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A NOVEL 1,4 CYCLOHEXENONE ANNULATION

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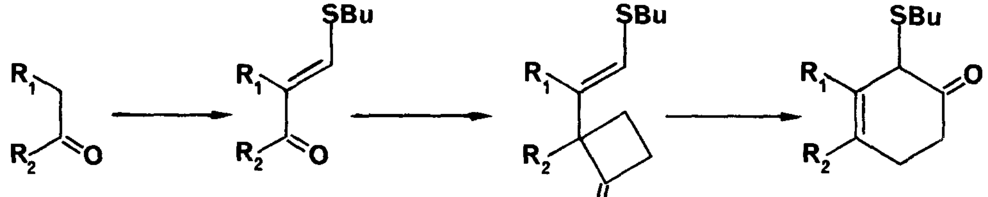
Abstract: A new cyclohexenone annulation has been developed which involves the reaction of α-*n*-butylthiomethylene ketones with 1-lithio-1-methoxycyclopropane to afford α-n-butylthiomethylene spirocyclobutanones which, as their trimethylsilyl cyanohydrins, undergo thermal ring expansion.

During the last decade annulation methods have been developed which yield a cyclohexenone with its carbonyl group in a 1,4 relationship to the carbonyl group of the starting material (a "1,4 annulation"),[1,2,3] in contrast to the 1,3 relationship afforded by the standard Robinson annulation.[4] More recently, cyclohexenol annulations based on vinyl cyclobutanol rearrangements have been reported which also produce such a 1,4 functional group relationship.[5,6] This Letter describes a new 1,4 cyclohexenone annulation comprising the sequence of conversions shown in eq. 1. Like several of the other 1,4 annulations,[1,5,6] this method involves rearrangement of cyclobutane intermediates.

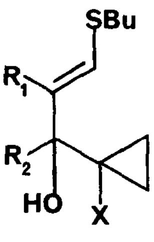
1)



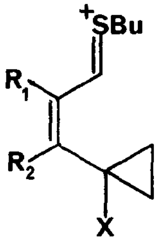
1 2 3

It was thought that a readily available α-hydroxymethylene ketone derivative, e.g. 1, could be used in reaction with a suitable cyclopropane nucleophile (a 3C+3C annulation approach) to afford spirocyclobutanone 2, just as Trost had done with simple enones.[7] It was hoped that conversion of 2 to a derivative which could stabilize negative charge at the carbonyl carbon atom would then permit fragmentation of the four-membered ring to a zwitterionic intermediate which, after reclosure to a six-membered ring and unmasking of the carbonyl group, would lead to 3. 2-Alkylthioenones like 3 have been shown to be useful synthetic intermediates in alkylation reactions.[8]

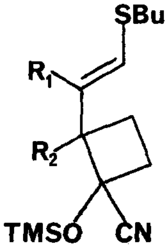
α-*n*-Butylthiomethylene ketones (1) were chosen as reactants because of their well-known proclivity for direct rather than conjugate addition of nucleophiles,[9,10] and because the desired role of sulfur's unshared electrons in promoting fragmentation of an appropriate derivative of 2 had precedent in our furan synthesis involving reaction of 1 with dimethylsulfonium methylide.[10] Reaction of 1 with cyclopropane nucleophiles such as 1-lithio-1-phenylthiocyclopropane[7] appeared to afford the desired adduct 4 efficiently, but rearrangement to 2 could not be effected cleanly, probably because carbocation 5 is more stable than its analog without the sulfur atom.[7] Better results were obtained by use of 1-lithio-1-methoxycyclopropane to produce 6, followed by treatment with 4:1 THF:48% aqueous HBF_4, according to the method of Cohen and Matz.[11] This procedure led, presumably via 7, to formation of spirocyclobutanones 8-10, which were obtained pure after chromatography in the yields listed in the Table.



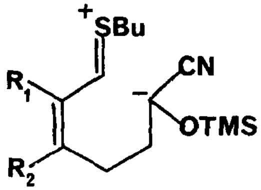
4, X=SPh
6, X=OCH_3



5, X=SPh
7, X=OCH_3



11



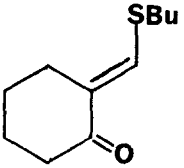
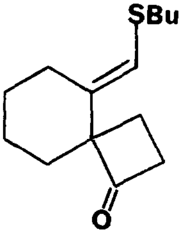
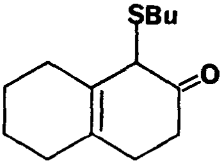
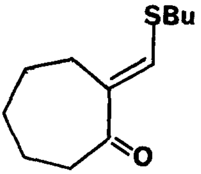
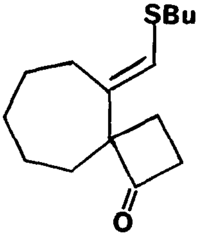
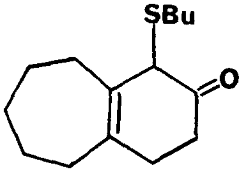
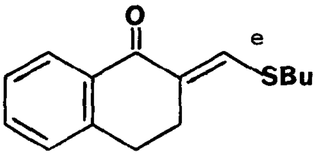
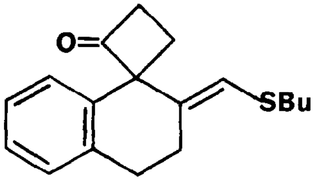
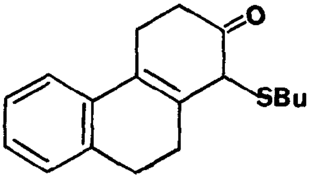
12

The derivative of the cyclobutanones chosen for the ring expansion was the trimethylsilyl cyanohydrin.[12] This derivative has the requisite electron-withdrawing group, and is both easily prepared and readily removed.[12] After formation of trimethylsilyl cyanohydrin 11, it was found that the desired ring expansion could indeed be thermally induced, and the following procedure was developed for effecting the conversion 2→3 without isolation of any intermediates. The spirocyclobutanone (1 g) was mixed with 1.5-2.0 equiv of trimethylsilyl cyanide and 2 mg of ZnI_2.[12] This mixture was stirred under Ar for 2 h at room temperature and then 50 mL of anhydrous diglyme was added. The resulting mixture was heated at reflux for 1.5-3.0 h and then was cooled to -78°C. Ten mL of $nBu_4N^+F^-$ was added and the mixture was stirred for 1 h at -78°C, diluted with ether, and extracted with water to remove the diglyme. The residual oil from the ether layer was purified by MPLC to give the yields of cyclohexenones 13-15 listed in the Table. This ring expansion was conceived as proceeding via zwitterion 12, but there is no evidence for the intermediacy of this species. The fact that 15 is formed more rapidly than 13 or 14 is also consistent with other mechanisms (e.g., diradical).

Under the conditions described above only β,γ-unsaturated ketones 3 were obtained. When the treatment with $nBu_4N^+F^-$ was conducted at room temperature

Table

Synthesis of 2-*n*-Butylthio-Δ^3-cyclohexenones[a]

α-*n*-Butylthiomethylene Ketone	Spirocyclobutanone Yield[b]	Cyclohexenone Yield[b] (Reaction Time[c])
 [d]	8  64%	13  59% (2.5 h)
 [e]	9  35%	14  42% (3.0 h)
 [e]	10  28%	15  36% (1.5 h)

[a] Satisfactory combustion analyses and IR and ^{1}H NMR spectra were obtained for all new compounds (8-10, 13-15).

[b] Yields are of purified material.

[c] Reaction time for the thermal rearrangement of the trimethylsilyl cyanohydrin derivative of the cyclobutanone.

[d] Coates, R.M.; Sowerby, R.L. J. Am. Chem. Soc. 1971, 94, 1027-1029.

[e] Garst, M.E., Ph.D. Dissertation, Dartmouth College, 1973.

for 12 h in one conversion of **8** to **13** in order to see if isomerization to the α,β-unsaturated ketone would occur, there were obtained 32% of **13** and 29% of a product in which cyanide ion had added conjugatively to the α,β-unsaturated isomer.

The overall sequence depicted in eq. 1 produces a 1,4 annulation product with a useful combination of functional groups. However, further work to improve the yields in both steps **1**→**2** and **2**→**3** is desirable.

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