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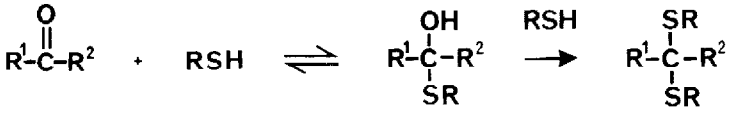
A SIMPLE AND EFFICIENT METHOD OF THIOACETAL- AND KETALIZATION[1]

Beng S. Ong
Xerox Research Centre of Canada
2480 Dunwin Drive
Mississauga, Ontario
Canada

Summary: $AlCl_3$ has been found to be an efficient reagent for promoting thioacetal- and ketalization of carbonyl compounds.

The synthetic utility of thioacetals and-ketals as carbonyl protecting groups[2], as masked methylene functions[3], and as acyl-nucleophile synthons[4] has been well-documented. In general, these compounds are obtained by the acid-catalysed or Lewis acid-promoted condensations[5,6] of carbonyl compounds with thiols (eq. 1). The exchange reactions[6,7] of acetals and ketals (or hemithioacetals and-ketals) with thiols have also become a standard procedure for their preparation. More recently, thioacetal- and ketalization of carbonyl compounds have been conveniently effected by the use of such reagent systems as RSH/Me_3SiCl[8] and $RSSiMe_3$/Lewis acid[9].

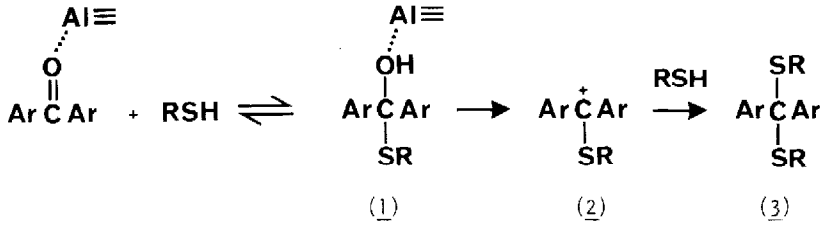


(1)

Although Lewis acid such as $ZnCl_2$[5b,c] and $BF_3 \cdot OEt_2$[5d] have long been employed as condensing agents for thioacetal- and ketalization reactions, the application of $AlCl_3$ for this purpose does not appear to have been fully investigated[10,11]. The simplicity with which solid $AlCl_3$ can be handled therefore prompted us to explore its potential as a condensing agent for thioacetal- and ketalization reactions. We report herein our findings of this investigation.

$AlCl_3$ is, indeed, an excellent coupling agent for carbonyl compounds with thiols. The high activity of $AlCl_3$ in initiating thioacetal- and ketalization reaction was clearly manifested in the thioketalization of the generally less reactive aromatic ketones, in particular, diaryl ketones. For example,an instantaneous reaction was observed when a solution of fluorenone and ethanethiol in 1,2-dichloroethane was treated with a stoichiometric quantity of $AlCl_3$ at room temperature; the desired thioketalization was essentially complete in less than 5 min., and the yield of the thioketal was near quantitative. The efficiency of this $AlCl_3$-promoted reaction may presumably be attributed to the strong affinity of the uncomplexed $AlCl_3$ for oxygen, thereby facilitating the breakdown of the sterically hindered tetrahedral hemithioketal intermediate (1) to the more

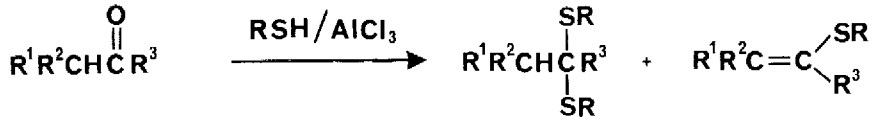
accessible trivalent carbonium ion intermediate (2, eq. 2); the latter afforded the thioketal (3) when reacted with a second mole of the thiol:



(2)

(1) (2) (3)

In general, carbonyl compounds with an α-proton reacted with monothiol (RSH) under similar conditions to give only moderate yields of the desired thioacetals or ketals (Table, entries 10 and 15); and in the case of highly enolizable carbonyl compounds, only the elimination products, i.e., vinyl sulfides (4, eq. 3) were formed (Table, entry 6). Nevertheless, this



(3)

(4)

competing reaction could be effectively subdued by employing a dithiol (e.g., 1,2-ethanedithiol or 1,3-propanedithiol) instead of a monothiol. Under these conditions, the desired thioacetal- or ketalization was observed to predominate to the virtual exclusion of the elimination reaction (Table, entries 5, 7, 9, 11, 14 and 16).

This reaction therefore represents a simple, yet fast and efficient, method of thioacetal- and ketalization of carbonyl compounds under mild reaction conditions. It is general in scope and does not require special reagents, and should therefore be regarded as a standard thioacetal- or ketalization procedure.

Experimental Procedure:

A solution of a carbonyl compound (10 mmol) and a thiol (25 mmol of monothiol or 13 mmol of dithiol) in 1,2-dichloroethane (15 mL) was stirred at room temperature. $AlCl_3$ (0.45g ~ 3.4 mmol) was added in small protions over a period of 1-2 min. The reaction mixture turned turbid as the reaction proceeded. After the addition, the mixture was further stirred for another 10-15 min., and was then hydrolysed with 15 mL of water. The resulting mixture was extracted with CH_2Cl_2 (20 mL). The extract was washed with brine, dried ($MgSO_4$), and evaporated to give the crude product which was generally of reasonably high purity. Further purification of the product could be carried out by distillation, recrystallization or by column chromatography on silica gel.

Other solvents such as methylene chloride and chloroform can also be employed as the reaction medium for this reaction.

Acknowledgements:

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References and Notes:

1. This contribution is dedicated to the memory of the late Professor R. B. Woodward.
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   b) the exchange reactions of cyclic hemithioacetals with thiols, see M. Martin and L. Bassery Compt. rend., 281C, 571 (1975).
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Table: Yields and physical data of Thioacetals and Thioketals

NO.	PRODUCT	ISOLATED YIELD(%)	b.p.(Torr)/(m.p), °C	^{1}H N.M.R., δ(ppm)[a]	^{13}C N.M.R., δ(ppm)[a]
1.		94	(48-9)[c]	0.95(t,6H);2.25(q,4H);7.3-7.8(m,8H)	13.7;25.2;62.1;120.0;125.0;128.0;128.5;139.0;147.6
2.		90	(123.5-24.5)[d]	3.8(s,4H);7.2-7.8(m,8H)	42.2;68.6;119.8;125.2;128.3;128.5;138.5;150.5
3.		91	(128-30)[c]	0.95(t,6H);2.15(q,4H);7.3-8.5(m,7H);9.6(br,1H)	g
4.		87	(104-5)[d]	3.4(s,4H);7.2-7.7(m,10H)	40.1;77.0;127.2;128.0;128.2;144.7
5.		88	(54-5)[c]	2.75(s,4H);3.25(s,4H);7.2-7.5(m,10H)	39.8;50.3;71.5;126.8;127.6;131.5;137.7
6.		90	e	3.6+3.8(2s,2H);6.75+6.85(2s,1H);7.1-7.6(m,15H)	37.4;44.4;126-139 (27 resolved C's)
7.		95	116-8(14)	1.95(t,6H);2.93(q,4H);2.95(m,2H);3.8(m,4H)	8.6;25.7;26.0;30.6;54.5
8.		82	(155-56.5)[d]	1.5-1.8(br,6H);1.9-2.0(br,4H);2.6-2.8(br,4H);7.3-7.8(m,10H)	27.5;33.6;35.6;39.2;75.9 128.3;128.4;132.8;135.5
9.		86	(65-6)[c]	0.85(s,9H);1.1(m,1H);1.3(m,2H);1.9(m,4H);2.2(m,2H);3.3(m,4H)	27.2;27.6;32.4;38.0;38.7;43.3;47.1;68.9
10.		55	e	1.2-1.8(m,10H);7.2-7.8(m,10H)	22.7;25.1;37.2;65.9;128.5;128.9;131.7;136.9
11.		94	165-7(15)	1.8(s,3H);2.0(m,2H);2.7(m,4H);7.2-8.0(m,5H)	24.8;28.2;32.8;54.0;127.1;127.8;128.5;144.1
12.		93	144-6(8)	1.2(t,6H);2.6(m,4H);4.95(s,1H);7.2-7.5(m,5H)	14.3;26.3;53.0;127.7;127.8;128.5;140.8
13.		94	(141-2)[d]	1.9-2.3(m,2H);2.8-3.2(m,4H);5.25(s,1H); 7.9(AB,4H)	24.9;31.8;50.4;124.0;129.0;146.3;147.8
14.		81	125-7(16)	0.9(t,3H);1.2-1.6(m,6H);1.8(m,2H);2.2(m,4H);4.45(t,1H)	13.9;22.5;29.0;31.5;38.4;39.3;54.0
15.		42	e	0.9(t,3H);1.3(m,4H);1.6(m,2H);1.9(m,2H);4.4(t,1H);7.2-7.5(m,10H)	13.9;22.4;26.7;31.3;35.9;58.6;127.6;128.9;132.7;134.5
16.		90	e	1.25(t,3H);1.75(s,3H);1.8-2.2(m,2H);2.6-3.1(m,4H);3.05(s,2H);4.15(q,2H)	14.2;24.7;27.0;28.5;45.9;46.1;60.6;168.8

a) N.M.R. spectra were taken in $CDCl_3$ with tetramethylsilane as internal reference; b) E/Z ratio determined by ^{1}H N.M.R. spectroscopy; c) recrystallized from methanol; d) recrystallized from methylene chloride/hexane; e) viscous liquid, purified by silica gel-column chromatography; f) reaction time, 1.5 hr; g) ^{13}C N.M.R.(ppm): 13.7; 25.2; 61.8; 125.0; 125.4; 125.8; 127.3; 128.7; 129.0; 129.6; 131.5; 137.6; 139.0; 148.3; 150.1; 172.6.

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