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A REGIO- AND STEREOSELECTIVE SYNTHESIS OF ALDOLIZED γ-DIKETONES *VIA* TIN(IV) BISENOLATES BY THE USE OF BIS(2-PYRIDINETHIOLATO)TIN(II)

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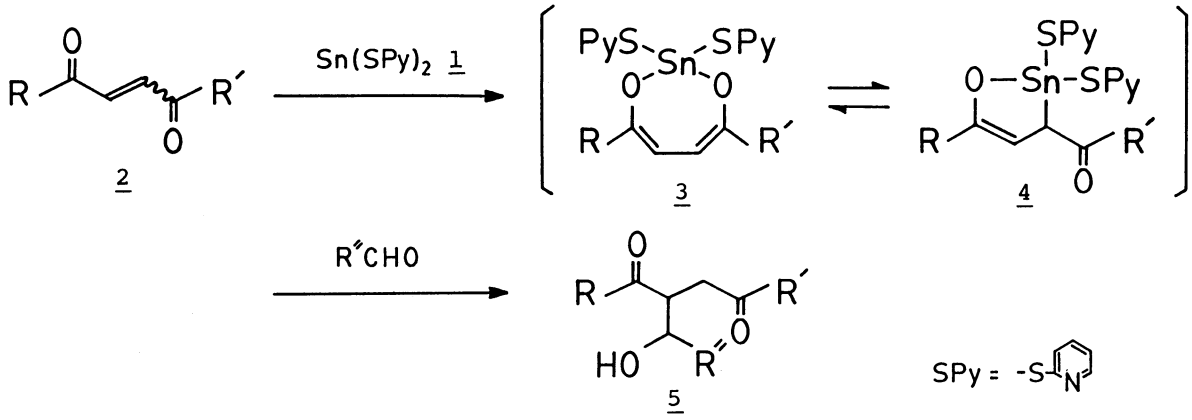
Tin(IV) bisenolates of γ-diketones, generated regioselectively from α,β-unsaturated γ-diketones by the reaction with bis(2-pyridinethiolato)tin(II), react with aldehydes stereoselectively to afford the corresponding aldolized γ-diketones in good yields.

γ-Diketones are valuable synthetic intermediates for further elaboration into natural products and related compounds involving furan or cyclopentenone ring systems.[1] Concerning the preparation of γ-diketones, a variety of synthetic methods have been developed,[2] however, few examples have been reported on the aldol reaction of γ-diketones in an intermolecular fashion, which is one of the fundamental reactions to construct carbon skeleton.[3] This is probably due to the facts that i) even under mild basic conditions γ-diketones are easily cyclized to cyclopentenones *via* intramolecular aldol condensation and dehydration; ii) the diketones have two sets of reaction sites (carbonyl groups) to be controlled. Therefore, a regioselective generation of γ-diketone enolates and their stereoselective aldol reaction are of synthetic value and remain to be effectd.

We have recently reported that bis(2-pyridinethiolato)tin(II) (1) acts as an effective reducing agent for α-dicarbonyl compounds to generate tin(IV) enediolates, which in turn react with aldehydes to give α,β-dihydroxy ketones.[4] These results suggested that this type of enolate generation might be applicable to the above mentioned aldol reaction because it proceeds in a regiocontrolled manner and under non-basic conditions.



On the basis of such an assumption, we next attempted to generate tin(IV) bisenolates of γ-diketones by treatment of 1 with enediones 2 in which two carbonyl groups of a diketone are linked by an ethylenic bond, and then examined the reaction of the bisenolates 3 with aldehydes shown in the above equation.[5] Now, we report here a regio- and stereoselective synthesis of aldolized γ-diketones 5 from α,β-unsaturated γ-diketones 2 and aldehydes by utilizing the reducing power of bis(2-pyridinethiolato)tin(II) (1).

In the first place, 1 was treated with 3-phenylpropanal and 1,4-diphenylbuten-1,4-dione (molar ratio of 1 : enedione : aldehyde = 1.5 : 1 : 1.5) according to the previously described procedure.[4] Usual work-up of the reaction mixture gave the desired aldol product composed of equimolecular amounts of the enedione and the aldehyde in 36% yield, although the Diels-Alder adduct between the enedione and methylcyclopentadiene formed in the preparation of 1 was also isolated as a by-product. Then, in order to prevent the side reaction, methylcyclopentadiene was removed by evaporation from the reaction mixture before the addition of the enedione. Consequently, the yield of the aldol product was raised up to 92%.

On the other hand, it should be pointed out that the attempted reaction of aldehydes with lithium enolates generated from γ-diketones and LDA was unsuccessful under several conditions even when 1,4-diphenylbuten-1,4-dione, which could not be led to a cyclopentenone, was employed.

Next, the reaction between various enediones and aldehydes was examined and results are summarized in Table 1.

These results reveal that i) the reaction of tin(IV) bisenolates with aldehydes takes place on either of two reaction sites, not on both; ii) both from a trans and a cis enedione the same aldol can be obtained with similar diastereoselectivities (Entries 1 and 5; 6 and 7), which suggests that the reactions proceed via the same transition state; iii) the bisenolates are successfully generated on the inner sites exclusively to give the corresponding adducts even in the case of methyl ketones (Entries 6-9); iv) the reaction takes place regioselectively when unsymmetrical enediones are employed (Entries 8 and 9).

A typical procedure is described for the reaction of 1,4-diphenylbuten-1,4-dione and 3-phenylpropanal; to a benzene solution (5 ml) of 1,1′-dimethylstannocene (266 mg, 0.96 mmol) was added 2-mercaptopyridine (214 mg, 1.92 mmol) in solid form at room temperature under an argon atmosphere. After stirring for 30 min at that temperature, the solvent was evaporated *in vacuo*.[7] A dichloromethane solution (4 ml) of 3-phenylpropanal (129 mg, 0.96 mmol) was added to the residue, and then at 0 °C a dichloromethane solution (1 ml) of 1,4-diphenylbuten-1,4-dione (151 mg, 0.64 mmol) was added dropwise. The reaction mixture was further stirred for 18 h at the same temperature, then quenched with pH 7 phosphate buffer. The organic materials were extracted with dichloromethane three times, and the combined extracts were washed with brine and dried over Na_2SO_4. After evaporation of the solvent, 2-(1-hydroxy-3-phenylpropyl)-1,4-diphenylbutan-1,4-dione (219 mg, 92%) was isolated by column chromatography on silica gel (hexane : Et_2O = 2 : 1).

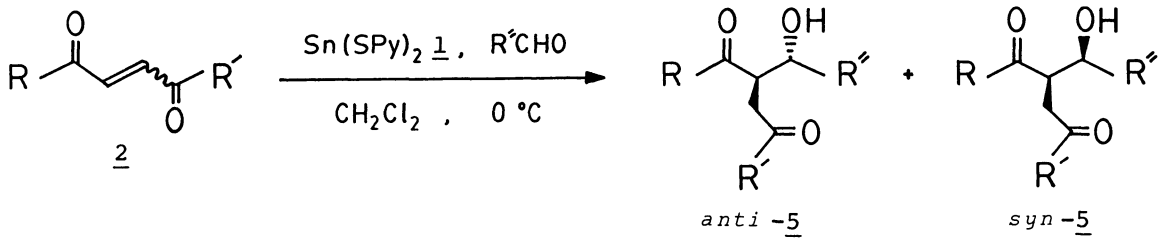


Table 1. Synthesis of Aldolized γ-Diketones[a)]

Entry	R	R′	Geometry of 2	R"	Time/h	Yield of 5/%[b)]	*anti* : *syn*
1	Ph	Ph	*trans*	$Ph(CH_2)_2$	18	92	81 : 19[d,h)]
2				*n*-C_5H_{11}	16	65	90 : 10[d,i)]
3				Ph	18	65	15 : 85[d,f,h)]
4				2-Furyl	16	92	28 : 72[f,i)]
5	Ph	Ph	*cis*	$Ph(CH_2)_2$	20	66	80 : 20[d,h)]
6	Me	Me	*trans*		20	80[c)]	65 : 35[e,i)]
7	Me	Me	*cis*		21	54[c)]	70 : 30[e,i)]
8	Ph	Me	*trans*		17	96[c,j)]	89 : 11[d,i,l)]
9	Me	*t*-Bu	*trans*		86	70[c,k)]	——[g)]

a) Reaction was carried out in CH_2Cl_2 at 0 °C. Molar ratio of 1 : 2 : R"CHO = 1.5 : 1 : 1.5
b) Isolated yield. All samples gave satisfactory ^1H NMR, ^{13}C NMR, and IR spectra.
c) An equilibrium mixture with its corresponding hemiketal, which is easily characterized as the acetate after acetylation (Ac_2O, pyridine, DMAP, 0 °C).
d) Ratio was determined by HPLC analysis of its acetate.
e) Ratio was determined by HPLC analysis of its benzoate.
f) Ratio was determined by ^1H NMR measurement of its acetate.
g) Not determined.
h) Relative configuration was assigned by comparison of NMR spectra with those of authentic sample.[6)]
i) Relative configuration was assigned by analogy of ^{13}C NMR shift.[6b)]
j) Regioisomer ratio (84:16) was determined by separating each isomer. Assignments for regioisomers were made by ^{13}C NMR measurement and converting to the corresponding 2,3,5-trisubstituted tetrahydrofurans. 3-Benzoyl-5-methyl-2-(2-phenylethyl)tetrahydrofuran was a major product.
k) Regioisomer ratio (>4:1) and assignments for regioisomers were estimated by ^{13}C NMR measurement.
l) That of the major regioisomer. Ratio of the minor regioisomer was 74:26.[d)]

Thus it is noted that the regio- and stereoselective aldol reaction of γ-diketones is readily achievable by employing tin(IV) bisenolates from α,β-unsaturated γ-diketones, which are easily obtained by the Wittig reaction, oxidative opening of furans,[8)] or aldol condensation and dehydration. Further studies on the application of this reaction to the stereocontrolled synthesis of substituted tetrahydrofurans are currently under way.

References

1) A. J. Waring, "Comprehensive Organic Chemistry," ed by J. F. Stoddart, Pergamon Press, Oxford (1979), Vol. 1, pp. 1062-1064.

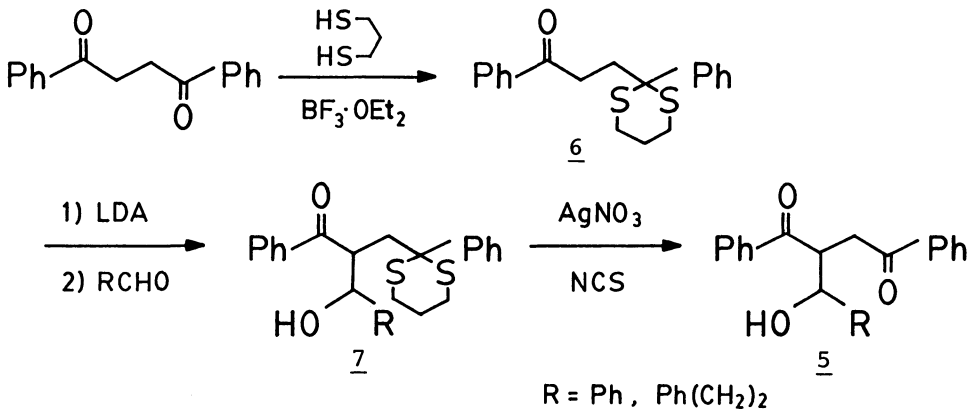
2) K. Takahashi, M. Matsuzaki, K. Ogura, and H. Iida, J. Org. Chem., 48, 1909 (1983) and references cited therein.

3) The photochemical equivalent to the aldol reaction of γ-diketones was reported. S. L. Schreiber, A. H. Hoveyda, and H.-J. Wu, J. Am. Chem. Soc., 105, 660 (1983).

4) J. Ichikawa and T. Mukaiyama, Chem. Lett., 1985, 1009.

5) Five-membered metallacyclic structure 4 cannot be ruled out for the stannyl derivatives.

6) a) Authentic samples for each isomer were prepared as follows:



Each isomer of 7 was separated and its relative configuration was determined by comparison of ^1H NMR coupling constant (R=Ph : *syn* J=3 Hz, *anti* J=7 Hz) and ^{13}C NMR shift of the carbinol carbon (R=Ph : *syn* 73.0 ppm, *anti* 77.1 ppm; R=$Ph(CH_2)_2$: *syn* 71.2 ppm, *anti* 73.2 ppm; the *syn* isomer exhibited upfield shift.)[9]

b) Similar trends of NMR spectra were also observed for 5. ^1H NMR coupling constant (R=Ph : *syn* J=4 Hz, *anti* J=7 Hz) and ^{13}C NMR shift of the carbinol carbon (R=Ph : *syn* 73.2 ppm, *anti* 76.0 ppm; R=$Ph(CH_2)_2$: *syn* 70.7 ppm, *anti* 72.2 ppm).

7) 1 prepared in this way is a yellow powder that can be stored under an inert atmosphere.

8) J. Jurczak and S. Pikul, Tetrahedron Lett., 26, 3039 (1985).

9) C. H. Heathcock, M. C. Pirrung, and J. E. Sohn, J. Org. Chem., 44, 4294 (1979).

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