Monatshefte für Chemie 138, 67–71 (2007)
DOI 10.1007/s00706-006-0559-0
Printed in The Netherlands

Monatshefte für Chemie
Chemical Monthly

Short Communication

2,4,6-Trichloro-1,3,5-triazine Catalyzed Chemoselective Transthioacetalization of Aldehyde Acetals and Oxathioacetals

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Received June 1, 2006; accepted (revised) August 3, 2006
Published online December 22, 2006

Summary. A mild and efficient transthioacetalization of aldehyde acetals and oxathioacetals was carried out using 2,4,6-trichloro-1,3,5-triazine as a mild and inexpensive catalyst. Chemoselective transacetalization is impressive as aldehyde *O*,*O*- and *O*,*S*-acetals are converted into the corresponding *S*,*S*-acetals in the presence of ketones or their acetals and oxathiocetals in nearly quantitative yields.

Keywords. Protection; Transthioacetalization; 2,4,6-Trichloro-1,3,5-triazine.

Introduction

The protection and subsequent deprotection of a functional group is a common practice in a multi-step synthetic strategy and switchover of one protective group to another one is also often required as demanded by their stability under the reaction conditions in subsequent steps. Thus, a direct method for this transformation bypassing the intermediate step of going back to the parent functionality is becoming more important in order to improve the overall synthesis efficiency [1]. *O*,*O*-Acetals, *O*,*S*-acetals, and *S*,*S*-acetals are important protecting groups for carbonyl compounds in organic synthesis. However, *S*,*S*-acetals are superior protecting groups than *O*,*O*-acetals and *O*,*S*-acetals because of their stability in acidic medium [2], and they are also used in organic synthesis as acyl anion equivalent [3] as well as intermediates for the conversion of carbonyl compounds to the parent hydrocarbons [4]. Therefore, conversion of *O*,*O*-acetals and *O*,*S*-acetals to *S*,*S*-acetals is an important synthesis transformation. Various methods have been developed and they

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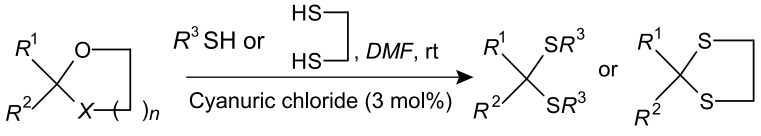
are usually carried out under the catalysis of a variety of *Lewis* acids with different amounts of loading, such as $InCl_3$ (5 mol%) [5], $MgBr_2$ (1.2 equiv.) [6], WCl_6 (4–10 mol%) [7], $ZrCl_4$ (3–5 mol%) [8], trichloroisocyanuric acid (10 mol%) [9], silica chloride (200–300 mg/mmol) [10], and I_2 (10 mol%) [11]. However, many of these methods require long reaction times, expensive and hazardeous reagents, and high catalyst loading, and thus lack generality. Accordingly, an improved alternative procedure involving inexpensive and easily available catalyst with low loading is desirable.

Recently, 2,4,6-trichloro-1,3,5-triazine (cyanuric chloride) has emerged as an inexpensive and easily available reagent in organic synthesis [12]. As a part of our continuing program [12n–p], we wish to report a new application of cyanuric chloride as a mild and chemoselective catalyst for transthioacetalization of *O*,*O*-acetals and *O*,*S*-acetals at room temperature (Scheme 1).



R^1 = alkyl, aryl, R^2 = alkyl, aryl, H, SR^3 = alkyl, aryl
X = O, S; n = 1, 2

Scheme 1

Table 1. Transthiacetalization of acetals and oxathioacetals catalyzed by 2,4,6-trichloro-1,3,5-triazine

Entry	Substrate	Thiol/dithiol	Time/min	Yield/%
1	$C_6H_5CH(OCH_2)_2$	$HS(CH_2)_2SH$	20	98 [14]
2	4-Cl–$C_6H_4CH(OCH_2)_2$	$HS(CH_2)_2SH$	35	97 [16]
3	4-NO_2–$C_6H_4CHO(CH_2)_3O$	$HS(CH_2)_2SH$	25	89 [13]
4	4-Me–$C_6H_4CHO(CH_2)_3O$	$HS(CH_2)_2SH$	60	90 [9]
5	4-OMe–$C_6H_4CHO(CH_2)_2S$	$HS(CH_2)_2SH$	50	91 [11]
6	4-CN–$C_6H_4CHO(CH_2)_2S$	$HS(CH_2)_2SH$	30	96
7	4-Br–$C_6H_4CHO(CH_2)_2S$	$HS(CH_2)_2SH$	50	97 [11]
8	$C_6H_5CH{=}CH(OCH_2)_2$	$HS(CH_2)_2SH$	35	98 [11]
9	Furfuryl-$CH(OCH_2)_2$	$HS(CH_2)_2SH$	30	90 [16]
10	Thiophene-$CH(OEt)_2$	$HS(CH_2)_2SH$	25	94
11	3,4-$(OCH_2O)C_6H_3CH(OEt)_2$	$HS(CH_2)_3SH$	35	97
12	$C_5H_{11}CH(OMe)_2$	$HS(CH_2)_3SH$	30	94
13	$C_5H_{11}CHO(CH_2)_2S$	$HS(CH_2)_2SH$	40	93 [15]
14	$C_6H_{13}CH(OCH_2CH_2CH_3)_2$	$HS(CH_2)_2SH$	40	95 [20]
15	Cyclohexyl-$(OCH_2)_2$	C_6H_5SH	45	90 [16]
16	Cyclohexyl-$O(CH_2)_2S$	C_6H_5SH	40	90 [16]
17	$(C_6H_5)_2$-$CO(CH_2)_2S$	*Et*SH	20	95 [17]
18	2-CH_2O*THP*-Cyclopentyl-$(OCH_2)_2$	$HS(CH_2)_2SH$	50	90
19	2-CH_2O*TBDMS*-Cyclopentyl-$(OCH_2)_2$	$HS(CH_2)_2SH$	50	91

Results and Discussion

A mixture of *O*,*O*-acetal or *O*,*S*-acetal and thiol or dithiol in the presence of cyanuric chloride in *DMF* was stirred for a specified time at room temperature to furnish the corresponding dithioacetals in excellent yields. The results are presented in Table 1.

The present method is applicable to open chain acetals, cyclic acetals, oxathioacetals of aliphatic, aromatic, and heterocylic aldehydes, and ketones furnishing the corresponding dithioacetals in excellent yields. The presence of an electron-donating or electron-withdrawing group on the aromatic ring of acetals or oxathioacetals does not make any difference in this transthioacetalization. Acetals or oxathioacetals of conjugated carbonyl compounds (Table 1, entry 8) are also converted to the corresponding thioacetals without any isomerization. It is also important to note that acetals or oxathioacetals of furfural and thiophene-2-aldehyde underwent smooth transthioacetalization under the present reaction conditions which are otherwise problematic under acidic conditions (Table 1, entries 9 and 10). Tolerance of a variety of functional groups such as *OTBDMS*, *OTHP*, O*Me*, methylenedioxy, ester, nitro, cyano, chloro, and bromo under the present reaction condition is also im-

Table 2. Chemoselective transthioacetalization

Entry	Substrate	Thiol/dithiol	Product (Yield/%)	Time/min
1	$CH_3(CH_2)_5CH(OCH_2)_2$ + $CH_3(OCH_2)_2CH_2CH_3$	$HS(CH_2)_2SH$	$CH_3(CH_2)_5CH(SCH_2)_2$ (90) + $CH_3C(SCH_2)_2CH_2CH_3$ (0)	45 [20]
2	Cyclohexyl-$(OCH_2)_2$ + $C_6H_5C(OCH_2)_2CH_3$	$HS(CH_2)_2SH$	Cyclohexyl $(SCH_2)_2$ (90) + $C_6H_5C(SCH_2)_2CH_3$ (0)	40 [I6]
3	$C_6H_5CH(OMe)_2$ + $C_6H_5C(CH_3)(OMe)_2$	$HS(CH_2)_2SH$	$C_6H_5CH(SCH_2)_2$ (96) + $C_6H_5C(CH_3)C(SCH_2)_2$ (0)	35 [14]
4	4-$NO_2C_6H_4CHO(CH_2)_2S$ + $C_6H_5C(CH_3)O(CH_2)_2S$	$HS(CH_2)_2SH$	4-$NO_2C_6H_4CH(SCH_2)_2$ (90) + $C_6H_5C(CH_3)(SCH_2)_2$ (0)	30 [13]
5	4-$ClC_6H_4CH(OCH_2)_3$ + $C_6H_5CH(OMe)_2$	$HS(CH_2)_2SH$	4-$ClC_6H_4CH(SCH_2)_2$ (0) + $C_6H_5CH(SCH_2)_2$ (95)	20 [14]
6	Cyclohexyl-$(OCH_2)_2$ + $C_6H_5COCH_2CH_3$	$HS(CH_2)_2SH$	Cyclohexyl-$(SCH_2)_2$ (98) + $C_6H_5C(SCH_2)_2CH_2CH_3$ (0)	45 [16]
7	$C_6H_5CH(OMe)_2$ + $C_6H_5COCH_3$	$HS(CH_2)_2SH$	$C_6H_5CH(SCH_2)_2$ (98) + $C_6H_5C(SCH_2)_2(CH_3)$ (0)	25 [14]
8	4-$ClC_6H_4CHO(CH_2)_2S$ + $C_6H_5CH_2CH_2COCH_3$	$HS(CH_2)_2SH$	4-$ClC_6H_4CH(SCH_2)_2$ (97) + $C_6H_5(CH_2)_2(SCH_2)_2CH_3$ (0)	35 [16]
9	$C_6H_5COCH_2CH(OCH_2)_2$	$HS(CH_2)_2SH$	$C_6H_5COCH_2CH(SCH_2)_2$ (98)	35 [19]
10	$CH_3COCH_2CHO(CH_2)_2S$	$HS(CH_2)_2SH$	$CH_3COCH_2CH(SCH_2)_2$ (97)	25
11	$CH_3COC_6H_4CH(OCH_2)_2$	$HS(CH_2)_2SH$	$CH_3COC_6H_4CH(SCH_2)_2$ (97)	30 [18]

portant to mention. The most important advantage of the present methodology as compared to the reported ones is the low catalytic amount (3 mol%) of cyanuric chloride sufficient to push the reaction efficiently and on large scale.

Another important feature of this methodology is the impressive chemoselective transthioacetalization of *O*,*O*-acetals or *O*,*S*-acetals of aldehydes in the presence of ketones or *O*,*O*-acetals and *O*,*S*-acetals of ketones. The results are presented in Table 2.

In conclusion, cyanuric chloride is found to be a mild, efficient, and chemoselective catalyst for transthioacetalization of acetals/oxathioacetals of aldehydes in the presence of ketones or their acetals/oxathioacetals. General applicability, operational simplicity, excellent yields, short reaction times, and mild reaction conditions are attractive features of this method.

Experimental

IR spectra were recorded on a Bomen MB-104 FTIR spectrometer whereas ^{1}H NMR were scanned on an AC-300F NMR (300 MHz) instrument using $CDCl_3$ as the solvent and *TMS* as internal standard. Elemental analyses were made by Carlo-Erba EA1110 CNNO-S analyzer and agreed favourably with the calculated values.

General Procedure

A mixture of 1 mmol *O*,*O*-acetal or 1 mmol *O*,*S*-acetal and 2.1 mmol thiol or 1.1 mmol dithiol in the presence of a catalytic amount of cyanuric chloride (0.03 mmol) in 5 cm^3 *DMF* was stirred at room temperature for the specified time (Table 1). After completion of the reaction (TLC), the product was extracted with 3×5 cm^3 diethyl ether. The organic layer was washed with H_2O, dried (Na_2SO_4), and evaporated under vacuum to furnish the crude product, which was further purified by column chromatography (petroleum ether:ethyl acetate = 9:1).

4-Cyanophenyl-1,3-dithiolane (Table 1, entry 6; $C_{10}H_9NS_2$)
Mp 62°C; IR ($CHCl_3$): $\bar{\nu} = 2225$, 1658, 1640, 1490, 1454, 1265, 1230, 1195, 1062, 1018, 970 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 5.50$ (s, 1H), 2.80 (m, 4H), 7.10 (d, $J = 7.2$ Hz, 2H), 7.28 (d, $J = 7.2$ Hz, 2H); MS: $m/z = 207$ (M^+).

2-Thiophene-1,3-dithiolane (Table 1, entry 10; $C_7H_8S_3$)
Bp 115°C; IR ($CHCl_3$): $\bar{\nu} = 1657$, 1648, 1490, 1465, 1275, 1245, 1190, 1060, 1015 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 3.30$ (m, 4H), 5.60 (s, 1H) 6.10 (d, 2H), 7.15 (t, 1H); MS: $m/z = 188.141$ (M^+).

1-Hexanal-1,3-dithiane (Table 1, entry 12; $C_9H_{18}S_2$)
Bp 165°C; IR ($CHCl_3$): $\bar{\nu} = 2301$, 1659, 1649, 1492, 1469, 1278, 1246, 1195, 1025 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.86$ (m, 1H), 2.10 (m, 1H), 2.98 (m, 4H), 4.40 (*t*, 3H) 0.80 (m, 9H); MS: $m/z = 190.243$ (M^+).

2-Acetophenyl-1,3-dithiane (Table 2, entry 9; $C_{11}H_{12}S_2O$)
Mp 70°C; IR ($CHCl_3$): $\bar{\nu} = 1670$ cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 3.76$ (s, 2H), 4.20 (m, 1H), 3.20 (m, 4H), 7.15 (m, 5H); MS: $m/z = 190.243$ (M^+).

2-Acetylmethyl-1,3-dithiolane (Table 2, entry 10; $C_6H_{10}S_2O$)
Bp 70°C; IR ($CHCl_3$): $\bar{\nu} = 1718$ cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.98$ (s, 3H), 3.11 (m, 4H), 3.70 (s, 2H), 4.35 (m, 1H); MS: $m/z = 162.146$ (M^+).

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