procedure for the Reaction of 1,3-Dithiolane-S-Oxide (1a–h) with MeMgI

In one portion, MeMgI (2 M solution in Et_2O, 5 mmol for **1a–d** or 3 mmol for **1e–h**) was added to a solution of 1,3-dithiolane-S-oxide (1.0 mmol) and benzene (10 mL) under a nitrogen atmosphere. The mixture was refluxed for 16 hours, then poured into saturated NH_4Cl solution and extracted with Et_2O (3 × 20 mL). The combined extracts were washed with water and brine and then dried ($MgSO_4$). The solvent was evaporated in vacuo and the residue was chromatographed on silica gel (hexane/EtOAc, 49:1) to afford **2** and **3**. Separation of **2** from **3** was achieved using preparative GC on a 6 ft 30% SE 30 column.

Isolation of Methyl Naphthalene-2-dithiocarboxylate (5) from the Reaction of **1b** *with MeMgI*

In one portion, MeMgI (1.5 mL, 2 M solution in Et_2O, 3.0 mmol) was added to a solution of **1b** (248 mg, 1.00 mmol) in benzene (10 mL) under a nitrogen atmosphere. The mixture was refluxed for 4 hours, cooled to room temperature, poured into water (10 mL), and extracted with Et_2O (3 × 20 mL). The combined extracts were washed with water and brine and dried ($MgSO_4$). The solvent was evaporated in vacuo, and the residue was purified by column chromatography on silica gel (hexane/EtOAc, 99:1) to give a mixture of **2b**, **3b** (61 mg, 36%, **2b**:**3b** = 21:1), and **4b** (42 mg, 17%). In addition, **5** was obtained (20 mg, 9%), mp: 85–86°C; ^1H NMR δ 2.82 (s, 3 H), 7.48–7.57 (m, 2 H), 7.78–8.06 (m, 4 H), 8.51 (bs, 1 H); ^{13}C NMR δ 20.7, 124.5, 126.6, 126.9, 127.7, 128.0, 129.7, 132.5, 135.3, 142.3, 228.7; accurate mass calcd for $C_{12}H_{10}S_2$ 218.0224, found 218.0203.

Reaction of **5** *with MeMgI*

According to the general procedure, **5** (219 mg, 1.00 mmol) was allowed to react with MeMgI (1.5 mL, 3.0 mmol) in benzene to give a 17:1 mixture of **2b** and **3b** (122 mg, 72%).

Isolation of 1,2-Dibromoethane from the Reaction of **1b** *with MeMgI*

In one portion, MeMgI (2.5 mL, 2 M solution in Et_2O, 5.0 mmol) was added to a solution of **1b** (248 mg, 1.00 mmol) and benzene (10 mL) under a nitrogen atmosphere. The mixture was refluxed for 16 hours, and the gaseous product was led to a trap containing bromine in CCl_4. The CCl_4 solution was then subjected to NMR analysis. The yield of 1,2-dibromoethane was 65%.

Isolation of Thiol 9 from the Reaction of **1f** *with MeMgI*

In one portion, MeMgI (1.0 mL of a 2 M solution in Et_2O, 2.0 mmol) was added to a solution of **1f** (264 mg, 1.01 mmol) and benzene (10 mL) under a nitrogen atmosphere. The mixture was refluxed for 2 hours, cooled to room temperature, poured into water (10 mL), and extracted with Et_2O (3 × 20 mL). The combined extracts were washed with water and brine and dried ($MgSO_4$). The solvent was evaporated in vacuo, and the residue was chromatographed on silica gel (hexane/EtOAc, 49:1) to give **2b** (7 mg, 4%), recovered **1f** (114 mg, 43%), and **9** (82 mg, 40%), ^1H NMR δ 1.93 (s, 6 H), 2.29 (s, 1 H), 7.41–7.53 (m, 3 H), 7.78–7.89 (m, 4 H); ^{13}C NMR δ 34.2, 46.0, 122.7, 125.0, 125.9, 126.1, 127.4, 127.9, 128.1, 132.1, 133.0, 145.8; MS *m/z* (relative intensity) 202 (M^+, 29), 188 (12), 169 (100), 155 (22); accurate mass calcd for $C_{13}H_{14}S$ 202.0816, found 202.0819.

Isolation of Dibenzyl Sulfide **10** *from the Reaction of* **9** *with MeMgI*

In one portion, MeMgI (1.0 mL, 2 M solution in Et_2O, 2.0 mmol) was added to a solution of **9** (198 mg, 0.98 mmol) and benzene (10 mL) under a nitrogen atmosphere. The mixture was refluxed for 16 hours and then treated with 10% aqueous NaOH (3.0 mL) and benzyl bromide (400 mg, 2.3 mmol). The mixture was refluxed for 4 hours, cooled to room temperature, poured into water (10 mL), and extracted with Et_2O (3 × 20 mL). The combined extracts were washed with water and brine and dried ($MgSO_4$). The solvent was evaporated in vacuo, and the residue was chromatographed on silica gel (hexane/EtOAc, 49:1) to give a 33:1 mixture of **2b** and **3b** (112 mg, 68%) and **10** (101 mg, 48%), mp: 47–48°C (Ref. [11] 49°C).

Isolation of **10** *from the Reaction of* **1f** *with MeMgI*

In one portion, MeMgI (1.5 mL of a 2 M solution in Et_2O, 3.0 mmol) was added to a solution of **1f** (262 mg, 1.00 mmol) and benzene (10 mL) under a nitrogen atmosphere. The mixture was refluxed for 16 hours and then worked up in a similar manner as that described above to give a 35:1 mixture of **2b** and **3b** (124 mg, 72%) and **10** (106 mg, 50%).

ACKNOWLEDGMENT

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