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

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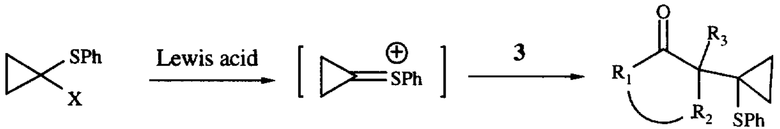
Abstract: α-Chloro-α-(phenylthio)cyclopropane and α-acetoxy-α-(phenylthio)cyclopropane were found to react with the silyl enol ethers of some ketones in the presence of Lewis acid in dichloromethane to provide α-(phenylthio)cyclopropyl ketones, which were subjected to reduction with Ra-Ni to give the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

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

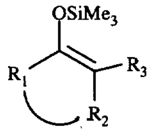
As recently reported by Kraus[10] that α-acetoxysulfides could be employed as convenient reagents for the Lewis acid-catalyzed α-phenylthioalkylation of ketones. We were prompted to turn our attention to investigate the reaction of α-acetoxy-α-(phenylthio)cyclopropane **1b**, expecting to gain a more 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.



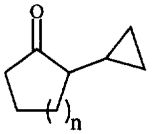
1a:X = Cl
1b:X = OAc

2

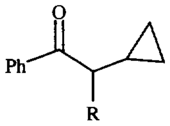
4



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.

References

1. Taken from the M.Sc. thesis of JT, Mahidol University, 1997.
2. Otte, A. R.; Wilde, A.; Hoffmann, H. M. R. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1280.
3. Wilde, A.; Otte, A. R.; Hoffmann, H. M. R. *J. Chem. Soc. Chem. Commun.* **1993**, 615 and references cited therein.
4. Tjaden, E. B.; Stryker, J. M. *J. Am. Chem. Soc.* **1990**, *112*, 6420.
5. Reetz, M. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 96.
6. The cyclopropyl thionium ion intermediate of type **2** has been proposed to occur, see for examples: (a) Bhupathy, M.; Cohen, T. *Tetrahedron Lett.* **1987**, *28*, 4793. (b) Jorritsma, R.; Steinberg, H.; de Boer, T. *J. Recl. Trav. Chim. Pays-Bas* **1981**, *100*, 94. (c) Jorritsma, R.; Steinberg, H.; de Boer, T. *J. Recl. Trav. Chim. Pays-Bas* **1982**, *101*, 288. (d) Ref. 7-9.
7. Masuda, T.; Furukawa, N.; Oae, S. *Chem. Lett.*, **1977**, 1103.
8. Masuda, T.; Numata, T.; Furukawa, N.; Oae,S. *Chem. Lett.* **1977**, 745.
9. Pohmakotr, M.; Sithikanchanakul, S.; Khosavanna, S. *Tetrahedron*, **1993**, *49*, 6651.
10. Kraus, G. A.; Maeda, H. *Tetrahedron Lett.*, **1995**, *36*, 2599.
11. See also, (a) Katritzky, A. R.; Chen, J.; Belyakov, S. A. *Tetrahedron Lett.*, **1996**, *37*, 6631. (b) Hermans, B.; Hevesi, L. *J. Org. Chem.* **1995**, *60*, 6141 and references cited therein.

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