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A NOVEL AND EFFICIENT METHOD FOR THE PREPARATION OF ASYMMETRIC DITHIOACETALS

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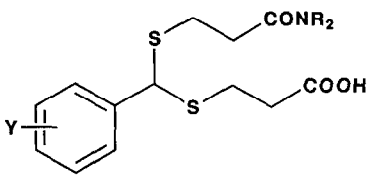
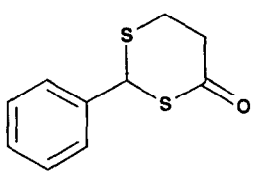
Abstract: Aldehydes and ketones react with one equivalent each of thiols and thiolacetic acid under acid catalysis to yield almost exclusively the mixed alkylthio-(or arylthio-) acylthioacetals. Reaction of the mixed thioacetal with a nucleophile (such as NaOMe) liberates the thiolate anion which can be trapped with a variety of electrophiles to provide asymmetric dithioacetals in high yields.

Thioacetals and thioketals are an important class of functional groups best known as protecting groups for aldehydes and ketones and, in the case of thioacetals, as units which can serve as acyl anion equivalents. This unit has also recently found considerable use in the medicinal chemistry of leukotriene antagonists where bis-thioalkanoic acid acetals have served as mimetics of the diacid polar portion (C1-C6) of leukotriene D_4 or leukotriene E_4.[1,2,3] The derivatives of this type reported to date have been generally symmetrical dithioacetals prepared in the normal manner from a thiol and an aldehyde or equivalent. We have recently developed a series of potent and specific leukotriene D_4 antagonists bearing an unsymmetrical dithioacetal moiety (I)[4].



I



II

To facilitate our structure activity studies in this area we sought a simple, efficient and versatile method for the preparation of dithioacetals (particularly aryldithioacetals) where the two acetal chains could be varied at will and thus rendered asymmetric.

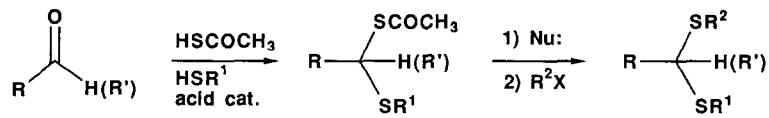
A number of methods to prepare unsymmetrical dithioacetals have been reported in the literature. Several authors have reported the stepwise addition of thiols to aldehydes and ketones[5,6] which can proceed in moderate yield especially when the two thiols differ greatly in reactivity. Reaction of dithioesters with grignard reagents[7] or under reductive alkylation procedures[8] can provide unsymmetrical dithioacetals in moderate to good yields. The preparation of mixed acylthioalkylthioacetals has also been reported from α-alkoxy-[9] or α-halothioethers (or thiolesters),[10,11] by reductive acylation of dithioesters[8] and

by alkylation promoted exchange from symmetrical dithioacetals.[10] A number of these procedures were investigated but were deemed to lack the facility and versatility which we required.

As an extension of our earlier work on the acid catalyzed reaction of activated alcohols with thiols or thiolacids to give thioethers or thiolesters[12,13] and based on the initial observation of the quantitative formation of the cyclic dithianone (II) from benzaldehyde and β-mercaptothiolpropionic acid (with zinc iodide catalyst in CH_2Cl_2), we were prompted to examine the three component system of an aldehyde, thiol and thiolacetic acid.

We have found that equivalent amounts of an aldehyde, a thiol and a thiolacid react under acid catalysis to give the mixed acyldithioacetals (III) in excellent yield. The mixed dithioacetals can subsequently be deacylated and the resulting thiolate alkylated with a wide variety of electrophiles to give asymmetric dithioacetals (IV) (Scheme 1). The results for the preparation of III are presented in Table I.

Scheme 1



III IV

Table I: Acid catalyzed reaction of aldehydes and ketones with thiols (HSR^1) and thiolacetic acid

Entry	Aldehyde (Ketone)	HSR^1	Conditions[a]	Yield of III (%)[b]
1	benzaldehyde	$HSCH_2CH_2CON(CH_3)_2$	A	84
2	benzaldehyde	$HSCH_2CH_2CON(CH_3)_2$	B	73
3	p-chlorobenzaldehyde	HSC_6H_5	B	71
4	p-chlorobenzaldehyde	$HSC_6H_4pOCH_3$	B	86
5	p-chlorobenzaldehyde	$HSC_6H_4pNO_2$	B	72
6	p-chlorobenzaldehyde	HSC_9H_{19}	B	87
7	p-chlorobenzaldehyde	$HSC(CH_3)_3$	B	91
8	n-nonylaldehyde	$HSC(CH_3)_3$	B	64
9	2-butanone	$HSCH_2C_6H_5pOCH_3$	C	14

a) Reaction conditions A: 0.1 eq. pTSOH, $ClCH_2CH_2Cl$, 2 hr. reflux; B: 0.2 eq ZnI_2, CH_2Cl_2, 2 hr. reflux; C: 0.7 eq., $BF_3{\cdot}OEt_2$, $ClCH_2CH_2Cl$, 0°C, 18 hr.
b) Isolated yields, all new products gave satisfactory elemental analysis.

The normal reaction conditions involve mixing thiol, thiolacid and aldehyde in an inert solvent such as dichloroethane and then adding the catalyst and stirring the mixture under N_2 for 1-4 hours at 20-60°C. Generally only traces of the corresponding symmetrical dithioacetals are observed and are readily removed by chromatography. As can be seen from

the table, reactions with benzaldehydes proceed in high yields unaffected by variations in nucleophilicity (entry 4 versus entry 5) or steric hindrance (entry 6 versus entry 7) of the thiols. Alkyl aldehydes also react well (entry 8) but alkyl ketones (entry 9) required more forcing conditions ($BF_3 \cdot OEt_2$) and even then proceeded in only moderate yield.

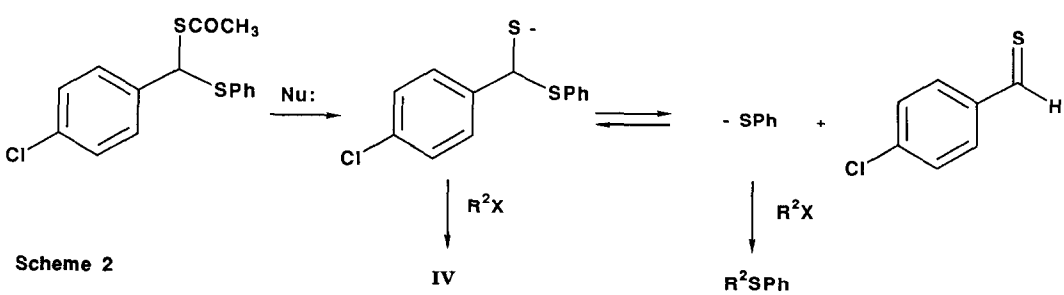
The deacylation of the thioacyl group and its subsequent alkylation can be achieved at low temperature in the presence of an electrophile using potassium carbonate in methanol or by treatment first with stronger nucleophiles such as methyllithium or preferrably sodium methoxide followed by addition of the electrophile. Some representative results are presented in Table II.

Table II: Deacylation and alkylation of mixed acyldithioacetals (III→IV)

Entry	Mixed Thioacetal (III)			R^2X	Conditions[a]	Yield (IV)[b] (%)
1	R=pClC_6H_4		$R^1=C_6H_5$	$BrCH_2CON_2(CH_3)_2$	A	40
2	R=pClC_6H_4		$R^1=C_6H_5$	$BrCH_2CON_2(CH_3)_2$	B	50
3	R=pClC_6H_4		$R^1=C_6H_5$	$BrCH_2CON_2(CH_3)_2$	C	69
4	R=pClC_6H_4		$R^1=C_9H_{19}$	$BrCH_2CON(CH_3)_2$	A	94
5	R=pClC_6H_4		$R^1=C_9H_{19}$	$BrCH_2CON(CH_3)_2$	C	93
6	R=pClC_6H_4		$R^1=C(CH_3)_3$	$BrCH_2CON(CH_3)_2$	A	97
7	R=pClC_6H_4		$R^1=C_9H_{19}$	$BrCH_2CH_3$	C	95
8	R=pClC_6H_4		$R^1=C_9H_{19}$	$ClCH_2CH_2COOCH_3$	C	87
9	R=pClC_6H_4		$R^1=CH_2CH_2CON(CH_3)_3$	$CH_2=CHCOOCH_3$	A	87
10	R=C_7H_{15}		$R^1=C(CH_3)_3$	$CH_2=CHCOOCH_3$	C	75
11	R=CH_2CH_3	R'=CH_3	$R^1=CH_2C_6H_4pOCH_3$	$BrCH_2COOCH_3$	C	86

a) Reaction conditions A: R^2X, K_2CO_3, CH_3OH, 2-butanone, -10°C, 1.5 hr.; B: CH_3Li, THF, -80°C, 5 min; RX, 1 hr. -80°C→RT; C: 1 eq. 1M $NaOCH_3$ in CH_3OH, THF, -80°C, 5 min.; R^2X, 20 min., -80°C→RT.
b) Isolated yields; all new compounds gave satisfactory elemental analysis.

Alkylations of arylthioacylthioacetals (entries 1,2,3) proceed in moderate yields under various conditions due to competing cleavage of the intermediate thiolate anion to liberate thioaldehyde and arylthiolate anion which may then compete for reaction with the electrophile (Scheme 2). However alkylthioacylthioacetals (entries 4-11) are alkylated in high yields even by relatively poor electrophiles such as bromoethane.



Scheme 2

Conclusions: The method described in this report provides a versatile and simple method for the synthesis of asymmetric dithioacetals. The preferential formation of the mixed thioacylthioalkylacetal in the first step suggests that this is the thermodynamically favored product. Strong evidence for this was obtained by an experiment monitored by NMR and tlc in parallel flasks. p-Chlorobenzaldehyde was reacted with ZnI_2 and either 1 eq. of t-BuSH or 1 eq. of CH_3COSH. Within 30 min. NMR and tlc indicated complete consumption of the thiol or thiolacid to form 0.5 equivalents of the corresponding symmetrical dithioalkyl- or dithioacylacetals (indicated by NMR signals at ca. 5.0 and ca. 6.2 ppm respectively). To each reaction was added a further 1 eq. of original thiol or thiolacid and then the two reactions were mixed. Within 15 min. at RT, NMR (and tlc) indicated essentially complete conversion to only the mixed dithioacetal (III; R=pClC_6H_4, R^1=$C(CH_3)_3$) showing characteristic methine absorption at 5.7 ppm. Further studies on the mechanism of this unusual reaction will be the subject of a full account to be published later.

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References

1. C.D. Perchonock, M.E. McCarthy, K.F. Erhard, J.G. Gleason, M.A. Wasserman, R.M. Muccitelli, J.F. DeVan, S.S. Tucker, L.M. Vickery, T. Kerchner, B.M. Weichman, S. Mong, S.T. Crooke and J.F. Newton, J. Med. Chem., 28, 1145 (1985).

2. A.K. Saksena, M.J. Green, P. Mangiaracina, J.K. Wong, W. Kreutner and A.R. Gulbenkian, Tetrahedron Lett., 26, 6427 (1985).

3. R.N. Young and J.Y. Gauthier, U.K. Patent Application #2190377, November 18, 1987.

4. R.N. Young, R. Zamboni and S. Leger, European Patent Application #233,763, Aug. 26, 1988.

5. T. Posner, Chem. Ber., 36, 296 (1903).

6. D.T. Gibson, J. Chem. Soc., 2637 (1931).

7. D. Paquer, Bul. Soc. Chim. France, 1439 (1975).

8. L. Kristenbrugger and J. Voss, Liebigs Ann. Chem., 472 (1980).

9. M. Martin and L. Bassery, C.R. Acad. Sci. Paris Ser. C., 281, 571 (1975).

10. P. Dubs and R. Stussi, Helv. Chim. Acta, 61, 2351 (1978).

11. H. Bohme, H. Bezzenberger and O. Muller, Arch. Pharmaz., 306, 268 (1973).

12. Y. Guindon, R. Frenette, R. Fortin and J. Rokach, J. Org. Chem., 48, 1357 (1984).

13. J.Y. Gauthier, F. Bourdon and R.N. Young, Tetrahedron Lett., 27, 15 (1986).

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