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2-CHLOROETHYL DIMETHYL SULFONIUM IODIDE.
A Convenient Reagent for Spiroannelation of Ketones

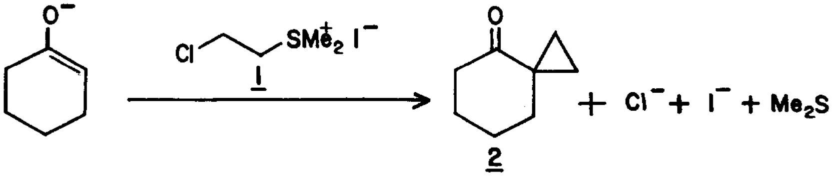
Suzanne M. Ruder and Robert C. Ronald*
Department of Chemistry, Washington State University
Pullman, Washington 99164-4630 U.S.A.

Abstract: Ketones are readily spiroannelated by 2-chloroethyldimethyl sulfonium iodide 1 in the presence of t-butoxide anion in t-butanol. The procedure affords a simple one step spirocyclopropanation of ketones in good yields.

As part of a program of investigation of hydrogen peroxide mediated solvolytic rearrangements of homoallylic and cyclopropylcarbinyl systems[1] we had need to prepare a variety of spiro[2,n]alkan-4-ones (n = 5-11). While there are a number of procedures described in the literature,[2] these either involved multistep preparations or costly reagents, and did not appear to be amenable to a simple and direct method for producing a homologous series of spirocyclopropyl ketones.

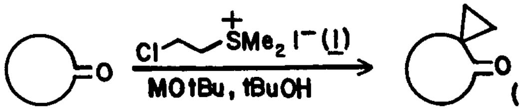
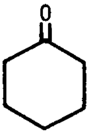
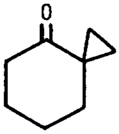
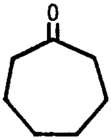
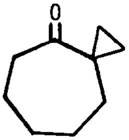
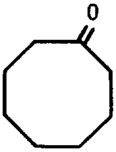
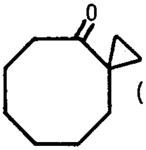
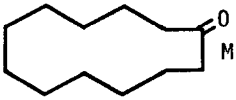
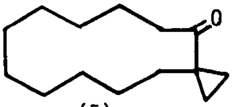
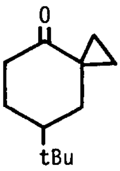
One attractive method for cyclopropanation is the conjugate addition of dimethylsulfoxonium methylide[3] to methylene ketones;[4] however, in our hands when applied to 2-methylene cyclohexanone the yield of spiro[2,5]octan-4-one was very low. Vinylphosphonium[5] and vinyl sulfone[6] reagents have been used in a similar manner to construct polycyclic systems from cyclohexenone enolates. In addition, vinylsulfonium salts[7] have been employed for the spiroalkylation of stabilized enolates.[8] However, the cyclopropanation of ordinary ketones with vinylsulfonium salts or other vinyl reagents has not been reported.

To avoid some of the problems in preparation and stability associated with vinylsulfonium salts,[7,9] we attempted the in situ generation of vinyldimethyl sulfonium salts from haloethyl precursors. With chloroethyl dimethyl sulfonium iodide[7] 1 and excess cyclohexanone enolate we were encouraged to observe formation of spiro[2,5]octan-4-one 2. By careful optimization of the reaction parameters it was found that the best results were



obtained by adding 1 in small portions to a rapidly stirred solution of the ketone and excess t-butoxide in t-butanol. In this way the formation of bis-cyclopropanated material was minimized and yields of spiro[2,n]alkan-4-ones of 40-85% were readily obtained (Table 1).

Table 1[a]

			(Yield)[b]	Bp (mm)	Mp(deriv.)
	M = Na	 (2)	(43%)	65-67°C (15 mm) Lit[2] 80-81°C (28 mm)	
	M = K	 (3)	(70%)	89-90°C (25 mm)	109-110°C (DNP) Lit[10] 110-111°C (DNP)
	M = K	 (4)	(85%)	107-9°C (15 mm)	87-89°C (oxime) Lit[10] 90-91°C (oxime)
	M = K	 (5)		78-80°C (0.02 mm) (50%)	Lit[11] (nmr)
	M = K	 (6)	(51%)	49-51°C (0.02 mm)	

[a] Satisfactory spectral and/or analytical data was obtained for all compounds reported.
[b] Yields are based on consumption of 1.

In a typical procedure KOtBu (20.3 mmoles) was suspended in tBuOH (20 mL) under a N_2 atmosphere and cyclooctanone (10.2 mmole) was added. After 15 min 1 (9.5 mmoles) was added in small portions over a 1 h period. The mixture was allowed to stir overnight after which normal aqueous workup and distillation afforded spiro[2,7]decan-4-one (4) in 85% yield. For the preparation of spirooctanone 2 the procedure was modified in that NaH was used as the base and NaI (0.2 equivalent) was added. Crude 2 was best purified by flash chromatography on silica gel eluted with 5% Et_2O-light petroleum.

Sulfonium reagent 1[7] is readily prepared by treating methyl 2-chloroethyl sulfide[12] with excess MeI for 24-48 h, followed by recrystallization of the crude product from MeOH-Et_2O and drying in vacuo, mp 83-85°C (Lit,[7] mp 82°C). The salt 1 slowly becomes brown upon standing at ambient temperature, but can be stored indefinitely in the freezer under N_2. The salt is non-hydroscopic and sufficiently stable in air for ordinary laboratory operations.

The reaction of 1 with ketones is sensitive to the reaction solvent. Only in tBuOH were we able to consistently achieve useful conversions to spiroannelated products. Reactions in other solvents (THF, DMSO, DMF, MeOH, EtOH) resulted only in recovery of unreacted ketone along with rapid destruction of 1 by the base.

The spiroannelation appears to occur initially by a halide displacement alkylation rather than by an elimination-addition Michael type alkylation involving the vinyl sulfonium species. Support for the direct displacement pathway is provided by the fact that under normal spiroannelation conditions ($tBuO^-$/tBuOH) neither the bromide salt (2-chloroethyl dimethyl sulfonium bromide) or a preformed vinyl reagent (vinyl methylphenyl sulfonium tetrafluoborate[13]) afforded more than traces of spirooctanone 2. The failure of the bromide to undergo spiroannelation suggests that, in fact, the active species is the iodoethylsulfonium salt formed by halide exchange as shown below. Indeed, addition of NaI to the reaction with cyclohexanone resulted in small but significant increases in the yield of 2.

Both the initial alkylation step and the subsequent displacement of dimethyl sulfide during ring closure appear to occur in rapid succession. Experiments run with limited quantities of base showed recovery of unreacted ketone commensurate with the amount of spiroannelated products formed, indicating that the alkylated dimethyl sulfonium intermediate must be rapidly converted to spiro product.

Reagent 1 is a convenient and stable agent for the spiroannelation of ketones. We are currently investigating the reactions of 1 with a variety of substituted as well as unsaturated ketones to further establish the utility of the reagent.

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