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ACID CATALYZED RING OPENING OF α-BIS(METHYLTHIO)METHYLENEALKYL CYCLOPROPYL KETONES: AN INTRAMOLECULAR ALKYLATION APPROACH TO SUBSTITUTED CYCLOPENTANONES[1]

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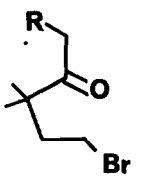
Summary: α-Bis(methylthio)methylenealkyl cyclopropyl ketones 4, prepared by the addition of dimethyloxosulphonium methylide to the respective α-cinnamoylketene dithioacetals 3, undergo facile acid catalyzed intramolecular cyclization with participation of bis(methylthio)methylene double bond to give substituted cyclopentanones 5a-d and 6a-e in good yields.

Cationic ring opening of cyclopropyl ketones has long been of synthetic and mechanistic interest[2]. It has been found, in general, that the ring opening occurs towards that carbon atom, which bears substituents best able to stabilize the positive charge. The resulting incepient carbocation is intercepted either by the external nucleophiles or by intramolecular participation of the neighbouring aryl or olefinic double bond[3]. Lewis acid catalyzed ring opening of rigid cyclopropanes to benzodecalones and other cyclic compounds via concerted intramolecular cyclization through aryl or olefinic π-participation has been reported[3]. Also, a number of aryltetralones and other naturally occurring lignans have been synthesized through acid catalyzed intramolecular 5-endo cyclization of arylcyclopropyl ketones in a non-concerted pathway[4]. These studies together with the reported[5] stereoelectronic bias of γ-haloketones 1 and β-ketoesters 2 for O-alkylation rather than intramolecular C-alkylation to give substituted cyclopentanones, prompted us to synthesize cyclopropyl ketones of the general formula 4 and study their acid catalyzed ring opening. The bis(methylthio)methylene group in 4, as masked ester functionality, is expected to undergo intramolecular π-participation with the developing carbocation during ring opening and the new C-C bond thus formed, would lead to cyclopentanones rather than furan derivatives. The successful realization of this objective is reported herein.



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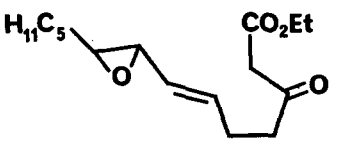

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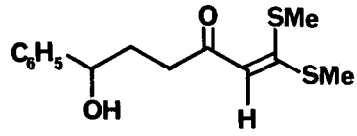
The desired cyclopropanes 4a-j[6] were obtained in nearly quantitative yields by addition of dimethyloxosulphonium methylide to the corresponding α-cinnamoylketene dithioacetals[7]

3a-j in the presence of phase transfer catalyst[8]. When 4a (0.01 mol) was heated in the presence of a mixture of formic and phosphoric acid (20 ml, 3:1 ratio) at 80°C for 1 hr, work-up of the reaction mixture afforded a low melting solid, which was characterized as 3-p-methoxyphenylcyclopentanone[9,10] (5a) (71%). The other methoxy substituted cyclopropyl ketones 4b-c similarly afforded the corresponding cyclopentanones 5b-c[6] in good yields. However the corresponding 4-methyl substituted ketone 4d gave the cyclopentanone 5d[6] in only 37% yield. On the otherhand, the phenyl substituted 4e failed to undergo cyclization under similar conditions and yielded only intractable product mixture, while in the presence of $BF_3.Et_2O$ in nitromethane, the corresponding open-chain alcohol 7 (77%) was isolated. Apparently, the cyclization of 4 to 5 is facilitated in the presence of carbonium ion stabilizing group present in the phenyl ring. When the ketone 4f was subjected to cyclization under identical conditions, the product isolated (81%) was identified as S-methyl-5-(p-methoxyphenyl)-1-methyl-2-oxocyclopentane carbothioate (6a)[11], which on demethylthiocarbonylation[12] in the presence of Raney Nickel yielded the corresponding cyclopentanone 8 (70%). The other α-methyl 4g-h and α, α'-dimethyl 4i-j cyclopropyl ketones similarly yielded the corresponding cyclopentanones 6b-e[6] in 76-80% overall yields[13].

The probable mechanism for the formation of 5 and 6 from 4 is depicted in the Scheme. The initially protonated cyclopropyl ketone after ring cleavage and intramolecular cyclization by participation of bis(methylthio)methylene double bond is transformed into the stabilized carbonium ion 9, which on hydration affords the intermediates 10 or 11. Subsequent cleavage of 10 through loss of dimethyldithiocarbonate affords 5, while the presence of 2-methyl group in 11 probably checks the similar cleavage, to yield 6 through elimination of methylmercaptan[14]. In summary, the present work demonstrates many future possibilities for the construction of more important cyclopentanone derivatives[15] as well as possible scope for reinvestigation of systems that have shown propensity for intramolecular O-alkylation[5] in the light of present findings. Further work in this direction and to explore the synthetic applications of cyclopropanes 4 is in progress.



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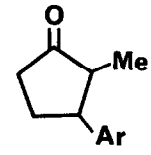
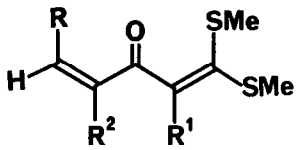
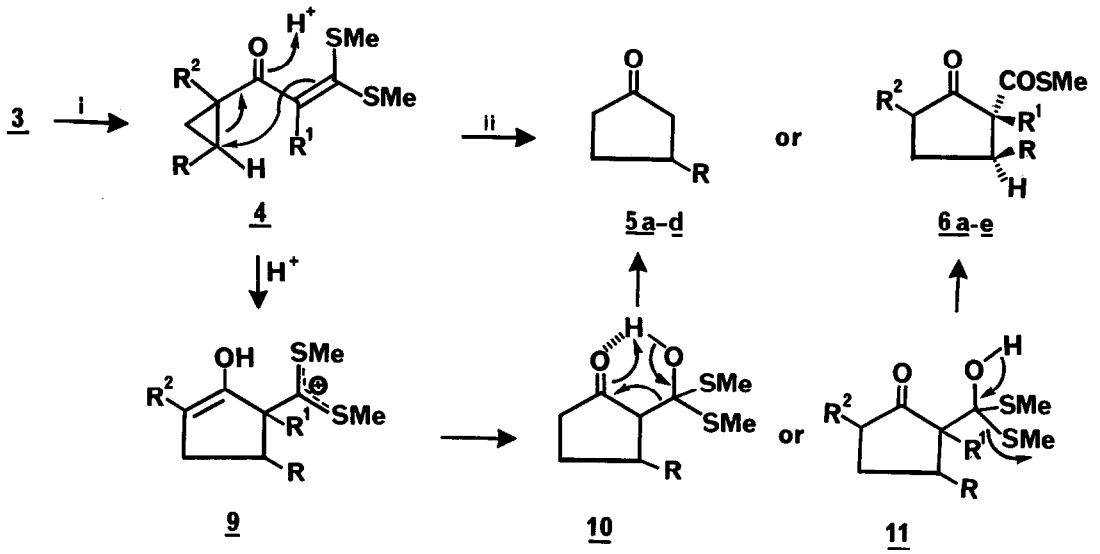


8, Ar = 4-MeOC6H4



3a-j



i $(Me)_3\overset{\oplus}{S}{=}O\ I^{\ominus}$, $(Bu)_4N^{\oplus}I^{\ominus}$, 50% NaOH, CH_2Cl_2 / 50°C

ii HCO_2H/ H_3PO_4/ △, 80°C

Entry		R	R^1	R^2	%Yield (4)	%Yield (5 or 6)
1	3a, 4a, 5a	4-$MeOC_6H_4$	H	H	98	71
2	3b 4b, 5b	3,4-di$MeOC_6H_3$	H	H	98	68
3	3c 4c, 5c	3,4,5-tri$MeOC_6H_2$	H	H	96	72
4	3d, 4d, 5d	4-MeC_6H_4	H	H	94	37
5	3e, 4e, 5e	C_6H_5	H	H	97	—
6	3f, 4f, 6a	4-$MeOC_6H_4$	Me	H	98	81
7	3g, 4g, 6b	3,4-di$MeOC_6H_3$	Me	H	95	76
8	3h, 4h, 6c	3,4,5-tri$MeOC_6H_2$	Me	H	96	78
9	3i, 4i, 6d	4-$MeOC_6H_4$	Me	Me	90	80
10	3j, 4j, 6e	3,4-di$MeOC_6H_3$	Me	Me	88	79

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References and Notes

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8. A. Merz and G. Märk, Angew Chem. Internat. Ed., 12, 845 (1973).
9. 5a: m.p. 47-48°C (lit.[10] 47-48°C); ν_{max} (KBr): 1740cm^{-1}; $\delta_H(CCl_4)$: 1.61-2.50(m,6H,C$\underline{H}_2$); 2.08-3.47(m.1H,ArC$\underline{H}$); 3.75(s,3H,C$\underline{H}_3$O); 6.65-7.20(dd,A_2B_2,4H,Ar$\underline{H}$); m/z: 190(M^+,100%).
10. A.L. Wilds and T.L. Johnson, J. Am. Chem. Soc., 67, 286 (1945).
11. 6a: m.p. 76°C; ν_{max}(KBr): 1738(ring CO); 1665(COSMe) cm^{-1}; $\delta_H(CCl_4)$; 0.98(s,3H,C$\underline{H}_3$); 1.90-2.61(m,4H,C$\underline{H}_2$); 2.30(s,3H,SC$\underline{H}_3$); 3.72(s,3H,OC$\underline{H}_3$); 4.05(t,J=7 Hz,1H,ArC$\underline{H}$); 6.63-7.12(dd,A_2B_2,4H,Ar$\underline{H}$); m/z: 278(M^+4%); 232(M^+-SMe,69%); 203(M^+-COSMe,100%).
12. H-J.Liu, H.K. Lai and S.K. Attah-Poku, Tetrahedron Lett. 20, 4121 (1979).
13. The cyclization of 4f-j was found to be highly stereoselective and only one isomer was obtained in each case. The stereochemistry at C-1 and C-5 in 6a-e is tentatively assigned as E on the basis of their ^{1}H NMR spectra. The absorption due to quaternary methyl group appears at comparatively higher field(δ 0.90-1.0) in agreement with the previous studies on the related system [B.M. Trost and T.A. Runge, J. Am. Chem. Soc., 103, 7550 (1981)]. The significant downfield absorption (δ 4.05-4.15) of benzylic methine proton due to the desheilding by cis methylthiocarbonyl group further supports the assigned stereochemistry.
14. Treatment of 4f with formic and phosphoric acid for prolonged time (10 hr) under identical conditions gave only 6a.
15. Synthesis of substituted cyclopentenones by base catalyzed ring opening and intramolecular cyclization of acyloxycyclopropyl ketone has been reported; E. Wenkert, R.A. Mueller, E.J. Reardon, Jr., S.S. Sathe, D.J. Scharf and G. Tosi, J. Am. Chem. Soc., 92, 7428(1970); J.E. McMurry and T.E. Glass, Tetrahedron Lett., 27, 2575 (1971).

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