

FORMATION AND NMR STUDY OF SOME CYCLIC β -KETODITHIOACETALS

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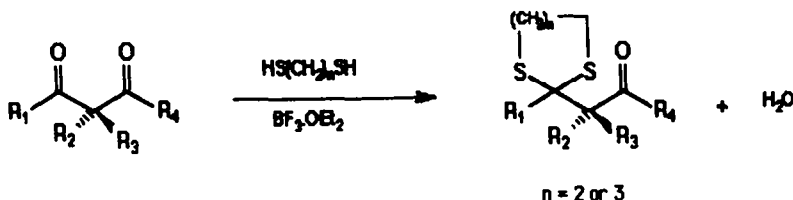
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Abstract - An efficient method has been found for the preparation of cyclic monodithioacetals of 1,3-dicarbonyl compounds using boron trifluoride etherate as the acid catalyst. Asymmetric 1,3-diketones react regioselectively in most of the cases tried. A study of the ¹³C and ¹H nmr characteristics of these compounds has been carried out.

INTRODUCTION

The monodithioacetals of 1,3-diketones are potentially useful compounds in synthesis since they are masked 1,3-dioxygen substituted moieties which can be selectively functionalized. Hence, it is possible to perform chain extension reactions as would be necessary in the synthesis of units of the polyol macrolides. Dithioacetals are stable under normal Bronsted acid conditions, hence, allowing much more flexibility in the reaction conditions subsequently used than would be possible for normal acetals. Efficient methods are now known for the reformation of a carbonyl group from 1,3-dithiolanes and 1,3-dithianes¹.



A previous study^{2,3} on a small number of 1,3-diketones and 3-ketoesters suggested that zinc chloride and/or hydrogen chloride were effective catalysts for the preparation of ethylene and propylene dithioacetals (dithiolanes and dithianes respectively) but that boron trifluoride etherate was not satisfactory since the boron 1,3-diketonate **16** was formed². We have shown that in fact the 1,3-diketonate **16** is formed only when the temperature of the reaction mixture⁴ (BF₃.OEt₂, dithiol, 1,3-dicarbonyl in dichloromethane) is allowed to rise above 15°C and we have obtained satisfactory yields of the title compounds using boron trifluoride etherate as 'catalyst' on cooling the mixture during the initial period of the reaction. Under these conditions no β -diketonate is formed and the only side product is the bis-acetal **14**. These conditions are considerably milder than those previously used for the preparation of these

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compounds^{2,3}.

It has been reported that the asymmetric dione 3'^{2,3} (a primed number refers to the corresponding dicarbonyl compound from which the unprimed compound is derived) undergoes dithioacetal formation to give exclusively the isomer 3. This rather surprising result tempted us to try a variety of reactions of this type using our conditions. The results (Table 1) indicate that considerable regioselectivity is normal and that even hexane-2,3-dione exhibits a remarkable degree of selectivity to this reaction. The proportions of each isomer were determined from an analysis of the ¹H NMR of the crude reaction product. Owing to impurities not related to the dithioacetals the accuracy of these determinations is not better than ±5%.

In order to minimize the formation of the bis-acetals it was necessary, in some cases, to use two equivalents of the 1,3-dione. During the work-up unreacted dicarbonyl compound could be removed by washing with an aqueous hydroxide solution.

Table 1. The yields and isomer ratios of the monodithioacetals prepared

Compound	R ₁	R ₂	R ₃	R ₄	Yield (%)	Isomer ratio	Characterization
1	CH ₃	H	H	CH ₃	95 ^a	-	Ref. 3,4
2	CF ₃	H	H	CH ₃	87	19:1	b.p. 120°C/0.1mm; $\nu(\text{C=O})$ 1763cm ⁻¹ ; Found S,27.81; Calc. S,27.85
3	Ph	H	H	CH ₃	94	19:1	Ref. 3
4	CH ₃ CH ₂	H	H	CH ₃	82	4:1	b.p. 160°C/15mm; $\nu(\text{C=O})$ 1710cm ⁻¹ Found C,50.79; H,7.49; S,33.95 Calc. C,50.49; H,7.41; S,33.69
5	CO ₂ Et	H	H	CH ₃	80 ^a	19:1	$\nu(\text{C=O})$ 1720cm ⁻¹ broad
6	CH ₃	see structure			76	9:1	b.p. 120°C/0.07mm; $\nu(\text{C=O})$ 1708cm ⁻¹ Found C,55.70; H,7.31; S,29.63 Calc. C,55.51; H,7.45; S,29.64
7 ^b	CH ₃	H	H	CH ₃	92	-	Ref. 2
8	Ph	H	H	CF ₃	89	19:1	$\nu(\text{C=O})$ 1760cm ⁻¹ ; Found C,49.04; H,3.52; S,21.63 ^c Calc. C,49.30; H,3.79; S,21.94
9	CH ₃	H	H	OEt	89	-	Ref. 3
10	CH ₃	H	CH ₃	CH ₃	87 ^a	-	b.p. 120°C/0.06mm; Found C,50.82; H,6.96 ^c Calc. C,50.49; H,7.41
11	CH ₃	H	H	CMe ₃	75	19:1	b.p. 130°C/0.1mm; $\nu(\text{C=O})$ 1705cm ^{-1c} Found C,55.12; H,8.35; S,29.39 Calc. C,55.00; H,8.31; S,29.37
12	CF ₃	H	H	CMe ₃	-	-	Starting material
13	CH ₂	H	H	CH ₂	-	-	Starting material
	CH ₂	CMe ₂		CH ₂			

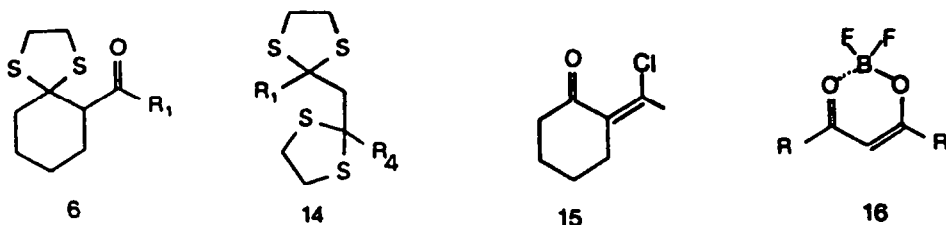
^a Prepared using two equivalents of 1,3-dione. ^b Dithiane; all others dithiolanes.

^c The NMR data for these compounds are not listed here but are concordant with the structure proposed.

In assigning the isomeric structure of these compounds, NMR was used for all but 8. The acyl groups show characteristic chemical shift values in the ¹H NMR-spectrum and the corresponding methyl, methylene or methine protons are moved significantly upfield on conversion to the dithioacetal. It was, therefore, easy to determine the site of attack by the dithiol. For compound 8, which does not have acyl protons, the infrared spectrum shows a strong peak at 1760 cm⁻¹ indicative of a trifluoroacetyl group (also observed for 2) and at much too high

a frequency to be a benzoyl carbonyl stretch.

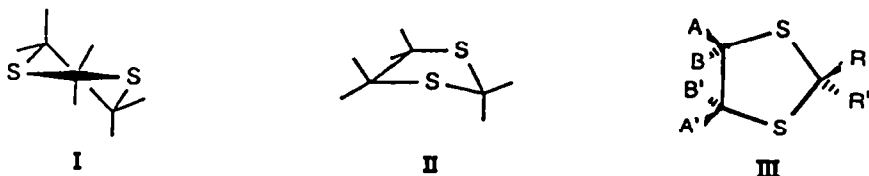
It can be seen that normally the dithioacetal is produced at the least sterically hindered carbonyl. In the case of the trifluoromethyl ketones, this is not so (compound 8) and when both the CF_3 and a bulky group are present no reaction occurs (compound 12)³. The cyclohexandione, dimedone, does not react at all and an alternative method of preparing its monodithioacetal has been found⁴. The yields for these reactions are normally high and selectivities of greater than 19:1 are normal with the trifluoroacetyl ketones or where great differences of steric bulk are present.



Purely on qualitative grounds, it appears that the carbonyl which is protected by this method is that which is the most carbonyl-like, that is the least enolized. The only outstanding exception is acetylcyclohexanone which is known to be enolized in the endocyclic manner. It is interesting to note, however, that the base catalyzed retro Claisen reaction of this compound also affords products resulting from attack at the ring carbonyl. Also, oxalyl chloride, which would be expected to react most readily with an enolic oxygen, reacts with acetylcyclohexanone to give predominantly the isomer 15⁶.

Enolization is not thought to explain the reduced but significant selectivity obtained for hexan-2,4-dione which, while not having great differences of electronic effects at the extremes of the dione system, would not be expected to enolize to a significantly greater extent in either direction. We can only assume that the selectivity observed, in this case, is due almost entirely to differences in steric bulk at the carbonyl groups, although these also do not appear to be large.

The β -ketodithiolanes 1-6, the bis-dithiolane 14 and the β -ketodithiane 7 were studied by ^1H and ^{13}C NMR spectroscopy. The corresponding chemical shift values are presented in Tables 2 and 3, respectively. The proton NMR chemical shift values obtained for compounds 1, 3, and 7 are in close agreement with the literature values^{2,3,7}. The resonances of the bridging methylene groups of the dithiolanes and dithianes, respectively, are of important diagnostic value since they are dependent upon the conformation of the five or six membered rings present in these compounds. The conformational properties of dithiolanes and dithianes have been studied previously to some extent^{2,8-11} by ^1H NMR. 1,3-Dithiolane rings are very flexible and at room temperature exist in a rapid equilibrium, on the NMR time-scale, between the C_2 half-chair I and the C_1 envelope II conformations⁸. Its C-4' and C-5' protons form an AA' BB' spin system consisting of two pairs of diastereotopic nuclei as in III. The C-4' and C-5' methylene protons of the 2',2'-asymmetrically disubstituted 1,3-dithiolanes are, however, isochronous in all cases where the molecules are flexible. Compound 6 has a locked conformation and retains the AA' BB' complex pattern whereas the other examples present only a singlet for the corresponding protons in each case. This property is also mirrored in the ^{13}C spectra, so that all the examples studied except compound 6 show a single resonance for the C-4' and C-5' carbon atoms with the above mentioned exception showing two.



The six-membered ring of the 1,3-dithiane **7** adopts the expected chair conformation⁹ with the bulkiest substituent occupying the equatorial position. The ¹H and ¹³C NMR spectra of compound **7** are considerably more complex, as would be expected since there are various factors inducing non-equivalence. A thorough study of the conformational aspects of these compounds was not carried out. This would require the measurement of the vicinal proton coupling constants of the ring methylene groups by direct observation at low temperature or indirectly, at room temperature, from the ¹³C satellites of the singlet resonance¹².

The above method of preparing the monodithioacetals of 1,3-dicarbonyl compounds is mild and efficient. The inconvenience experienced previously of using boron trifluoride etherate has been overcome. Considerable regioselectivity can be achieved in asymmetric diones. This latter observation is the subject of further investigation, the results of which will be published in the near future.

EXPERIMENTAL

The 1,3-dicarbonyl compounds used were available commercially or were prepared by standard procedures¹³ and characterized by comparison with the published data.

General Procedures for the Preparation of Dithioacetals.

(i) Symmetrical 1,3-Diones

A cold (0-5°) solution of the diketone (c.a. 0.1 mol.) in dichloromethane (30ml) was treated with boron trifluoride etherate (0.05 mol.) and slowly over 1h with ethan-1,2-dithiol (or propan-1,3-dithiol) (0.05 mol.) whilst maintaining the temperature of the reaction mixture within the aforementioned range. The mixture was stirred at room temperature overnight and then a 10% solution of sodium hydrogen carbonate (70ml) was added and the whole stirred vigorously for a further 3h. The organic phase was then separated and the aqueous layer extracted with dichloromethane (3 * 10ml). After combining the dichloromethane extracts they were washed quickly with a small quantity of 1M sodium hydroxide solution. Drying (MgSO₄) and evaporation of the solvent afforded the crude product which by NMR appeared to be almost pure. Short path distillation (Kugelrohr), chromatography on silica gel or recrystallization furnished the pure product.

(ii) Asymmetrical Diones

The procedure was identical except that normally equimolar proportions of the reagents were used and that the sodium hydroxide wash eliminated.

Refer to the Table 1 for yields and characterization data.

For the NMR study 0.1M solutions of the compounds were prepared in CDCl₃ (99.8% D), from Stohler Isotope Chemicals. The NMR measurements were carried out at room temperature on a Varian XL-200 spectrometer equipped with FT facilities and using the ²H resonance of the solvent as an internal lock reference. The proton spectra were obtained at 200.053 MHz and the broadband proton decoupled ¹³C spectra were recorded at 50.300 MHz. TMS was used as an internal reference and the chemical shift values quoted are relative to this (0.00 ppm). The precision of the chemical shift values was ±0.01 ppm for ¹H and ±0.05 ppm for ¹³C. Peak assignments were made by analyzing the results of homonuclear proton decoupling experiments or by proton-coupled or off-resonance proton-decoupled, ¹³C spectra.

Table 2. Proton chemical shift values, δ (ppm), of β -ketodithiolanes and β -ketodithianes in CDCl₃ solutions.

Compound	Central Part ^b			R ₁						R ₄
	CH ₂	SCH ₂ ⁱ	CH ₂ ⁱ	CH ₃	CH ₂	OCH ₂	CH(ortho)	CH(meta)	CH(para)	CH ₃
1	3.17	3.30	-	2.15	-	-	-	-	-	1.81
2	3.47	3.34	-	-	-	-	-	-	-	1.91
3	3.78	3.34	-	-	-	-	7.97	7.47	7.55	1.96
4	3.17	3.32	-	1.06	2.45	-	-	-	-	1.86
5	2.90	3.40	-	1.92	-	4.32	-	-	-	1.92
6	3.12	3.24 ^a	-	2.23	-	-	-	-	-	-
		3.21								
7	3.09	2.90	1.99	2.26	-	-	-	-	-	1.75
14	2.88	3.32	-	1.90	-	-	-	-	-	1.90

^a Non-equivalent

^b Primed (') groups refer to the dithiolane (dithiane) rings.

Table 3. ^{13}C chemical shifts, δ (ppm), of β -ketodithiolanes and β -ketodithianes in CDCl_3 solutions.

Cpd.	Central Part ^b									R ₁			R ₄		
	C(1)	C(2)	C(3)	SCH ₂ ¹	CH ₂ ¹	CH ₃	CH ₂	CF ₃	OCH ₂	C(1')	C(2',6')	C(3',5') aromatic-C	C(4')	CO	CH ₃
1	204.5	57.8	61.5	38.8	-	30.4	-	-	-	-	-	-	-	-	31.6
2	188.2	52.4	60.2	41.2	-	-	-	115.4	-	-	-	-	-	-	31.5
3	195.8	53.2	62.2	38.5	-	-	-	-	-	135.5	127.3	126.9	132.8	-	31.5
4	207.6	56.8	67.2	39.3	-	31.4	61.7	-	-	-	-	-	-	-	36.4
5	191.5	51.7	61.5	39.9	-	31.0	-	-	53.6	-	-	-	-	158.8	31.3
6	209.9	60.6	68.4	38.2	-	-	-	-	-	-	-	-	-	-	30.6
				37.6											
7	204.4	52.7	45.5	26.5	24.4	27.9	-	-	-	-	-	-	-	-	32.1
14	65.7	58.2	65.7	39.2	-	33.4	-	-	-	-	-	-	-	-	33.4

^a Non-equivalent

^b Primed (') groups refer to the dithiolane (dithiane) rings.

Acknowledgments

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