

Intramolecular Condensation of 1,2- $\text{C}_6\text{H}_4(\text{CH}_2\text{RH})_2$ ($\text{R} = \text{O}, \text{S}, \text{and NH}$) to Yield Heterocyclic Compounds over Halide-cluster Catalysts

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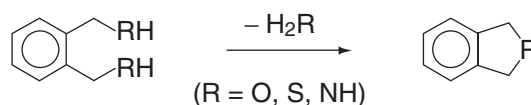
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1,2-Benzenedimethanol was reacted under a helium stream in the presence of $[(\text{Nb}_6\text{Cl}_{12})\text{Cl}_2(\text{H}_2\text{O})_4] \cdot 4\text{H}_2\text{O}$ supported on silica gel. When the temperature was raised above 200 °C, catalytic activity of the cluster for cyclization appeared, yielding 1,3-dihydroisobenzofuran in 91% selectivity at 350 °C. The corresponding halide clusters of tantalum and tungsten also catalyzed the reaction. *cis*-1,2-Cyclohexanedimethanol and 1,4-butanediol exclusively produced the corresponding furans. 1,2-Benzenedimethanamine and 1,2-benzenedimethanethiol selectively afforded isoindoline and 1,3-dihydrobenzo[*c*]thiophene, respectively.

Various types of halide clusters have been synthesized by combining 19 types of Group 3–7, lanthanide, and actinide transition metals with four types of halogen atoms as ligand.¹ These halide clusters have several characteristic features: metal–metal bonds that are similar to those in bulk metals, intermediate oxidation states of the metal atoms between 1+ and 3+, multicenter and multielectron systems, low vapor pressure, and high melting point for metal halogenated compounds. The clusters are expected to be thermally stable, because high temperatures above 650 °C are required for the syntheses. Taking all of these features into consideration, we have started to use halide clusters as catalysts. Halide clusters have been found to catalyze various types of reactions, the characteristics of which can be seen in the one-step synthesis of indenenes from benzaldehyde with alkyl ketones² and that of 3-methylbenzofuran from phenol and acetone.³ In these ring-closure reactions, the number of product molecules increases, which is thermodynamically favorable at higher temperatures under constant pressure, according to Le Chatelier's principle. This paper describes another type of eliminative ring-closure reaction for compounds containing –OH, –SH, or –NH₂ groups (Scheme 1), by taking advantage of the thermal stabilities of the cluster catalysts.

Halide-cluster complexes were synthesized according to published procedures. Methanol (330 mL) was added to a 1-L flask containing $[(\text{Nb}_6\text{Cl}_{12})\text{Cl}_2(\text{H}_2\text{O})_4] \cdot 4\text{H}_2\text{O}$ (**1**) (1.0 g). After dissolution of the cluster, silica gel (Nippon Aerosil, Tokyo, Aerosil 380 m² g^{−1}, 19.0 g) was added and allowed to stand for 1 h with occasional shaking. Then the solvent was evaporated to dryness under vacuum at ambient temperature. Samples of the dried silica gel were crushed and screened to 150–200 mesh. All of the clusters were supported on the silica gel in the same way at 5.0% by weight. The other chemicals were commercially available and used as received. The reaction was performed in a conventional continuous-flow microreactor operated at atmospheric pressure. In a typical experiment, a weighed sample (10 mg) of **1** supported on silica gel was packed in a borosilicate glass tube (3 mm i.d.) and placed in the center of an electric



Scheme 1.

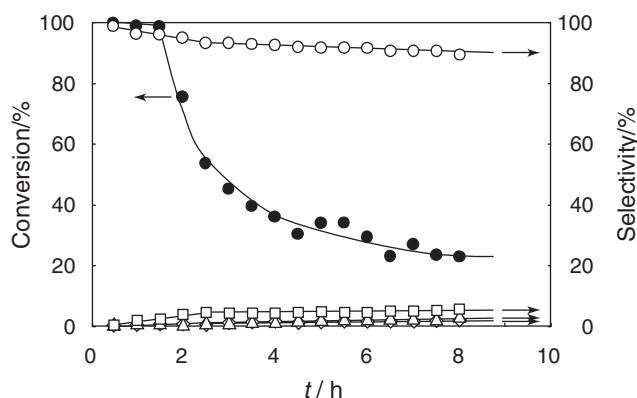


Figure 1. A typical reaction profile for the cyclization of 1,2-benzenedimethanol in a helium stream over $[(\text{Nb}_6\text{Cl}_{12})\text{Cl}_2(\text{H}_2\text{O})_4] \cdot 4\text{H}_2\text{O}$ (**1**)/SiO₂ at 350 °C. Following the treatment of **1**/SiO₂ (10 mg) in a helium stream (600 mL h^{−1}) at 350 °C for 1 h, reaction was started by introduction of 1,2-benzenedimethanol (10% aqueous solution, 0.69 mL h^{−1}, 0.50 mmol h^{−1}) to the helium stream without changing the temperature. Conversion = products/(products + recovered 1,2-benzenedimethanol) × 100%, selectivity = product/(total amount of products) × 100%. Conversion of 1,2-benzenedimethanol (●), selectivity for 1,3-dihydroisobenzofuran (○), selectivity for 2-methylbenzyl alcohol (□), selectivity for 2-methylbenzaldehyde (△), selectivity for combined amount of *o*-xylene and toluene (◇).

furnace. The catalyst sample was initially heated to 350 °C for 1 h in a helium stream (600 mL h^{−1}), followed by introduction of 1,2-benzenedimethanol (10% aqueous solution, 0.69 mL h^{−1}, 0.50 mmol h^{−1}) into the stream using a syringe pump at 350 °C. The reaction was monitored every 30 min by trapping the reaction gas followed by analysis using GLC. The reactor effluent was collected in an ice-cold trap containing water–methanol or tetrahydrofuran for subsequent analyses with GLC and GC/MS. Each product was identified by comparison of the GLC retention time with that of an authentic sample.

Figure 1 shows a typical reaction profile for **1**/SiO₂ at 350 °C. The catalytic activity decreased with time, while the selectivity leveled off after reaction for 3 h. Cyclization yielding

Table 1. Cyclization of 1,2-benzenedimethanol over halide-cluster catalysts^a

Catalyst	Conversion /% ^b	Selectivity/% ^c				
		1,3-Dihydro- isobenzofuran	2-Methylbenzyl alcohol	2-Methyl- benzaldehyde	<i>o</i> -Xylene	Toluene
[(Nb ₆ Cl ₁₂)Cl ₂ (H ₂ O) ₄]·4H ₂ O (1)/SiO ₂	26.3	91.0	4.6	1.7	1.6	1.1
[(Nb ₆ Cl ₁₂)Cl ₂ (H ₂ O) ₄]·4H ₂ O (1)/SiO ₂ ^d	21.0	90.4	4.4	0.1	2.6	1.9
(H ₃ O) ₂ [(Mo ₆ Cl ₈)Cl ₆]·6H ₂ O/SiO ₂	11.5	51.0	35.9	5.6	4.5	3.0
[(Ta ₆ Cl ₁₂)Cl ₂ (H ₂ O) ₄]·4H ₂ O/SiO ₂	16.8	88.7	5.4	1.7	2.5	1.7
(H ₃ O) ₂ [(W ₆ Cl ₈)Cl ₆]·6H ₂ O/SiO ₂	15.3	81.4	12.0	2.0	2.6	2.0
[(Nb ₆ Cl ₁₂)Cl ₂ (H ₂ O) ₄]·4H ₂ O (1) ^e	3.3	68.7	21.8	4.7	2.5	2.2
SiO ₂	0.7					
No catalyst	0.1					

^aAfter treatment of the catalyst (10 mg) in a helium stream (600 mL h⁻¹) at 350 °C for 1 h, reaction was initiated by introduction of 1,2-benzenedimethanol (10% aqueous solution, 0.69 mL h⁻¹, 0.50 mmol h⁻¹) into the stream at 350 °C. ^bConversion = products/(products + recovered 1,2-benzenedimethanol) × 100% at 6–7 h after the reaction had commenced. ^cSelectivity = product/(total amount of products) × 100% at 6–7 h after the reaction had commenced. ^dIn a hydrogen stream. ^eUnsupported crushed crystals of **1**.

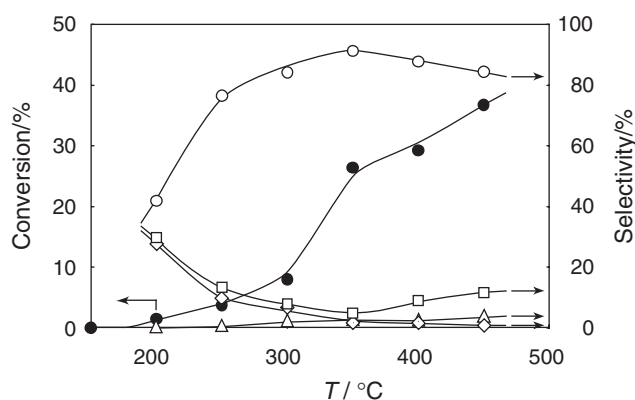


Figure 2. Temperature effect on the cyclization of 1,2-benzenedimethanol in a helium stream over [(Nb₆Cl₁₂)Cl₂(H₂O)₄]·4H₂O (**1**)/SiO₂ at 6–7 h after the reaction started. Both initial treatment and reaction temperatures were altered concomitantly. The other reaction conditions are the same as described for Figure 1. Conversion = products/(products + recovered 1,2-benzenedimethanol) × 100%, selectivity = product/(total amount of products) × 100%. Conversion of 1,2-benzenedimethanol (●), selectivity for 1,3-dihydroisobenzofuran (○), selectivity for 2-methylbenzyl alcohol (□), selectivity for 2-methylbenzaldehyde (△), selectivity for combined amount of *o*-xylene and toluene (◇).

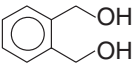
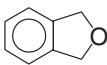
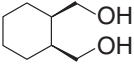
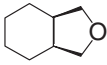




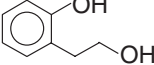
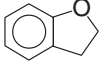
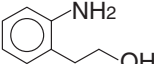
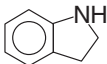
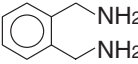
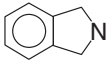
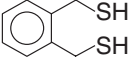
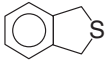
1,3-dihydroisobenzofuran proceeded with a selectivity of 92% at 31% conversion during a period of 3–8 h, and the turnover frequency per Nb₆-cluster molecule was 0.33 s⁻¹, assuming that all of the cluster molecules were active. The material balance was 98% at 3–8 h after the reaction had started. When **1**/SiO₂ was treated at 350 °C, the development of a Brønsted acid site was observed. The Brønsted acid site can be attributed to a hydroxo ligand of [(Nb₆Cl₁₂)Cl(OH)(H₂O)₃] that was formed by elimination of hydrogen chloride formed from the aqua and chloro ligands of **1**.⁴ The effect of the reaction temperature on activity and selectivity over **1** is presented in Figure 2. Substantial catalytic activity developed above 200 °C. Cyclization was the main reaction at all of the temperatures tested.

Table 1 lists the catalytic activity of some halide clusters and related compounds at 6–7 h after the reactions had started at 350 °C. Niobium, tantalum, and tungsten halide clusters supported on SiO₂ catalyzed the cyclization with a selectivity of higher than 81%. Unsupported crystalline niobium clusters, whose specific surface area was 4.55 m² g⁻¹, also catalyzed the reaction regardless of the low activity. In contrast, the selectivity was not greatly increased over a supported molybdenum cluster, which has platinum-like character to activate hydrogen,⁵ to yield the hydrogenolysis product 2-methylbenzyl alcohol with 36% selectivity.

Some α,δ -diols were allowed to react, and the results are listed in Table 2. *cis*-1,2-Cyclohexanedimethanol, 1,4-butanediol, and 2-hydroxyphenethyl alcohol afforded the corresponding cyclization products selectively, although they have α -hydrogens to yield olefins. On the other hand, *cis*-2-butene-1,4-diol scarcely afforded the corresponding cyclization product. Isomerization of olefins has been observed over halide-cluster catalysts,⁶ and hence most of the reactant would be changed to 4-hydroxybutylaldehyde followed by decomposition at high temperature. As Table 2 shows, 2-aminophenethyl alcohol exclusively produced indoline. We have reported *N*-alkylation of amines with alcohols over halide-cluster catalysts, where the C–O bonds of the alcohols were cleaved.⁷ Not the C–N but the C–O bond of 2-aminophenethyl alcohol was cleaved in this case as well. When 1,2-benzenedimethanamine was applied to the reaction, cyclization proceeded to yield isoindoline with 94% selectivity. 1,2-Benzenedimethanethiol afforded the cyclization product 1,3-dihydrobenzo[*c*]thiophene (62% selectivity) with its dehydrogenation product 2-benzothiophene (11% selectivity).

There have been many reports on the catalytic cyclization of 1,2-benzenedimethanol; solid acids such as alumina and zeolites have been reported for the catalyst. However, there is no report of the catalytic cyclization of 1,2-benzenedimethanamine or 1,2-benzenedimethanethiol, as far as we know. Even in the cases of α,δ -diamine or α,δ -dithiol, examples of catalytic cyclization are rare. There are some reports of the catalytic cyclization of 1,4-butanediamine,⁸ and ZSM-5⁹ and pentasil zeolite¹⁰ have been reported for the catalyst. There is only one report on the catalytic

Table 2. Intramolecular cyclization over $[(\text{Nb}_6\text{Cl}_{12})\text{Cl}_2(\text{H}_2\text{O})_4] \cdot 4\text{H}_2\text{O}$ (1)/ SiO_2^{a}

Substrate	Conversion/%	Product	Selectivity/% ^b
	26.3		91.0
	100.0		98.9
	99.7		1.1
	99.9		99.9
	9.7		73.0 (1.7)
	100.0		96.9 (2.3)
	99.6		94.3 (4.5)
	56.8		61.8 (10.9)

^aNo solvent to introduce the reactants was used for reaction of *cis*-2-butene-1,4-diol. Water was used as solvent to introduce the other diols and 1,2-benzenedimethanamine (5–25% solution), and tetrahydrofuran was used to introduce the other substrates (5–33% solution) as nearly saturated solutions or light viscosity liquids at ambient temperature. The other reaction conditions are the same as in Figure 1. ^bValues shown in parentheses are the corresponding dehydrogenation products: benzofuran, indole, isoindole, and 2-benzothiophene, respectively.

cyclization of 1,4-butanedithiol over montmorillonite.¹¹ Thus, some zeolites catalyze particular intramolecular cyclization to yield heterocyclic compounds. Halide clusters have provided all types of heterocyclic compounds. A weak Brønsted acid site developed on the cluster during thermal treatment would be the active site of the catalyst.⁴

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