Transdithioacetalization of acetals, ketals, oximes, enamines and tosylhydrazones catalysed by natural kaolinitic clay

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Natural kaolinitic clay efficiently catalyses the transdithioacetalization of acetals, ketals, oximes, enamines and tosylhydrazones with ethane-1,2-dithiol and propane-1,3-dithiol to produce the corresponding dithiolanes in high yields.

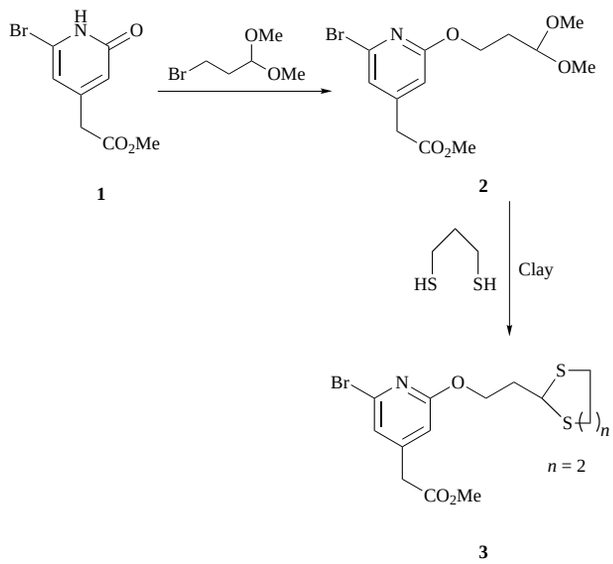
Introduction

The protection of carbonyl groups as acetals or dithioacetals is often necessary during the synthesis of many compounds.[1] More particularly, 1,3-dithianes have found wide synthetic uses as precursors of acyl anion equivalents displaying a reactivity of umpolung.[2] For example, 1,3-dithianes can be metallated with BuLi and the resultant anions are sufficiently stable to serve as effective nucleophiles in C–C bond-forming reactions. Although, generally, thioacetals have been prepared by protic acid,[3] solid acid[4] or Lewis acid-catalysed condensation of carbonyl compounds with thiols,[1] of late, transdithioacetalization of acetals has gained favour as the method of choice in which catalysts such as $BF_3{\cdot}OEt_2$,[5] $Bu^i_2AlS(CH_2)_2SAlBu^i_2$[6] and $CoCl_2{\cdot}Me_3SiCl$[7] have been employed. However, since such catalysts are either expensive or ineffective with hindered ketones, a reusable and solid clay catalyst would have advantages over classical acids because of its strong acidity (Hammett function, $H_o = -9$ to -11), non-corrosive nature, high selectivity and ease of subsequent product work-up.[8]

Aldehydes and ketones are generally purified and characterized *via* their corresponding oximes and tosylhydrazones since they form crystalline products which may be employed as versatile synthetic intermediates and used in other reactions;[10] they can also be prepared from non-carbonyl compounds.[11] Since many useful reactions have been developed to prepare oximes from non-carbonyl compounds (*e.g.* the Barton reaction)[11] an efficient catalytic transdithioacetalization of oximes is of importance since it leads to a novel, and direct method for thioacetal preparation.

In connection with our work on the synthesis of camptothecin, we attempted to alkylate the bromopyridone **1**, prepared by a known method,[12] with 3-bromopropionaldehyde dimethyl acetal[13] to obtain the *N*-alkylated product; however, the *O*-alkylated product **2** was produced exclusively instead. Although the latter product was of no use in the synthesis of camptothecin, we decided to study its transdithioacetalization in the presence of clay. Accordingly, compound **2** was subjected to transdithioacetalization with propane-1,3-dithiol in the presence of clay when it gave the corresponding 1,3-dithiane derivative **3** in high yields.

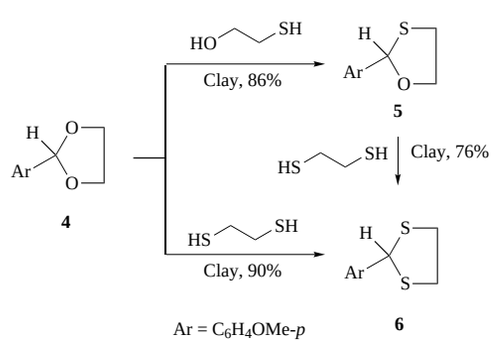
Clays have many useful properties, *e.g.* they are easy to handle, non-corrosive, inexpensive and may be regenerated. Further, their acidity, both Bronsted and Lewis, in their natural and ion-exchanged forms, enables them to function as efficient catalysts for various organic transformations.[8] To the best of our knowledge, the direct transformation of oximes, enamines, tosylhydrazones and 1,3-dioxalanes to dithiolanes and dithianes has not been reported in the literature.



Scheme 1

Recently, we have reported the catalytic application of natural kaolinitic clay for the selective protection of carbonyl compounds,[14] hydroxy compounds[15] and selective regeneration of carboxylic acids from their corresponding allyl and cinnamyl esters.[16] Here, we report that natural kaolinitic clay efficiently catalyses transdithioacetalization of acetals, ketals, oximes, enamines and tosylhydrazones in high yields, thereby constituting an important synthetic method for dithioacetalization of carbonyl compounds.

The 1,3-dioxolane **4** (Scheme 2) when refluxed with either



Scheme 2

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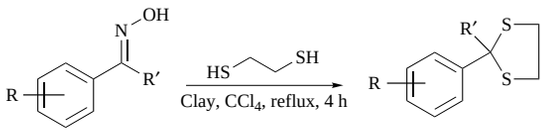
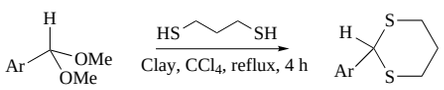
Table 1 Transdithioacetalization of aldoximes and ketoximes



Entry	R (or oxime used)	Yield (%)
1	H	94
2	4-OMe	85 (87)[b]
3	4-Cl	80
4	4-NO_2	82
5	3-NO_2	84
6	(Cinnamaldehyde)	94
7	(Butyraldehyde)	79
8	(Cyclohexanone)	91
9	(3-Methylcyclohexenone)	75
10	(Acetophenone)	0
11	(Benzophenone)	0

[a] All products were characterized on the basis of IR, NMR, mass and ^{13}C NMR spectral results; yields are those isolated after column chromatography. [b] Yield corresponds to 1,3-dithiane.

Table 2 Transdithioacetalization of aryl acetals with propane-1,3-dithiol catalysed by clay



Entry	Subst's on Ar (or acetal used)	Catalyst	Yield (%)[a]
1	4-OMe	Clay	88[b]
		Al_2O_3	0
		SiO_2	60
		Sulfated ZrO_2	72
		Hβ-Zeolite	76
		Montmorillonite	80
2	4-Cl	Clay	80
3	2-NO_2	Clay	82
4	2-OH	Clay	94
5	2-CO_2H	Clay	90
6	3,4,5-$(OMe)_3$	Clay	90
7	3-OMe, 4-OH, 5-NO_2	Clay	87
8	3,5-$(OMe)_2$, 4-OH	Clay	92
9	(Cinnamaldehyde)	Clay	79
10	(Furan-2-carbaldehyde)	Clay	69

[a] Isolated yield, characterized on the basis of IR, ^1H and ^{13}C NMR and MS spectral evidence. [b] Catalyst recovered and re-used at least 3 times without any loss of activity.

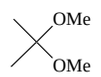
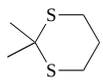
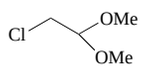
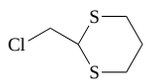
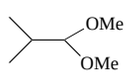
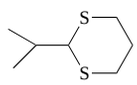
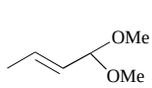
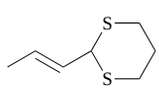
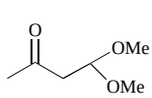
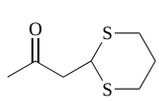
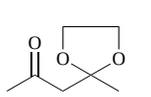
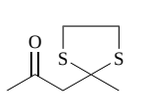
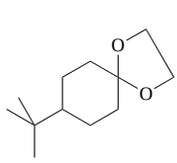
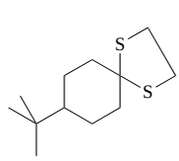
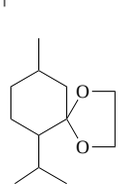
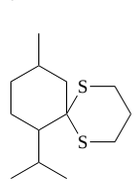
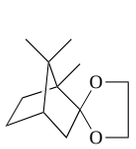
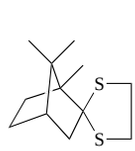
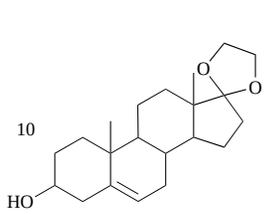
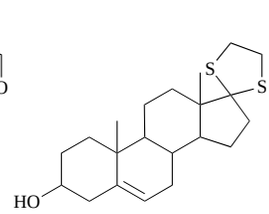
ethane-1,2-dithiol or mercaptoethanol in the presence of kaolinitic clay gave the 1,3-oxothiolane **5** (86%) or the 1,3-dithiolane **6** (90%); similarly, the 1,3-oxothiolane **5** gave the 1,3-dithiolane **6** (76%).

Table 1 lists a variety of aldoximes and ketoximes which underwent transdithioacetalization with ethane-1,2-dithiol in the presence of clay to produce their corresponding 1,3-dithianes in excellent yields. However, aromatic ketoximes failed to undergo the reaction (entries 10 and 11).

The enamines **7** and **9** when subjected to transdithioacetalization with ethane-1,2-dithiol, gave the corresponding dithiolane derivative **8** (75%) and **10** (80%) respectively. Furthermore, it is interesting to note that the tosylhydrazone **11** also underwent transdithioacetalization in high yield under similar conditions to give the corresponding dithiane products **12** (see Scheme 3). The clay catalyst was recovered and re-used at least three times with no loss of activity.

The kaolinitic clay, procured from the Padappakara mine of Quilon District, Kerala, India, after purification and characterization,[17] had the following composition as determined by wet chemical analysis: $SiO_2 = 67.45\%$, $Al_2O_3 = 22.2\%$, $Fe_2O_3 = 6.1\%$, $TiO_2 = 3.45\%$ and $K = 0.8\%$.

Table 3 Transdithioacetalization of aliphatic acetals and ketals catalysed by clay

Entry	Substrate	Product	Yield (%)[a]
1			86
2			89
3			81
4			50
5			78
6			78
7			67
8			80
9			76
10			81

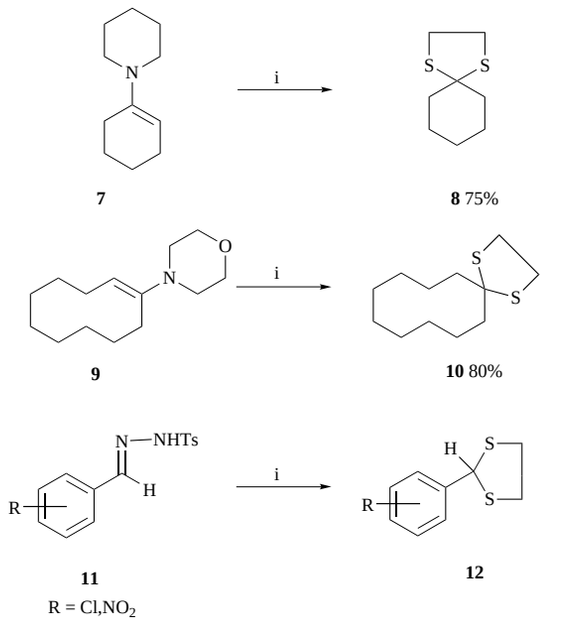
[a] Isolated yield, characterized on the basis of IR, ^1H and ^{13}C NMR and mass spectral evidence.

Table 2 shows the transdithioacetalization of aryl acetals using clay and other catalysts. It has been found that other acidic catalysts such as silica gel, sulfated ZrO_2, Hβ zeolite and montmorillonite clay are also efficient in catalysing

Table 4 Spectroscopic data for selected products

No.	Key No. (T_xn)*	Compound	ν_{max}/cm^{-1}	^{1}H NMR δ($CDCl_3$), a = 200 MHz, b = 90 MHz	MS *m*/*z* (%)
1	$T_2$1	2-(4-Methoxyphenyl)-1,3-dithiane	2925, 2895, 1600, 1500, 1250 and 1050	a = 1.82–2.00 (m, 1H), 2.10–2.25 (m, 1H), 2.80–3.15 (m, 4H), 3.80 (s, 3H), 5.15 (s, 1H), 6.83 (d, *J* 9) and 7.43 (d, *J* 9, 2H)	226 (M^+, 81), 151 (100) and 121 (30)
2	$T_2$2	2-(4-Chlorophenyl)-1,3-dithiane	2950, 1600 and 760	a = 1.80–1.85 (m, 2H), 1.80–3.30 (m, 4H), 5.40 (s, 1H), 7.70 (d, *J* 9, 2H) and 7.80 (d, *J* 9, 2H)	230 (M^+, 100), 155 (93) and 74 (64)
3	$T_2$3	2-(2-Nitrophenyl)-1,3-dithiane	2120, 1210 and 760	b = 1.85–2.30 (m, 2H), 2.70–3.40 (m, 4H), 5.80 (s, 1H) and 7.00–7.80 (m, 4H)	241 (M^+, 30), 166 (30) and 106 (100)
4	$T_2$4	2-(2-Hydroxyphenyl)-1,3-dithiane	3200 and 760	a = 1.85–2.25 (m, 2H), 2.85–3.15 (m, 4H), 525 (s, 1H), 6.80–6.95 (m, 2H) and 7.30–7.40	212 (M^+, 52), 138 (100) and 77 (25)
5	$T_2$7	2-(3-Methoxy-4-hydroxy-5-nitrophenyl)-1,3-dithiane	3250, 1250 and 760	b = 1.85–2.10 (m, 2H), 2.87–3.00 (m, 4H), 3.15 (s, 3H), 5.16 (s, 1H) and 6.50 (s, 1H)	287 (M^+, 55), 213 (100) and 37 (70)
6	$T_2$9	2-(2-Phenylethylidene)-1,3-dithiane	2560 and 760	b = 1.90–2.10 (m, 2H), 2.80–3.00 (m, 4H), 4.76 (d, *J* 8, 1H), 6.10–6.92 (m, 2H) and 7.40–7.80 (m, 5H)	222 (M^+, 35), 147 (70), 131 (93) and 77 (100)
7	$T_2$10	2-(1,3-Dithian-2-yl)-furan	2900, 1250, 1050 and 760	a = 1.85–2.10 (m, 2H), 2.90–3.00 (m, 4H), 5.25 (s, 1H), 6.36 (dt, 2H), 7.45 (br s, 1H)	186 (M^+, 50), 121 (40), 112 (100) and 84 (30)
8	$T_2$6	2-(3,4,5-Trimethoxyphenyl)-1,3-dithiane	1600 and 760	b = 1.80–2.10 (m, 2H), 2.80–3.20 (m, 4H), 3.80 (s, 6H), 3.85 (s, 3H), 5.10 (s, 1H), 6.60 (s, 1H) and 7.15 (s, 1H)	286 (M^+, s), 196 (55), 125 (35) and 78 (100)
9	$T_2$8	2-(3,5-Dimethoxy-4-hydroxyphenyl)-1,3-dithiane	3450, 1600 and 760	b = 1.80–2.10 (m, 2H), 2.80–3.20 (m, 4H), 3.75 (s, 6H), 5.16 (s, 1H), 6.62 (s, 1H) and 7.00 (s, 1H)	276 (M^+, 25), 198 (32), 154 (85), 83 (100) and 55 (40)
10	$T_3$1	2,2-Dimethyl-1,3-dithiane	3100 and 760	a = 1.65 (s, 6H), 1.90–2.00 (m, 2H) and 2.85–2.90 (m, 4H)	148 (M^+, 65), 133 (48), 115 (35), 74 (100) and 59 (70)
11	$T_3$2	2-(1-Chloromethyl)-1,3-dithiane	3100, 1520 and 760	a = 1.85–2.20 (m, 2H), 2.82–2.87 (m, 4H), 3.87 (d, *J* 7, 2H), 4.17 (t, *J* 7, 1H)	168 (M^+, 30), 134 (70), 119 (100) and 74 (75)
12	$T_3$3	2-Isopropyl-1,3-dithiane	2560, 1220 and 760	a = 1.55 (d, *J* 7, 6H), 2.10–2.50 (m, 2H), 3.10–3.30 (m, 5H) and 4.48 (d, *J* 6, 1H)	162 (M^+, 35), 119 (100) and 55 (45)
13	$T_3$4	2-(1-Prop-1-enyl)-1,3-dithiane	3150, 1220 and 760	b = 1.70 (d, *J* 7, 3H), 1.75 (m, 2H), 2.80–3.40 (m, 4H), 4.35 (d, *J* 8, 1H) and 6.20–6.50 (m, 2H)	160 (M^+, 30) and 85 (100)
14	$T_3$5	1-(1,3-Dithian-2-yl)-propan-2-one	3150, 2900, 1710, 1410, 1360 and 1160	a = 1.70–2.15 (m, 2H), 2.21 (s, 3H), 2.80–2.95 (m, 8H) and 4.47 (t, *J* 9, 1H)	176 (M^+, 95), 133 (98), 119 (82), 91 (60), 73 (100) and 59 (72)
15	$T_3$6	1-(2-Methyl-1,3-dithian-2-yl)-propan-2-one	3150, 2905, 1715 and 760	a = 1.60 (s, 3H), 2.15 (s, 3H), 1.80–2.20 (m, 2H), 2.85–3.00 (m, 4H) and 3.1 (s, 2H)	190 (M^+, 60), 147 (100), 133 (55), 107 (651), 87 (70) and 59 (58)
16	$T_3$7	4-*tert*-Butylcyclohexanone thioketal	3150, 2910 and 760	a = 0.85 (s, 6H), 0.95 (s, 3H), 0.95–1.92 (m, 6H), 1.95–2.25 (m, 2H), 2.25–2.40 (m, 3H) and 2.70–2.90 (m, 4H)	244 (M^+, 100)
17	$T_3$8	2-Menthone thioketal	3000, 1410, 1220 and 760	a = 0.80–1.10 (m, 9H), 1.15–1.60 (m, 5H), 1.65–2.20 (m, 5H), 2.50–3.00 (m, 4H)	244 (M^+, 100), 159 (90), 137 (62) and 81 (52)
18	$T_3$9	Camphor 2-thioketal	3150 and 760	a = 0.90–1.00 (m, 4H), 1.25 (s, 9H), 1.50–1.80 (m, 5H) and 1.82 (m, 4H)	256 (M^+, 5), 217 (5), 69 (70) and 55 (100)
19	$T_1$1	2-Phenyl-1,3-dithiolane	—	a = 3.35–3.60 (m, 4H), 5.65 (s, 1H), 7.25–7.40 (m, 3H), 7.45–7.60 (m, 2H)	182 (M^+, 68), 153 (100), 121 (82) and 77 (35)
20	$T_1$2	2-(4-Methoxyphenyl)-1,3-dithiolane	—	a = 3.30–3.45 (m, 4H), 3.8 (s, 3H), 5.6 (s, 1H), 6.87 (d, *J* 9, 2H), 7.47 (d, *J* 9, 2H)	212 (M^+, 5), 168 (181) and 135 (100)
21	$T_1$3	2-(4-Chlorophenyl)-1,3-dithiolane	—	a = 3.30–3.60 (m, 4H), 5.60 (s, 1H), 7.30 (d, *J* 9, 2H) and 7.50 (d, *J* 9, 2H)	216 (M^+, 33), 188 (22), 155 (100) and 137 (28)
22	$T_1$4	2-(4-Nitrophenyl)-1,3-dithiolane	—	a = 3.35–3.60 (m, 4H), 5.60 (s, H), 7.67 (d, *J* 9, 2H) and 8.15 (d, *J* 9, 2H)	227 (M^+, 95), 199 (68), 182 (100), 166 (69), 152 (71) and 77 (80)
23	$T_1$6	2-(2-Phenethylidene)-1,3-dithiolane	—	a = 3.20–3.45 (m, 2H), 5.23 (d, *J* 9, 1H), 6.15–6.25 (d, *J* 9, 1H), 6.50 (d, *J* 18, 1H) and 7.20–7.40 (m, 5H)	208 (M^+, 82), 179 (32), 147 (75) and 115 (100)
24	$T_1$8	Cyclohexanone thioketal	—	a = 1.35–1.45 (m, 2H), 1.55–1.70 (m, 4H), 2.00 (t, *J* 6, 4H) and 3.25 (s, 4H)	174 (M^+, 38), 146 (46) and 131 (100)
25	$T_1$9	3-Methylcyclohex-2-enone thioketal	—	a = 1.70 (s, 3H), 1.75–2.00 (m, 4H), 2.10–2.20 (m, 2H), 3.25–3.45 (m, 4H) and 5.6 (s, 1H)	186 (M^+, 46), 158 (75), 126 (63) and 111 (32)
26	$S_3$10	Cyclodecanone thioketal	—	a = 1.30–1.60 (br s, 14H), 1.95–2.10 (m, 4H) and 3.3 (s, 4H)	230 (M^+, 23), 197 (60) and 131 (100)

* T_xn = compound number n of Table x. $S_3$10 = compound **10** of Scheme 3.



Scheme 3 *Reagents and conditions*: i = HS⁓SH, Clay, CCl_4, reflux, 4 h

transdithiocaetalization, although Al_2O_3 was found to be inactive. A variety of aryl acetals having substituents such as NO_2, CO_2H, OH, Cl *etc.* including unsaturated acetals have been successfully transformed into 1,3-dithianes in high yields. Table 3 summarizes the transdithioacetalization of a variety of aliphatic acetals and ketals catalysed by kaolinitic clay. A remarkable feature observed here is that keto acetals underwent chemoselective transdithioacetalization in preference to ketone in excellent yields (entries 5 and 6). Even sterically hindered ketones (entries 7–10), halogeno and unsaturated acetals (entries 2 and 4) have been successfully transformed into dithianes and dithiolanes in high yields (see Table 4 for spectroscopic data on selected products).

The enhanced catalytic activity of the acid activated clay may be attributed to a significant level of Lewis acidity derived from Al remaining in the platelet edges and the Bronsted acidity of coordinated hydroxy groups of Al^{3+}, Fe^{3+} and Ti^{4+} ions relocated in the interlamellar space of the clay.[18,19] In conclusion, natural clay is an effective and convenient catalyst for transdithioacetalization of acetals, ketals, oximes, enamines and tosylhydrazones, a novel method likely to have wide application in organic synthesis.

Experimental

Preparation of 6-bromo-4-methoxycarbonylmethyl-2-pyridyl 3,3-dimethoxypropyl ether 2

A mixture of bromopyridone (245 mg, 1 mmol), 3-bromopropionaldehyde dimethyl acetal (183 mg, 1 mmol) and potassium carbonate (207 mg, 1.5 mmol) in dry acetonitrile (25 ml) was refluxed on a water-bath for 6 h. After the reaction was complete (TLC), acetonitrile was removed from the mixture under reduced pressure and the residue was diluted with water (10 ml) and extracted with chloroform. Evaporation of the extract gave the crude product, which was purified by column chromatography to give the pure title compound **2** (247 mg, 87%).

Typical procedure for the preparation of 2-(4-methoxyphenyl)-1,3-dithiolane

4-Methoxyphenyl-1,3-dioxolane (1.8 g, 0.01 mol), ethane-1,2-dithiol (940 mg, 10 mmol) and clay (100 mg) in either benzene or CCl_4 (25 ml) was refluxed for 4 h. After the reaction was complete (TLC), the clay catalyst was filtered off and the filtrate worked up to give the product which was purified by flash chromatography to afford the 1,3-dithiolane derivative (1.9 g, 90%) as a colourless liquid.

General procedure for transdithioacetalization of oximes, enamines and tosylhydrazones

The oxime, enamine or tosylhydrazone (10 mmol), ethane-1,2-dithiol (10 mmol) and clay (10% by wt. of starting material) in CCl_4 was refluxed for 4–6 h. After completion of the reaction (TLC), the clay catalyst was filtered off and the filtrate worked up to give a crude product, purification of which by flash chromatography gave the dithiolanes.

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