PREPARATION OF DIHYDROTHIOPYRAN-3-ONES BY ALDOL CONDENSATION OF DIKETO SULFIDES AND ACID-CATALYZED REARRANGEMENT OF KETOL INTERMEDIATES LEADING TO THIOLAN-3-ONE DERIVATIVES

Juzo Nakayama,* Keiko Hidaka, and Masamatsu Hoshino
Department of Chemistry, Faculty of Science, Saitama University,
Urawa, Saitama 338, Japan

Abstract — Acid-catalyzed intramolecular aldol condensation of diketo sulfides generally affords 2,6-dihydrothiopyran-3-ones and/or their 2,4-dihydro isomers in good yields. The ketol intermediates, in a few cases, undergo sulfur-participated rearrangement to give thiolan-3-one derivatives in addition to dihydrothiopyranones.

Both 2,6-dihydrothiopyran-3-ones (2) and their 2,4-dihydro isomers (3) show antiinflammatory and diuretic properties[1] and may serve as useful synthetic intermediates since they contain carbonyl, double bond, and sulfide functionalities in the molecule.[2] The only reported synthesis of these compounds involves the Friedel-Crafts type cyclization of allylthioglycolic acid chlorides.[3] This method, however, suffers several disadvantages, *e.g.*, relatively low reported yields (30-49%), multistep synthesis of the starting materials, difficulty of introducing diverse substituents, *etc*. Diketo sulfides (1) are readily accessible compounds. Symmetrically substituted 1 are obtained by reaction of α-haloketones with sodium sulfide and unsymmetrically substituted ones from α-haloketones and α-mercapto ketones. As a part of our synthetic study with 1,[4] herein we report the preparation of dihydrothiopyran-3-ones by intramolecular aldol condensation of 1 and acid-catalyzed rearrangement of the ketol intermediates leading to thiolan-3-one derivatives, which is observed with a few cases. During this study, Klein and Horak reported that acid-catalyzed condensation of 2-[(2'-oxopropyl)thio]-cyclopentanone affords a 9:1 mixture of cyclopentano-[*b*]-2,4-dihydrothiopyran-3-one and its 2,6-dihydro isomer.[5]

A mixture of diketo sulfides (1a-e) and a catalytic amount of *p*-toluenesulfonic acid (TsOH)[6] in benzene was refluxed until the starting sulfides are completely consumed (3-8 h). Usual wokup of the mixture afforded the expected dihydrothiopyranones in good yields. Results are summarized in Table 1. Analysis by tlc and ^{1}H-nmr showed that the ketols 4 are first formed with consumption of 1 and then dehydrated to dihydrothiopyranones. Although 2,6-dihydro isomers (2) are almost exclusively formed in runs a and b, both 2,6- and 2,4-dihydro isomers (2 and 3) are formed in runs c-e in comparable yields. The ratio of 2 and 3 observed above is the equilibrium one, since, for example, heating pure 2c with TsOH in boiling benzene affords an isomeric mixture of 2c and 3c in the same ratio as that observed with run c.[7]

Base-catalyzed condensation of 1 easily allows the isolation of the ketols 4. Treatment of 1a with a catalytic amount of potassium hydroxide in aqueous ethanol at room temperature gives the corresponding ketol 4a in 65% yield.

One-pot preparation of dihydrothiopyranones is also possible in some cases though in low yields. For example, when commercially available chloroacetone was allowed to react with sodium sulfide and then the resulting mixture was heated with added potassium hydroxide, 2a was obtained in 22% yield.

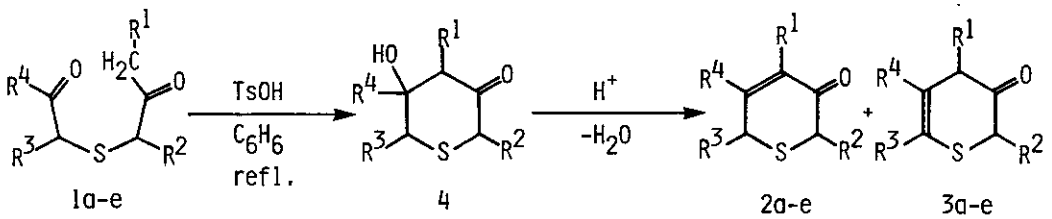
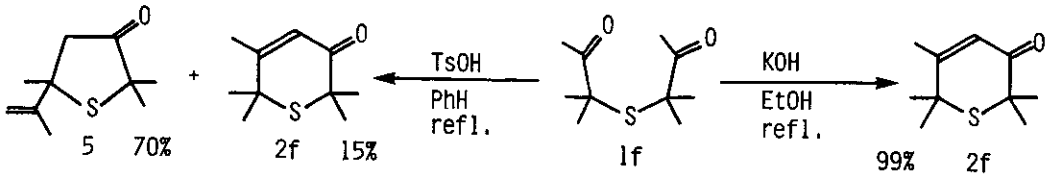


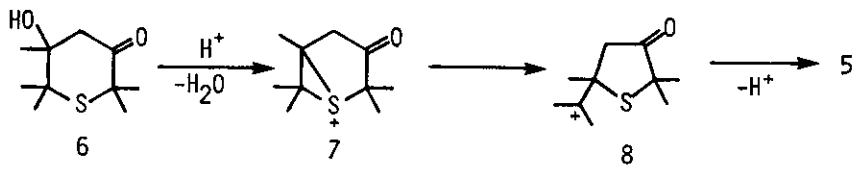
Table 1 Preparation of Dihydrothiopyran-3-ones by Aldol Condensation of Diketo Sulfides

Run	R^1	R^2	R^3	R^4	Yield of 2[a] (%)	Yield of 3[a] (%)	Total Yield (%)
a	H	H	H	Me	79	-[b]	79
b	Me	H	H	Et	96	-[b]	96
c	H	Me	H	Ph	57[c]	36	93
d	H	H	Me	Ph	26	16	42 (74)[d]
e	H	Me	Me	Me	36[c]	45.5	81.5

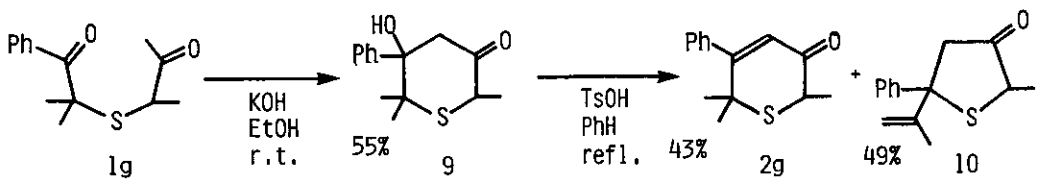
a) Isomers 2 and 3 are separable by silica gel column chromatography. Yields based on isolated products. b) Trace, if any. c) A mixture of *cis* and *trans* isomers. d) Conversion yield.

Heating the diketo sulfide 1f with TsOH in refluxing benzene unexpectedly produced the thiolanone derivative 5[8] (70%) in addition to the dihydrothiopyranone 2f (15%). This provides an interesting example that sulfur participation controls the product formation. The episulfonium ion 7 produced from the ketol intermediate 6 rearranges to the stable tertiary carbonium ion 8, deprotonation of which leads to 5.[9] The dihydrothiopyranone 2f is satisfactorily obtained by base-catalyzed condensation. Heating 1f with potassium hydroxide in refluxing ethanol afforded 2f in 99% yield.





A slightly more complicated case is encountered with the sulfide 1g. The TsOH-catalyzed condensation of 1g gives a complex mixture containing isobutyrophenone as a sole identified product. The KOH-catalyzed reaction in refluxing ethanol again gives a complex mixture, whereas the reaction at room temperature affords the ketol 9 in 55% yield. The ketol 9, when heated with TsOH in boiling benzene, produces the dihydrothiopyranone 2g (43%) and a 1:1 cis-trans mixture of the thiolanone 10[10] (49%). It is thus concluded that the rearrangement leading to thiolanones becomes a prevailing path when the formation of stable tertiary carbonium ions from episulfonium ions is possible.



In summary the aldol condensation of diketo sulfides provides a convenient synthesis of dihydrothiopyranones which are otherwise laborious to prepare and also results in an interesting example of sulfur-participated ring contraction yielding thiolanones in a few cases.

REFERENCES AND NOTES

1. K. Ishikawa and K. Sato, Japanese Patent 7426274 (1974); Chem. Abstr., 81, 77805w (1974).
2. S. Baklien, P. Groth, and K. Undheim, J. Chem. Soc., Perkin Trans. 1, 1975, 2099.
3. K. Sato, S. Inoue, and K. Kondo, J. Org. Chem., 1971, 36, 2077. It was very recently reported that one of two [2+4]cycloadducts of thiobenzophenone and Danishefsky's diene is converted to 2,6-dihydro-6,6-diphenylthiopyran-3-one on acidic workup; T. Katada, S. Eguchi, and T. Sasaki, J. Org. Chem., 1986, 51, 314.
4. J. Nakayama, H. Machida, and M. Hoshino, Tetrahedron Lett., 1985, 26, 1981; J. Nakayama, H. Machida, R. Saito, and M. Hoshino, ibid., 1985, 26, 1983; J. Nakayama, S. Yamaoka, and M. Hoshino, ibid., in press; J. Nakayama, H. Machida, R. Saito, K. Akimoto, and M. Hoshino, Chem. Lett., 1985, 1173; J. Nakayama, H. Motoyama, H. Machida, M. Shimomura, and M. Hoshino, Heterocycles, 1984, 22, 1527; J. Nakayama, M. Shimomura, M. Iwamoto, and M. Hoshino, ibid., 1985, 23, 1907; J. Nakayama, Y. Nakamura, T. Tajiri, and M. Hoshino, ibid., 1986, 24, 637.
5. R. F. X. Klein and V. Horak, J. Org. Chem., 1986, 51, 4644.
6. A considerable amount of TsOH was needed to complete the reaction in run c. In run d, even the use of a large amount of TsOH could not complete the reaction and prolonged heating gave a complex mixture.
7. Factors governing the relative thermodynamic stability of 2 and 3 are not clear, but substituents on C_5 and C_6 seem to stabilize 3 in which conjugation between double bond and sulfur is possible.
8. 5; oil; ^{1}H-nmr ($CDCl_3$) δ 1.41 (3H, s), 1.45 (3H, s), 1.53 (3H, s), 1.91 (3H, m), 2.76 (1H, d, J=16Hz), 3.24 (1H, d, J=16Hz), 4.85 (2H, m).
9. For sulfur-participated ring contraction of six-membered ring to five-membered one, see, for example, E. Block, 'Reactions of Organosulfur Compounds', Academic Press, New York, 1978, Chapter 4.
10. One isomer; ^{1}H-nmr ($CDCl_3$) δ 1.44 (3H, d, J=7Hz), 1.69 (3H, broad s), 2.85 (1H, d, J=18Hz), 3.34 (1H, d, J=18Hz), 3.58 (1H, q, J=7Hz), 5.01 (2H, broad, s), 7.34 (5H, m) and the other isomer; ^{1}H-nmr ($CDCl_3$) δ 1.43 (3H, broad d, J=7Hz), 1.66 (3H, broad s), 3.18 (2H, broad s), 3.52 (1H, broad q, J=7Hz), 4.98 (1H, broad s), 5.13 (1H, broad s), 7.2-7.6 (5H, m).

Received, 13th April, 1987