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One-pot Preparation of 2-Chloromethyldioxolanes and 2-Aminothiazoles from Chloromethyltrioxanes

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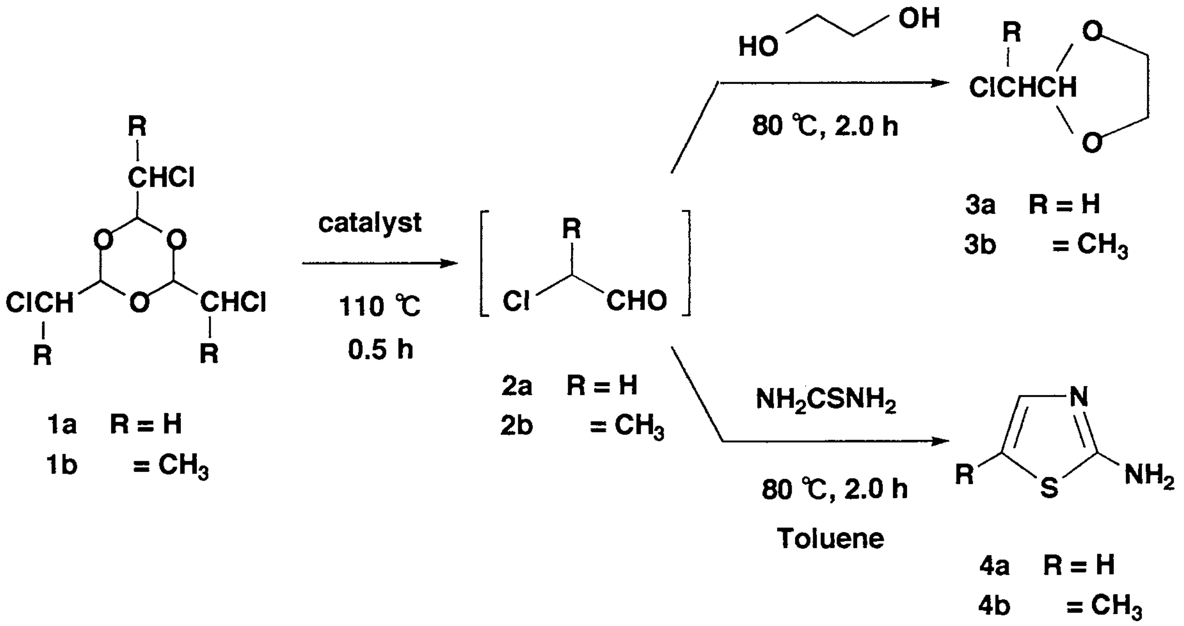
Thermal degradation of chloromethyltrioxanes in the presence of catalytic amount of montmorillonite clay generated α-chloroaldehydes with high purity, which were treated *in situ* with ethylene glycol or thiourea to afford 2-chloromethyldioxolanes and 2-aminothiazoles, respectively. The clay catalysts used were removed by filtration.

α-Halogenated aldehydes have a very attractive structure as useful synthon in organic synthesis. They act as halides, aldehydes, and active methylene compounds. Because of the diversity of reactivity α-haloaldehydes are important starting materials for various kinds of organic compounds including polymers.1) α-Haloaldehydes, however, are usually unstable and extremely labile to form amorphous polymeric materials which can not reproduce a starting α-haloaldehyde monomer.2) α-Chloroaldehydes, for example, are commercially available only in aqueous solution, which sometimes prevent their use in non-aqueous system. One of the most practical routes to obtain pure α-chloroaldehyde is thermal degradation of chloromethyltrioxane. In our continuous study on α-halo carbonyl compounds we found that 2,4,6-tris(chloromethyl)trioxane, a cyclic trimer of α-chloroacetaldehyde, was readily prepared from chlorination of paraldehyde and was stable precursor of α-chloroacetaldehyde.3) While we investigated catalysts for the degradation, montmorillonite clay was found to be efficient catalyst. α-Chloroacetaldehyde generated was then treated *in situ* with ethylene glycol to afford 2-chloromethyldioxolane in high yield. Similarly, treatment with thiourea yielded 2-aminothiazole. In this communication we wish to report a simple one-pot process of 2-chloromethyldioxolanes and 2-aminothiazoles synthesis from chloromethyltrioxanes.

Trioxanes having cyclic trimer structure of aldehyde are known to yield their parent aldehyde by acid-catalyzed thermal degradation.4) Thus the distillation conditions for the isolation of α-chloroaldehyde have been investigated. Without any catalyst chloromethyltrioxane (1a) is too stable to thermal degradation.

On the other hand, *p*-dodecylbenzenesulfonic acid was found to be an effective catalyst for the degradation to give 2a in 85% isolated yield. Using *p*-dodecylbenzenesulfonic acid as catalyst, however, side products including oligomers of 2a and aldol condensation products are still involved in the distilled products. During the distillation process several side reactions were unavoidable because of instability of 2a. Thus 2a should be submitted to further chemical transformation without its isolation. In order to show the possibility of this approach, one-pot synthesis of 2-chloromethyldioxolanes (3) and 2-aminothiazoles (4) from chloromethyltrioxanes has been investigated as shown in Scheme 1.



Scheme 1.

In the presence of *p*-toluenesulfonic acid or H_2SO_4 1a was thermally degradated, followed by the treatment with ethylene glycol to give 3a with only low yield (entries 14,16). A variety of acids were examined in order to find a suitable catalyst for this practical one-pot process. We found that some montmorillonite clays catalyzed the reaction quite efficiently to furnish 2a without side products. The obtained 2a was quite pure enough to use for the following acetalization reaction without isolation. The clay catalyst used for the thermal degradation did not need to be removed and was then utilized also as the acetal formation catalyst. For example, heating the mixture of 1a and 6wt% of K10 catalyst5) without organic solvent 1a was completely degradated into 2a within 30min, which was detected by gas chromatographic analysis. Subsequent treatment of 2a with ethylene glycol afforded 3a in 90% yield (entry 2). Using this catalyst 3b was also obtained similarly from 1b in good yield (entry 9). Heating time for the catalytic thermal degradation of 1 should be less than 1h, otherwise 2 was gradually changed to the undesired oligomeric materials, which resulted in lowering the final yield of 3 (entry 3).

If ethylene glycol is present in the thermal degradation step, the catalytic activity of the catalyst depressed significantly. Ethylene glycol should be introduced after degradation completed. Other montmorillonite clays such as KS, KP10, KSF/O, Fuller's earth[6] also act as effective catalyst for the thermal degradation of 1 in this process. The clay catalysts used in this system could be removed readily by simple filtration after the reactions completed. Without catalyst the thermal degradation occurs very slowly to result in low yield of 3a under the reaction conditions (entry 19).

Table 1. Synthesis of α-Chloroaldehyde Derivatives

Entry	Chloromethyl-trioxane	Catalyst[a)]	Amount of Catalyst[b)] %	Depolymerization Time min	Product	Isolated Yield %
1	1a	K10	1	30	3a	85
2	1a	K10	6	30	3a	90
3	1a	K10	6	120	3a	54
4	1a	K10	10	30	3a	76
5	1a	KS	6	15	3a	81
6	1a	KP10	6	30	3a	77
7	1a	KSF/O	6	15	3a	72
8	1a	Fuller's Earth	5	30	3a	76
9	1b	K10	6	30	3b	88
10	1b	Fuller's Earth	6	30	3b	82
11	1a	K10	6	30	4a	81
12	1b	K10	6	30	4b	78
13	1a	HSZ-620HOA[c)]	6	30	3a	47
14	1a	*p*-TsOH	6	30	3a	33
15	1a	$(COOH)_2$	6	30	3a	26
16	1a	H_2SO_4	6	30	3a	24
17	1a	$H_3[P(W_3O_{10})_4]$	6	30	3a	68
18	1a	$NiSO_4$	6	30	3a	3
19	1a	—— d)	0	30	3a	18

a) Catalysts were used without calcination or further purification.
b) Based on 1. c) H-Mordenite is commercially available from Tosoh Co.,Ltd.(Japan). d) Without catalyst.

This process was applied to prepare 2-aminothiazoles which are important starting materials for pharmaceuticals. Satisfactory yields of 4a and 4b were obtained again using K10 catalyst (entries 11,12). Results of the preparation of 3 and 4 are summarized in Table 1.

Although acidic sites in montmorillonite clays may act as an acid catalyst for the above reactions, the detailed mechanism is not clear.

Typical procedure for the preparation of 2-chloromethyl-1,3-dioxolane is as follows: Mixture of 1a (0.50 g, 2.12 mmol) and montmorillonite K10(0.03 g) was heated at 110 ℃ for 0.5 h, where GC analysis showed generation of 2a. To 2a generated ethylene glycol(0.47 g, 7.57 mmol) was added and the mixture was stirred for 2 h at 80 ℃. After the reaction completed K10 was removed by simple filtration. Distillation of the filtrate afforded 2-chloromethyl-1,3-dioxolane (3a) (0.70 g, 5.73 mmol) in 90% yield.

In conclusion, this method has enabled one-pot preparation of α-chloroaldehyde derivatives. To our knowledge, this would be a simple and economical method to obtain α-chloroaldehyde derivatives in excellent yield.

References

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4) "The Merck Index, Ninth Edition," Merck & Co.,Inc. (1976), p6837.
5) Montmorillonite K10 is commercially available from Aldrich Chemical Company,Inc. and Fluka Chemie AG. Other Montmorillonite K series are commercially available from Nissan Girdler Catalyst Co.,Ltd.(Japan).
6) Fuller's earth is commercially available from Aldrich Chemical Company,Inc. and Kanto Chemical Co.,Inc.(Japan).

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