Tetrahedron Letters No. 38, pp 3603 - 3606.

0040-4039/78/0915-3603$02.00/0

A DITHIOKETENAL FRAGMENT AS AN INITIATING GROUP IN ELECTROPHILIC 1,5-POLYENE CYCLIZATION REACTION

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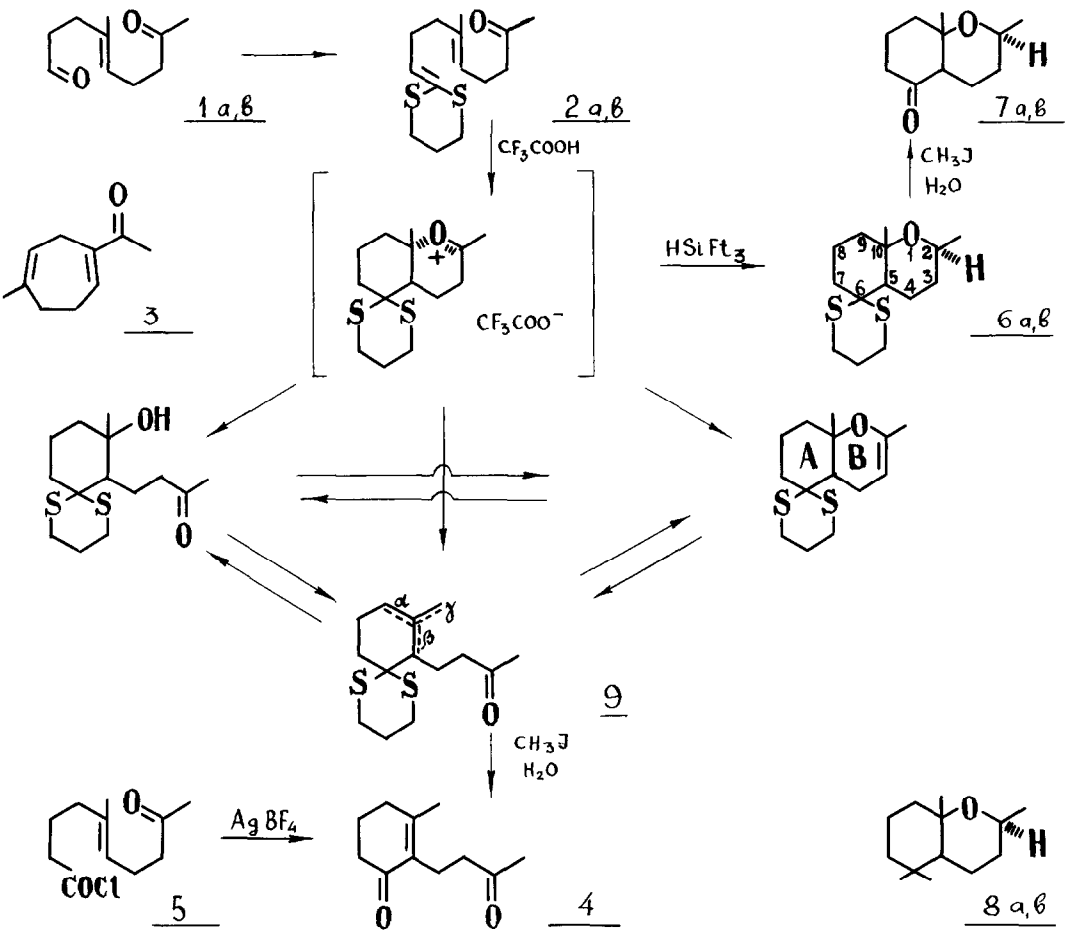
To provide regioselectivity of 1,5-polyene electrophilic cyclization, the acyclic precursor must possess some specific group, which should be more sensitive to electrophilic attack than any other unsaturated bond in the molecule and must allow introduction of the correct functionality into the prospective ring A of the polycyclic molecule. For special cases, to ensure the stereospecificity of the A/B-ring junction (cis-6,7 double bond → cis-A/B; trans-6,7 double bond → trans-A/B), this starting group must imitate sterically the terminal isopropenyl grouping of regular isoprenoids[1].

The terminal tri-substituted epoxide ring which is usually involved in biochemical cyclizations, is not always suitable for synthetic purposes[2]. W.S.Johnson and co-workers[3] have used successfully for the biomimetic cyclization reaction precursors with solvolytically labile groups such as tosylates, acetals or allylic alcohols. Our synthetic strategy has involved the use of acyclic keto aldehydes, produced by partial ozonolysis of regular isoprenoids or isoprene cyclooligomers[4], and the construction of the corresponding starting group would therefore be based upon a terminal aldehyde function.

For the reasons mentioned above, we chose a dithioketenal fragment. Isomeric keto aldehydes 1a [4,5] and 1b[5] were used as model compounds.

Dithioketenals 2 were prepared from keto aldehydes 1a or 1b according to[6] (1 mol.equiv. of 1, 1.1 mol.equiv. trimethylenetrithiocarbonate, excess of triethylphosphite, 24 hr, ca. 20°, followed by hydrolysis with KOH in MeOH) in 45% yield after chromatography on Al_2O_3. For 2a: b.p. 165-167°/0.7 mm Hg; PMR (CCl_4) δ: 1.66 (d, J=1 Hz, 3H, CH_3-C=C), 2.04 (s, 3H, CH_3-C=O), 1.9-2.5 (10H, CH_2), 2.80 (m, 4H, S-$CH_2CH_2CH_2$-S), 5.04 (t, J=6.5 Hz, 1H, HC=CCH_3), 5.78 ppm (t, J=7.5 Hz, 1H, HC=CS); IR(neat)ν: 1710(C=O), 1670 cm^{-1} (C=C<$^{S}_{S}$), no OH absorbtion; UV(EtOH): λ_{max} 257 nm, ε7400. For 2b: PMR(CCl_4)

Scheme



α-cis c=c bond or $^{A}/_{B}$ β-trans c=c bond or $^{A}/_{B}$

Table

Compound	Chemical shift, δ ppm		
	H at C - 2*	CH_3 at C - 2	CH_3 at C - 10
8a	3.53	1.00	1.27
8b	3.60	1.00	1.18
6a	3.53	1.02	1.48
6b	3.60	1.02	1.31

* Centre of multiplete

δ:1.63 (s,3H, $C\underline{H}_3$-C=C), 2.04 (s,3H, $C\underline{H}_3$-C=O), 2.0-2.7 (10H, $C\underline{H}_2$), 2.7-3.1 (m,4H, $SC\underline{H}_2CH_2C\underline{H}_2S$), 5.04 (m, 1H, $\underline{H}C{=}CCH_3$), 5.74 ppm (t, J=6,5 Hz, 1H, $\underline{H}C{=}CS$); IR (neat)ν: 1712 cm^{-1} (C=O).

Besides 2a about 15% of 1-acetyl-5-methylcycloheptadiene-1,5 3[7] was isolated its formation being due to the intramolecular condensation of 1a.

The cyclization of 2a with CF_3COOH in CH_2Cl_2 (1.5hr, 20°C) results in (after treatment with H_2O-$NaHCO_3$) the formation of a mixture of interconverting mono- and bicyclic products shown on Scheme[8]. However the removal of protecting thioketal group (CH_3J, acetone-H_2O, reflux, 6 h) transformed this mixture into a single product-diketone 4 (total yield ca. 60%), which proved to be identical to the authentical sample prepared by cyclization of acid chloride 5 under the action of $AgBF_4$[9,10].

Alternatively the reaction mixture was treated with $HSiEt_3$ according to[11]. After chromatography on SiO_2 the crystalline thioketal 6a was obtained in about 25% yield[12]. M.p. 74-75°C, PMR (CCl_4)δ: 1.02 (d, J=6 Hz, $C\underline{H}_3$ at C-2), 1.48 (s, 3H, $C\underline{H}_3$ at C-10), 1,1-2.2 (13H, $C\underline{H}_2$, $\underline{H}$ at C-5), 2,6-2,9 (m, 4H, $SC\underline{H}_2CH_2C\underline{H}S$), 3.53 ppm (m, 1H, $\underline{H}$ at C-2). IR (neat): absence of carbonyl and hydroxyl absorbtion; UV(EtOH):λ_{max} 250 nm, ε 695.MS : M^+272.

Deprotection of 6a in the manner described above produced respective bicyclic ketone 7a, its structure being ascertained by PMR and IR data. PMR: (CCl_4)δ : 1.12 and 1.18 (singlets, 6H $C\underline{H}_3$ at C-2 and C-10), 1.2 -2.6 (m,11H), 3.6-4.05 ppm (m, 1H, H at C-2); IR (CCl_4)ν : 1710 cm^{-1} (C=O).

The cyclization of 2b under the same conditions affords (after hydride reduction) isomeric dithioketal 6b, m.p. 71-72°C. PMR (CCl_4) δ:1.02 (d,J=6,5 Hz, 3H, $C\underline{H}_3$ at C-2), 1.30 (s, 3H, $C\underline{H}_3$ at C-10), 1.2-2.3 (13H), 2.6-2.9 (m, 4H, $SC\underline{H}_2CH_2C\underline{H}_2S$), 3.60 ppm (m, 1H, $\underline{H}$ at C-2).

To determine the stereochemistry of the prepared bicyclic products 6a and 6b we compared their PMR spectral data with those of previously described[13] perhydrochromanes 8a and 8b of the known configuration. The data given in Table reveal the close resemblance in the chemical shifts of characteristic protons for the pairs 6a—8a and 6b—8b. This result taken together with the previous observation on the stereochemistry of the isoprenoid cyclization reaction[14] enables us to ascribe the configuration of both isomers as shown in 6a and 6b and leads to the conclusion that the conversion 2a → 6a and 2b → 6b proceeds stereospecifically at both sites, i.e. at the ring-junction and C-2.

Thus we demonstrated that the thioketenal fragment can be considered as a promising initiating group for 1,5-polyene electrophylic cyclization reaction.

References and Notes.

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7. The structure 3 is in a good agreement with PMR, IR and UV data [PMR(CCl_4) δ :1.64 (s, 3H, CH_3-C=C), 2.18 (s, 3H, CH_3-C=O), 3.00 (d, J=6 Hz, 2H, C=C-CH_2-C=C), 6.81 ppm (t, J=6 Hz, 1H, HC=C-C=O). IR (neat) ν : 1672, 1640 cm^{-1} (C=C-C=O), UV (EtOH): λ_{max} 233 nm, ε 5480] and was additionally proved by direct synthesis from 1a (12 hr, 0.1 mol.equiv. KOH in MeOH, containing H_2O).
8. This mixture was not investigated more closely, but the interconversions similar to those shown on Scheme are known to occur in the course of geranylacetone cyclization under nearly the same conditions.
9. We found that the best method for the conversion of 2 into the corresponding acid (5-acid) is reaction with CH_3J in acetone-H_2O solution (10 hr, 50°) followed by the hydrolysis with 10% KOH in MeOH.
10. The COCl-function might have been expected to be a good initiating group with a high regioselectivity of the cyclization reaction. But it turned out that under the action of $AgBF_4$ or $AgSbF_6$ 5 yields solely monocyclic conjugated ketone 4 not accompanied by the formation of bicyclic products.
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12. Unfortunately the hydride reduction proved to be not very effective either and ca. 20% of 9 [PMR (CCl_4) δ : 1.69 (s, 3H, CH_3-C=C), 2.06 (s, 3H, CH_3-C=O), 1.5-2.6 (11H), 2.6-3.0 (m, 4H, $SCH_2CH_2CH_2S$), 5.27 ppm (m, 1H, HC=C)] was also obtained after chromatography of the reaction mixture.
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(Received in UK 17 July 1978; accepted for publication 21 July 1978)