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# α-(Phenylthio)cyclopropylation of Carbonyl Compounds: Preparation of α-Cyclopropyl Ketones.

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***Abstract:*** α-Chloro-α-(phenylthio)cyclopropane and α-acetoxy-α-(phenylthio)cyclopropane were found to react with the silyl enol ethers of some ketones in the presence of Lewis acid in dichloromethane to provide α-(phenylthio)cyclopropyl ketones, which were subjected to reduction with Ra-Ni to give the corresponding α-cyclopropyl ketones. © 1997 Elsevier Science Ltd.

Few methods for α-cyclopropylation of carbonyl compounds and esters have appeared in the literatures, which involve the reactions of (π-allyl)palladium complexes with enolate anions of carbonyl compounds and esters.[2-4] Lack of such general methods prompted us to search for a new entry to α-cyclopropyl carbonyl compounds. By taking advantage of α-alkylthioalkylation methods based on the reactions of α-thiosubstituted electrophiles with silyl enol ethers or esters,[5] we studied the possibilities of generating cyclopropyl thionium ion intermediate **2**[6] from α-chloro and α-acetoxy (phenylthio)cyclopropanes **1a**[7] and **1b**[8,9] and its reaction with silyl enol ethers **3** expecting to obtain the desired α-(phenylthio)cyclopropyl ketones **4**.

At the beginning of our investigation, the reactions of silyl enol ether **3a** with α–chlorosulfide **1a** in the presence of various Lewis acids were examined. It was found that treatment of a mixture of **1a** (1 equiv) and **3a** (1 equiv) with $TiCl_4$ (1 equiv) in $CH_2Cl_2$ at -20 °C for 4 h afforded the desired product **4a** in 39 % yield accompanied by the recovered starting chlorosulfide **1a** in 40% yield (entry 1). A comparable yield of **4a** (38%) together with 13% of **1a** was resulted when using 1.6 equiv of $TiCl_4$ (entry 2). Lower yields of the expected product **4a** were achieved in 28% and 20% when employing anh. $ZnCl_2$ and $AlCl_3$, respectively (entries 3 and 4). Fortunately, the reaction in the presence of $SnCl_4$ in $CH_2Cl_2$ at -10 °C for 4 h yielded **4a** in 72-75% yield (entries 7-8). The silyl enol ether of cyclopentanone **3b** reacted with **1a** under the same conditions to give only moderate yield (35%) of the desired product **4b**. Extension of this finding by using these standard conditions employing $SnCl_4$ in $CH_2Cl_2$ to other silyl enol ethers **3c**, **3d** and **3f** failed to furnish the expected α-(phenylthio)cyclopropyl compounds of type **4**; the starting chlorosulfide **1a** was mainly recovered (up to 60%) along with a small amount of bis(phenylthio)cyclopropane (3-5%). The same result was observed, when silyl enol ether **3f** was employed. The failure of the above results may be due to rapid decomposition of silyl enol ethers **3c**, **3d** and **3f** under the attempted conditions.

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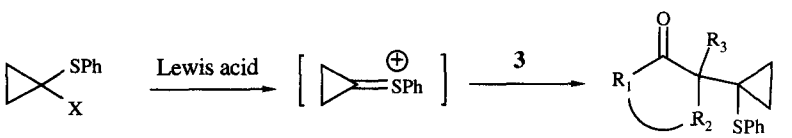
Dedicated to Prof. Dieter Seebach on the occasion of his 60th birthday.

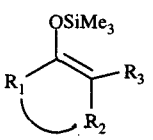
As recently reported by Kraus[10] that α-acetoxysulfides could be employed as convenient reagents for the Lewis acid-catalyzed α-phenylthioalkylation of ketones. We were prompted to turn our attention to investigate the reaction of α-acetoxy-α-(phenylthio)cyclopropane **1b**, expecting to gain a more general and useful α-(phenylthio)cyclopropylating agent for carbonyl compounds. Thus, treatment of α-acetoxysulfide **1b** (1 equiv) with silyl enol ether **3a** in $CH_2Cl_2$ in the presence of $SnCl_4$ (3 equiv) at 0 °C for 4 h gave the desired α-(phenylthio)cyclopropyl cyclohexanone **4a** in 70 % yield after chromatography (entry 10). The reactions of **1b** with silyl enol ethers **3d** and **3e** under the same conditions provided **4d** (47% yield accompanied by 10% of bis(phenylthio)cyclopropane and **4e** (70% yield), respectively (entries 11-12). However, attempts to combine silyl enol ether **3c** with **1b** under the standard conditions were unsuccessful: the starting acetoxysulfide **1b** and cycloheptanone could be partially recovered. This may be due to decomposition of **3c** in the presence of $SnCl_4$. In order to circumvent this difficulty, we therefore examined the reactions of using a milder Lewis acid such as anhydrous $ZnBr_2$. Optimization of the reaction conditions employing $ZnBr_2$ was tried by using silyl enol ether **3d**. Thus, the addition of a mixture of α-acetoxysulfide **1b** (1 equiv) and **3d** (2 equiv) in dry $CH_2Cl_2$ to a suspension of $ZnBr_2$ (1 equiv) in dry $CH_2Cl_2$ followed by stirring at room temperature for 24 to 48 h afforded the expected product **4d** in 58 to 73% yield. A comparable yield of **4d** ( 66%) was achieved, when the reaction mixture was refluxed for 24 h. Extension of these successful conditions of using $ZnBr_2$ as a catalyst was made with other silyl enol ethers. As summarized in the Table 1 (entries 13-17), α-acetoxysulfide **1b** reacted smoothly in the presence of $ZnBr_2$ in good yield. In particular, silyl enol ether **3c** reacted smoothly with **1b** to furnish **4c** (85% yield) in the presence of $ZnBr_2$, while the reaction employing $SnCl_4$ was unsuccessful. Unfortunately, the reactions of silyl enol ethers **3f**, **3g** and **3h** under the same conditions were unsuccessful; α-acetoxysulfide **1b** was mainly recovered.

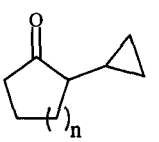


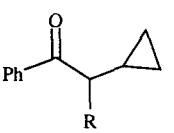

**1a:** X = Cl
**1b:** X = OAc

**2**

**4**




**3a:** $R_1$-$R_2$ = -$(CH_2)_4$- ; $R_3$ = H
**3b:** $R_1$-$R_2$ = -$(CH_2)_3$- ; $R_3$ = H
**3c:** $R_1$-$R_2$ = -$(CH_2)_5$- ; $R_3$ = H
**3d:** $R_1$ = Ph; $R_2$,$R_3$ = H
**3e:** $R_1$ = Ph; $R_2$ = H; $R_3$ = Me
**3f:** $R_1$ = H; $R_2$,$R_3$ = Me
**3g:** $R_1$ = t-Bu; $R_2$,$R_3$ = H
**3h:** $R_1$ = H; $R_2$= H; $R_3$ = $PhCH_2$

**5a:** n = 2 (64%)
**5b:** n = 1 (10%)
**5c:** n = 3 (72%)

**5d:** R = H (26%)
**5e:** R = Me (72%)

Having succeeded in performing the α-(phenylthio)cyclopropylation of carbonyl compounds, it was of interest to demonstrate the synthetic utilities of this reaction as a general method for the preparation of α-cyclopropyl carbonyl compounds. Thus, treatment of α-(phenylthio)cyclopropylcyclohexanone **4a** with Ra-Ni (2.4 equiv) in ethanol at 70 °C for 4 h and at room temperature for 20 h afforded the desired product **5a** along with a small amount of the corresponding alcohol derived from **5a**, as revealed by $^1$H NMR spectrum of the crude product, which was readily oxidized with PCC in $CH_2Cl_2$ at room temperature for 3 h to provide **5a** in 64 % overall yield. Reductive desulfurization of **4c** and **4e** under the same conditions proceeded smoothly to lead to α-cyclopropylcycloheptanone **5c** and propiophenone **5e** in good yields (72% yield in each case). A low yield of **5b** (10%) together with 6% of α-propylcyclopentanone was obtained when the reaction was carried out with **4b**. Similar cleavage of the cyclopropane ring did occur with **4d**. Thus treatment of **4d** under the standard conditions followed by oxidation with PCC in $CH_2Cl_2$ gave α-cyclopropylacetophenone **5d** in 26% yield accompanied by 15% yield of valerophenone.

**Table 1** Reactions of silyl enol ethers **3** with α-chloro and α-acetoxy sulfides **3a** and **3b.**

| Entry | **1** | **3** (equiv) | Lewis acid (equiv) | Conditions [a] | Products **4** (%) [b,c] |
|---|---|---|---|---|---|
| 1 | **1a** | **3a** (1) | $TiCl_4$ (1) | -20 °, 4 h | **4a**, 39 % |
| 2 | **1a** | **3a** (1) | $TiCl_4$ (1.6) | -20 °, 1 h | **4a**, 38 % |
| 3 | **1a** | **3a** (1) | $ZnCl_2$ (1.1) | -20 °, 1 h; 0 °, 1.5 h | **4a**, 28 % |
| 4 | **1a** | **3a** (1.2) | $AlCl_3$ (1) | 0 °, 2 h | **4a**, 20 % |
| 5 | **1a** | **3a** (0.8) | $SnCl_4$ (1) | -20 °, 3 h, | **4a**, 45 % |
| 6 | **1a** | **3a** (0.5) | $SnCl_4$ (2) | -20 °, 2 h, | **4a**, 53 % |
| 7 | **1a** | **3a** (2) | $SnCl_4$ (1) | -10 °, 4 h, | **4a**, 75 % |
| 8 | **1a** | **3a** (2) | $SnCl_4$ (3) | -10 °, 4 h, | **4a**, 72 % |
| 9 | **1a** | **3b** (2) | $SnCl_4$ (1) | -20 °, 2 h, | **4b**, 35 % |
| 10 | **1b** | **3a** (2) | $SnCl_4$ (3) | 0 °, 4 h, | **4a**, 70 % |
| 11 | **1b** | **3d** (2) | $SnCl_4$ (3) | 0 °, 3 h, | **4d**, 47 % |
| 12 | **1b** | **3e** (2) | $SnCl_4$ (3) | 0 °, 3 h, | **4e**, 70 % |
| 13 | **1b** | **3a** (2) | $ZnBr_2$ (1) | RT, 24 h, | **4a**, 78 % |
| 14 | **1b** | **3b** (1.5) | $ZnBr_2$ (1) | RT, 24 h, | **4b**, 86 % |
| 15 | **1b** | **3c** (2) | $ZnBr_2$ (1) | RT, 24 h, | **4c**, 85 % |
| 16 | **1b** | **3d** (2) | $ZnBr_2$ (1) | RT, 24-48 h, | **4d**, 58-73 % |
| 17 | **1b** | **3e** (2) | $ZnBr_2$ (1) | RT, 24 h, | **4e**, 78 % |

a) All reactions were carried out in $CH_2Cl_2$ ( 1 mmol of compound **1** per 10 ml of $CH_2Cl_2$).
b) Yields were calculated based on compound **1**.
c) All products were fully characterized by IR, $^1$H-NMR, MS and elemental analyses.

We found that α-acetoxy-α-(phenylthio)cyclopropane **1b** could serve as a good candidate for α-(phenylthio)cyclopropylating agent, since it could react with most silyl enol ethers of ketones tested. The mechanism for the formation of α-(phenylthio)cyclopropyl ketones **4** proceeded presumably *via* the thionium ion **2**.[11] Reductive cleavage of the phenylthio group of **4** using Ra-Ni afforded α-cyclopropyl ketones **5** in moderate yields.

In conclusion, we have developed a synthetic route for the preparation of α-cyclopropyl ketones by the reaction of α-chloro and α–acetoxy(phenylthio)cyclopropanes with silyl enol ethers of ketones employing Lewis acids as catalysts.

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