An Expeditious Synthesis of Dithioacetals Using Zeolites[#]

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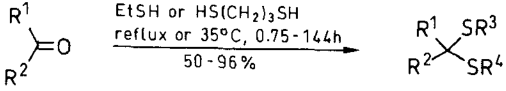
A simple and efficient catalytic method for dithioacetalization of various carbonyl compounds (saturated and α,β-unsaturated aliphatic, aromatic, heteroaromatic and hindered) with ethanethiol and 1,3-propanedithiol using H–Y and H-mordenite (H–M) zeolites is described. The reaction affords moderate to excellent yields of the corresponding products.

Zeolites as catalysts have received considerable attention in recent years due to their characteristic properties such as shape selectivity, acidity and thermal stability.[1] Their catalytic potential in petrochemistry and in oil processing is well documented.[2] However, their application in general organic synthesis has not been fully explored. The acid and base properties of zeolites which can be modified by exchanging the cations have made them versatile catalysts for a wide range of reactions.[3] Recently, in our preliminary communication we have reported the thioacetalization of carbonyl compounds by 1,2-ethanedithiol using H–Y zeolite (Si/Al = 2.43).[4] Further, we have studied and extended the scope of this reaction for the protection of carbonyl compounds with ethanethiol and 1,3-propanedithiol. Also, the efficacy of some other zeolites for dithioacetalization has been investigated.

In recent years, there have been continuing improvements in the methods of preparation of dithioacetals. The synthetic utility of dithioacetal as a protecting group,[5] as a masked methylene function,[6] and as an acyl-nucleophile[7] synthon has been well documented. In general, dithioacetals have been prepared by protic acid or Lewis acid catalyzed condensations of carbonyl compounds with thiols.[5,8–9] Lewis acids used for this purpose are boron trifluoride–diethyl ether complex, zinc chloride or aluminum chloride. More recently, Nafion-H catalyst,[10] silica gel treated with thionyl chloride,[11] anhydrous lanthanum chloride,[7] anhydrous iron(III) chloride[12] dispersed on silica gel, have been developed for this purpose. However, in many of these methods results obtained were erratic and yields often disappointing.

Now we report that H–Y and H-mordenite zeolites[13] serve as excellent catalysts for dithioacetalization of carbonyl compounds (Scheme).



1a-s **2a-s**

Scheme

Thus, dithioacetals were prepared in moderate to excellent yields by the direct condensation of ethanethiol or 1,3-propanedithiol with carbonyl compounds using H–Y or H–M zeolites. The results are summarized in the Table. The reaction is clean and workup procedure is exceedingly simple only involving the filtration of zeolite and removal of the solvent to obtain the product in high state of purity. The recovered zeolite can be reactivated for reuse by heating it at 500 °C in the presence of air.

The present procedure for thioacetalization is quite general as a wide range of carbonyl compounds such as saturated, **1a,c,i,m,n**, and α,β-unsaturated, **1d**, aliphatic, aromatic **1f–h**, **1j–k**, **1o–q**, heteroaromatic, **1b**, and hindered, **1k**, **1q–s**, can be thioacetalized under very mild conditions. The superiority of zeolites over conventional methods can be clearly visualized in the case of sterically hindered ketones and bulky substrates where the corresponding dithioacetals have been obtained in excellent yields (Table, **2o–s**). In this connection our methodology for dithioacetalization is noteworthy. However, aromatic and hindered ketones on reaction with ethanethiol afforded only a moderate yield of the desired products (Table, **2j–l**) which is in accordance with the earlier observation with aluminum chloride.[22]

It may be pertinent to mention here that use of other acidic zeolites such as H-ZSM-5 (Si/Al = 45)[14] and molecular sieves 4 Å or 5 Å was a failure. The comparative data presented in the Table reveal that H–Y zeolite may be considered superior to H-mordenite particularly in the case of aromatic and hindered ketones where the time required for the reaction is less and relatively the yield is better. The observed best performance of H–Y zeolites compared to H-ZSM-5 (pore size, 0.54 × 0.56 and 0.51 × 0.55 nm) and H-mordenite (pore size 0.67 × 0.70 nm) may be attributed to its large pore opening (0.74 nm), three dimensional channel system and higher concentration of acid sites.[15]

In conclusion, from commercially available H–Y and H–M zeolites we have developed a convenient heterogeneous catalytic method for dithioacetalization of a variety of carbonyl compounds including the aromatic and hindered ketones. Thus, the method described here provides a convenient access to dithioacetals which are important as protecting groups in organic synthesis. In addition the heterogeneous catalytic method brings advantages in respect of easy separation, higher and consistent yields and regeneration of the catalyst.

Prior to use zeolites were calcined at 500 °C in the presence of air. The carbonyl compounds and solvents used for reaction were freshly distilled.

Dithioacetals 2a–s; General Procedure:

To a solution of the appropriate carbonyl compound (20 mmol) in hexane or CH_2Cl_2 were added successively H–Y or H–M zeolite (0.5 equiv. by weight with respect to the carbonyl compound) and C_2H_5SH or $HS(CH_2)_3SH$ (30 mmol) and the mixture was refluxed with stirring for the specified period of time (Table). The solution was just warmed to 35 °C in case where CH_2Cl_2 was used as a solvent. The process of reaction was monitored by TLC followed by GLC analysis (column OV-101). After the reaction was complete, the zeolite was filtered and the filtrate was diluted with hexane or

Table. Dithioacetals **2a**–**s** Prepared

Product[a]	R^1	R^2	R^3	R^4	H–Y Zeolite		H–M Zeolite		mp (°C) or bp (°C)/Torr	Lit. mp (°C) bp (°C)/Torr
					Time (h)[b]	Yield[c] (%)	Time (h)[b]	Yield[c] (%)		
2a	Pr	H	Et	Et	3	92[e]	4	91[e]	225	219–220/750[16]
2b	2-furyl	H	Et	Et	3	93[e]	5	91[e]	125/10	135/17[17]
2c	n-C_6H_{13}	H	$(CH_2)_3$		2.5	93	2.5	93	–[f]	–[18]
2d	MeCH=CH	H	$(CH_2)_3$		1	91	1	91	85/1	72/0.4[19]
2e	2-furyl	H	$(CH_2)_3$		1	94	1	94	41	43[20]
2f	Ph	H	$(CH_2)_3$		1	95	1	94	73	74–75[21], 71[26], 73[22]
2g	4-$(O_2N)C_6H_4$	H	$(CH_2)_3$		0.75	95	0.75	94	144–145	145–146[22]
2h	3,4,5-$(MeO)_3C_6H_2$	H	$(CH_2)_3$		1.5	96	1.5	96	93–94	98–100[23]
2i	$(CH_2)_5$		Et	Et	3	93[e]	6	90[e]	60/10	35/2[18]
2j	Ph	Me	Et	Et	30[d]	65[e]	50[d]	60[e]	–[f]	–[18]
2k	[g]		Et	Et	20[d]	90[e]	50[d]	50[e]	32	31–33[24]
2l	[g]		Et	Et	30[d]	70[e]	50[d]	60[e]	–[f]	–
2m	n-C_6H_{13}	Me	$(CH_2)_3$		1.5	94	1.5	93	130/0.1	122–123/0.05[21]
2n	$(CH_2)_4$		$(CH_2)_3$		2	95	2	95	100/0.1	86–87/0.05[25]
2o	Ph	Me	$(CH_2)_3$		1	94.5	1	93	34–35	35[26]
2p	Ph	Ph	$(CH_2)_3$		6[d]	92	7[d]	92	114	110[27]
2q	[g]		$(CH_2)_3$		2[d]	96	2.5[d]	94	87–88	–[28]
2r	[g]		$(CH_2)_3$		10[d]	93	40[d]	85	41	41–42[7]
2s	[g]		$(CH_2)_3$		96[d]	60	144[d]	66	–[f]	140–143/4[7]

[a] All products were characterized by their IR, ^1H NMR and mass spectroscopic data.
[b] Completion of the reaction monitored by GC analyses (column OV-101).
[c] Unoptimized yields of isolated pure products.
[d] The equivalent amount (by weight) of zeolite with respect to carbonyl compound used for completion of the reaction.
[e] Reaction performed in CH_2Cl_2 at 35 °C.
[f] Viscous undistilled liquid purified by silica gel column chromatography. Satisfactory microanalysis obtained for **2l**.
[g] In these cases as educts were used: 1-indanone for **2k**, (–)-menthone for **2l** and **2r**, α-tetralone for **2q** and (±)-camphor for **2s**.

CH_2Cl_2 (40 mL), washed with 10% aq NaOH (2 × 30 mL) to remove the excess thiol. The organic layer was then washed with H_2O, brine and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford the pure product or could be purified by column chromatography, recrystallization or distillation.

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