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IMPROVED PREPARATION AND NEW REACTIONS OF β-(1-PHENYLTHIO)CYCLOPROPYL ENONES

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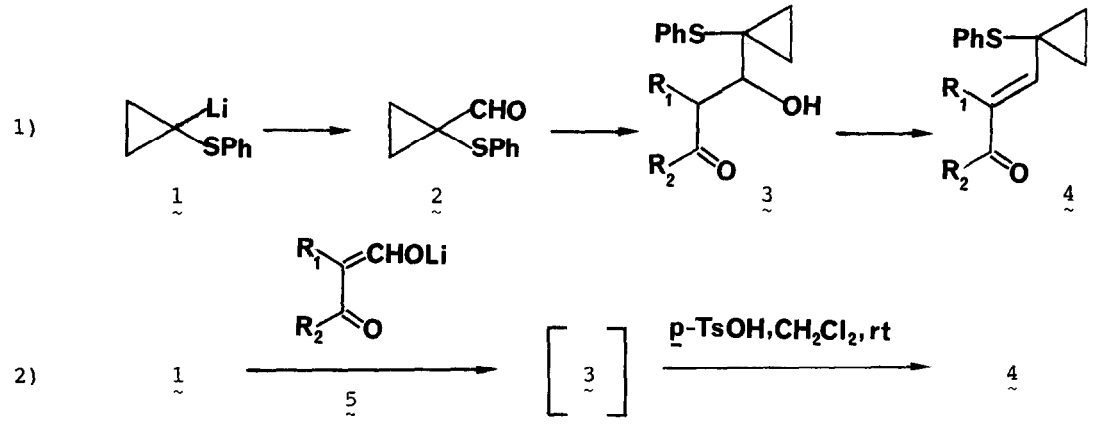
Abstract: β-(1-Phenylthio)cyclopropyl enones can be conveniently prepared via reaction of the lithium salts of α-hydroxymethylene ketones with 1-lithio-1-phenylthiocyclopropane and are converted efficiently by treatment with aqueous acid to γ-keto cyclobutanones and less successfully by thermolysis to γ-keto phenylthiocyclopentenes.

Trost and Jungheim[1] prepared β-(1-phenylthio)cyclopropyl enones (4) by the sequence shown in eq. 1, involving reaction of 1-lithio-1-phenylthiocyclopropane (1) with DMF to form aldehyde 2, which was treated with enolate anions to form aldol products 3, followed by dehydration to 4 by use of $POCl_3$. We report here a much simpler synthesis of β-(1-phenylthio)cyclopropyl enones consisting in treatment of 1 with the lithium salt of α-hydroxymethylene ketones (5), followed by acid catalyzed dehydration of the crude intermediates 3, as indicated in eq. 2.



A representative procedure for the synthesis of E-2-[(1-phenylthio)cyclopropylmethylene]cyclohexanone (6) follows. To a solution of 1.00 g (6.66 mmol) of cyclopropyl phenyl sulfide (Aldrich) in 30 mL of THF at 0°C

under Ar was added 7.3 mmol of n-BuLi and the mixture was stirred for 2 h. The resulting solution of 1 was added via cannula over 10 min to the mixture formed by adding 10.0 mmol of phenyllithium to a solution of 1.22 g (9.7 mmol) of α-hydroxymethylenecyclohexanone[2] in 50 mL of dry THF at -78°C. The resulting mixture was stirred for 2.5 h while the temperature was allowed to rise to 0°C, and then was diluted with water and extracted with ether. The ether extract was washed with water and brine, dried, filtered and evaporated to give an oil (IR: 3415 and 1705 cm^{-1}) which was dissolved in 100 mL of CH_2Cl_2 and 200 mg of p-TsOH·H_2O was added. This mixture was stirred for 16 h at room temperature and then 50 mL of 10% Na_2CO_3 solution was added and stirring was continued for an additional 30 min. The organic layer was dried, filtered, and evaporated to afford a product mixture which was purified by flash chromatography[3] using 65:35 $CHCl_3$:hexane to give 0.22 g (22%) of cyclopropyl phenyl sulfide followed by 1.19 g (89% based on unrecovered cyclopropyl phenyl sulfide) of 6 which was homogeneous by TLC. Recrystallization from MeOH:H_2O gave 6, mp 69-70° (lit.[1] mp 69.5-70°).

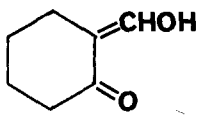
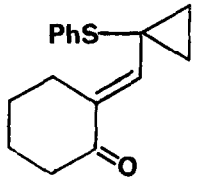
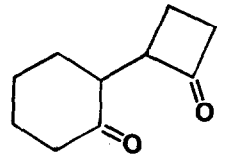
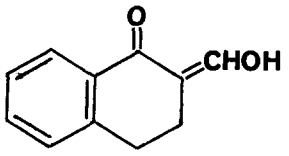
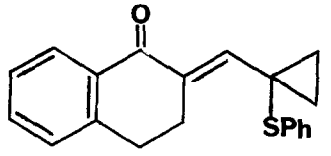
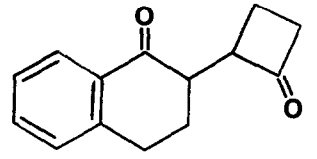
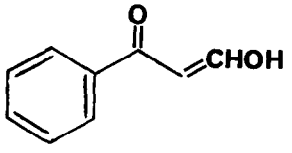
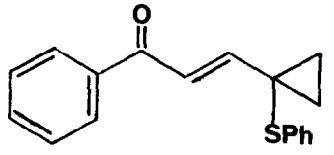
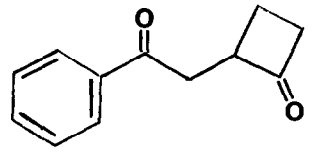
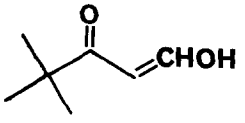
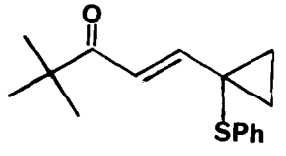
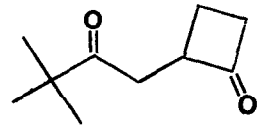
This preparation of 6 and that of three other β-(1-phenylthio)cyclopropyl enones (4) are listed in the Table. Two aspects of this sequence 1+5→3→4 deserve mention. First, 1-lithio-1-phenylthiocyclopropane (1) reacts more efficiently at the α-hydroxymethylene group carbon atom of 5 than do methyl or n-butyl lithium, which give yields of 2-alkylidene ketones which are lower than the yields of 4 from 5.[4] The other point worth noting is the ease of dehydration of 3 to 4 found in the present work, which contrasts with the observations of Trost and Jungheim.[1] They reported that "typical dehydration conditions were unsatisfactory" and developed a procedure involving the use of $POCl_3$ in HMPA-pyridine at elevated temperatures to effect 3→4.[1]

With ready access to β-(1-phenylthio)cyclopropyl enones, it was decided to explore chemistry of these substances which differs from that reported earlier.[1] It was found that compounds 4 are converted to γ-keto cyclobutanones upon treatment with Lewis acids (e.g., $AlCl_3$, $SnCl_4$, $TiCl_4$) in CH_2Cl_2, followed by basic aqueous workup.[5] A more convenient and efficient procedure involves treatment with refluxing 50% aqueous trifluoroacetic acid (ca. 1 mL/10 mg 4). The yields of γ-keto cyclobutanones obtained by this procedure are also listed in the Table. The two conversions summarized in the Table provide convenient access to a wide variety γ-keto cyclobutanones, and it will be of interest to explore further transformations of these compounds, which have been termed "particularly exciting"[1] synthetic intermediates.

The thermal vinyl cyclopropane rearrangement of the β-(1-phenylthio)cyclopropyl enones was also investigated.[6] When 9 was heated in xylene at 305° for 42 min in a sealed, evacuated glass tube, 83% of cyclopentene 14 was obtained. Similar thermolyses of 7 and 8 afforded cyclopentenoid products in 52% and 72% yield respectively. However, these products appeared to be mixtures of double bond isomers (viz., 15 plus 16 and 17 plus 18).[7]

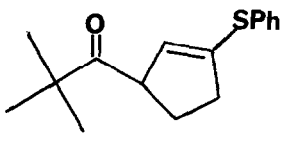
Table

Synthesis of β-(1-Phenylthio)cyclopropyl Enones and Their Conversion To γ-Keto Cyclobutanones[a]

α-Hydroxymethylene Ketone[b]	β-(1-Phenylthio)cyclopropyl Enone Yield[c]	γ-Keto Cyclobutanone Yield[d] (Reaction Time)
		
	6 89%	10 90% (12 h)
		
	7 86%	11 95% (18 h)
		
	8 77%	12 99% (36 h)
		
	9 91%	13 83% (12 h)

[a]Satisfactory combustion analyses and IR and ^{1}H NMR spectra were obtained for all new compounds (7-13). [b]All these known compounds were prepared by the standard procedure in ref. 2. [c]Yields are of purified material and are based on unrecovered cyclopropyl phenyl sulfide. [d]Yields are of purified material. [e]Compound 10 can exist in two diastereomeric forms, but no evidence for the presence of two isomers was observed. [f]Compound 11 was formed as a mixture of two isomers which were separated by MPLC and had mp's of 79-80°C and 70.5-71°C.

Substantial effort was devoted to the analogous thermal rearrangement of enone 6, because the anticipated product 19 has the spiro[4.5]decane skeleton characteristic of several natural products.[8] Barnier and Salaün[5] have in fact recently reported a synthesis of spirovetivane which employed a similar thermal rearrangement of a vinyl 1-(t-butyldimethylsiloxy)cyclopropane. Disappointingly, however, all attempts to effect the conversion 6→19 using either sealed tube or flow tube pyrolyses essentially failed, and at best a 9% yield of incompletely characterized 19 was obtained. The reason for the difference in thermal behavior between 9 and 6 is not apparent.



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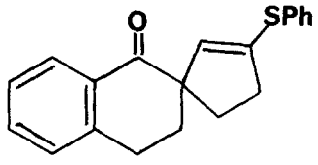

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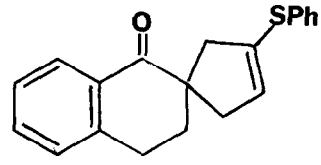

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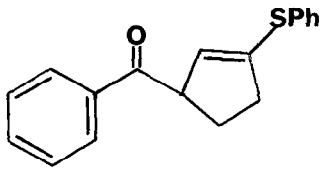

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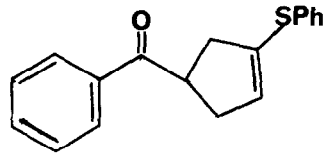

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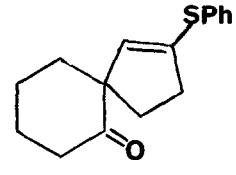

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References and Notes

1. Trost, B.M.; Jungheim, L.N. J. Am. Chem. Soc. 1980, 102, 7910-7925.
2. Ainsworth, C. Organic Syntheses 1963, Coll. Vol. IV, 536-539, Method 2.
3. Still, W.C.; Kahn, M.; Mitra, A. J. Org. Chem. 1978, 43, 2923-2925.
4. Smith, R.A.J.; Spencer, T.A. J. Org. Chem. 1970, 35, 3220-3223.
5. Barnier, J.P.; Salaün, J. Tetrahedron Lett. 1984, 25, 1273-1276 have observed an analogous rearrangement of a β-(1-alkoxy)cyclopropyl enone to a γ-keto cyclobutanone. As would be expected, this occurred under much milder conditions.
6. Vinyl cyclopropane to cyclopentene rearrangements have been effected in systems which possess either an enone moiety (Piers, E.; Banville, J.; Lau, C.K.; Nakagura, I. Can. J. Chem. 1982, 60, 2965-2975) or a phenylthiocyclopropyl moiety (Trost, B.M.; Keeley, D.E. J. Am. Chem. Soc. 1976, 98, 248-250) like those in 6-9.
7. The thermolysis products from 7 and 8 showed two components of almost identical polarity by TLC and showed a broad ill-defined peak at 5.8 and 5.6 ppm respectively in their ^{1}H NMR spectra. Efforts to achieve separation of the supposed isomers failed.
8. For a recent review of synthetic endeavors on spirocyclic sesquiterpenes see: Heathcock, C.H.; Graham, S.L.; Pirrung, M.C.; Plavac, F.; White, C.T. in The Total Synthesis of Natural Products, ApSimon, J. ed., Vol. 5, John Wiley and Sons, New York, 1983, pp. 264-313.

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