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Fe(III)-CATALYZED RADICAL CYCLIZATION OF CYCLOPROPANONE THIOACETAL*

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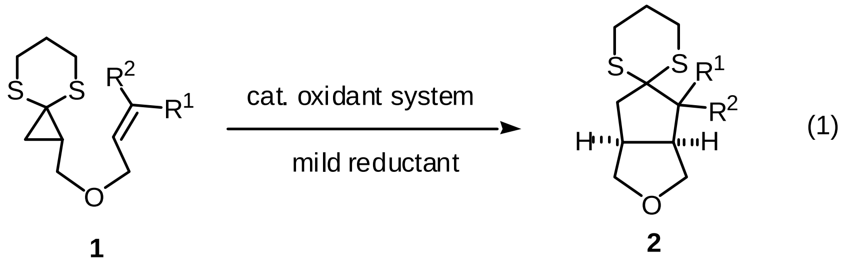
Abstract- Oxidative severance of the cyclopropane ring of cyclopropanonethioacetal derivatives caused by treatment of 10 mol% of Iron(III) perchlorate in acetonitrile under air, subsequent cyclization with the olefinic part and reduction by an addtional 1,3-dithiane giving *cis*-fused oxabicyclo[3.3.0]octane-1,1-trimethylenethioacetals in good yield.

The functionalized cyclopropane derivatives methylenecyclopropanes, [1]cyclopropanoneacetals,[2] and cyclopropylsulfides [3] have been used as convenient three-carbon unit building blocks in organic synthesis. Among the reactions using cyclopropanes, we were attracted by the cyclization of cyclopropanone acetal derivatives [2,3] *via* single electron transfer reaction. Several reports have been published inthifield, however, they require excess amounts of oxidants to realize the cyclization, except for a single report in which Iwata and his colleagues demonstrated [3+2] cycloaddition of cyclopropyl sulfides using 0.5 eq. of aminium salt. [3a] The stable nature of radical cation species of the MeS-SMe system due to its two-center three-electron bond is well recognized. [4] We thus hypothesized that a catalytic cyclization system may be produced by a proper choice of combination of an oxidant as single electron transfer initiator and a mild reductant using cyclopropanonetrimethylenethioacetals (**1**) [5,6] as a substrate, and the reaction would give oxabicyclo[3.3.0]octanethioacetals (**2**) (Eq. 1). In this communication, we describe how we have realized our initial idea in that intramolecular [3+2] cycloaddition of cyclopropanonethioacetals was accomplished by a catalytic reaction system; this is a record of this type of reaction using minimum amount of cationic oxidant as radical initiator. A very interesting finding is also described in that 1,3-dithiane works as a mild reducing agent and is essential to improve the efficiency of this reaction system.



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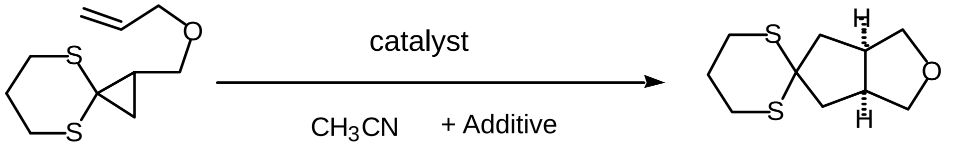

1a **2a** (2)

Table1. Oxidative radical cyclization *via* cyclopropane ring opening pathway

Entry	Catalyst [a]	Reaction Conditions	Yield (%) of **2a** [b]
1	CAN 20 mol%	80°C, 52 h	34
2	CAN 10 mol%	$NaClO_4$ (1.0 eq.), 80°C, 72 h	36
3	$Fe(ClO_4)_3$ 100 mol%	rt, 24 h	50
4	$Fe(ClO_4)_3$ 50 mol%	rt, 72 h	47
5	$Fe(ClO_4)_3$ 10 mol%	rt, air, 5 h	55
6	$Fe(ClO_4)_3$ 10 mol%	Additive 1 (2 eq.), rt, air, 5 h	43
7	$Fe(ClO_4)_3$ 10 mol%	Additive 2 (10 eq.), rt, air, 2 h	53
8	$Fe(ClO_4)_3$ 10 mol%	Additive 3 (10 eq.), rt, air, 2 h	46
9	$Fe(ClO_4)_3$ 10 mol%	Additive 4 (10 eq.), rt, air, 120 h	32
10	$Fe(ClO_4)_3$ 10 mol%	Additive 5 (1 eq.), rt, air, 1 h	68

a) Used as acetonitrile solution. b) Isolated yield. Additive 1: Benzyl alcoholl Additive 2: 2-Propanol Additive 3: Allyl alcohol. Additive 4: Dimethyl sulfide Additive 5: 1,3-Dithiane

Synthesis of oxabicyclo[3.3.0]octanedithioacetal (**2a**) has been attempted using several types of oxidants as a reaction initiator: Ceric (IV) ammonium nitrate (CAN), Manganese(III) acetate, Cerium(IV) ammonium sulfate, and Iron(III) perchlorate ($Fe(ClO_4)_3$). Reactions using CAN and $Fe(ClO_4)_3$ as oxidants gave the desired cyclized products (**2a**) [7] and (**3**). [8] This reaction was very sensitive for the solvent system and use of dried CH_3CN was essential to achieve the cyclization. [9] CAN/CH_3CN was initially chosen as an oxidant-solvent combination [10] and the desired *cis*-fused bicyclooctane (**2a**) was obtained as a single stereoisomer; [11] however, the chemical yield of **2a** was less than 40% even when the reaction was carried out in the presence of a larger amount of CAN, and use of an excess amount caused a significant drop of the chemical yield of **2a**. Ion(III) cation reportedly works well to complete the oxidative radical cyclization. [2c] We therefore focused on optimizing the reaction condition using Iron(III) salt instead of CAN as an oxidant, and succeeded in obtaining 55% of the desired product (**2a**) when dithioacetal (**1a**) was treated with 10 mol% of $Fe(ClO_4)_3$ in CH_3CN under atmospheric conditions (Table 1, Entry 5). It was assumed that an oxygen molecule works nicely to regenerate Iron(III) cation from the Iron(II) cation produced and to realize the catalytic system of the oxidant. However, the yield of **2a** was remained less than 50% when 1.0 eq. of $Fe(ClO_4)_3$ was employed as oxidant (Table 1, Entry 3), so other factors were believed to have spoiled the catalytic cycle, and to have reduced the chemical yield of the final product.

Since a fair amount of oxidized compound (**3**) was formed in this reaction, [8] it was assumed that the stable radical cation species of dithioacetal [4] may suffer from further undesired oxidation by oxygen molecule present in the solvent. Hence we sought to find a proper reducing agent (Entries 6-10), and

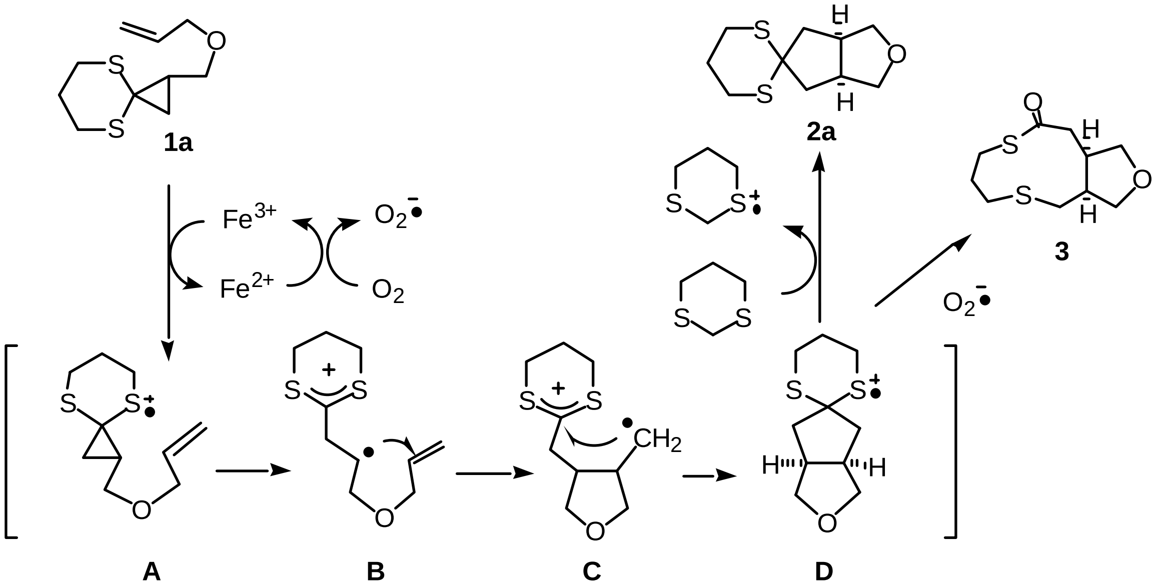

Figure 1. A plausible reaction mechanism of the cation-radical mediated cyclization

found that 1,3-dithian worked as an efficient mild reductant to improve the chemical yield (Entry 10*)*. We initially hypothesized a mechanism in which the starting cyclopropanonethioacetal (**1**) could form the self-reducing system, but in fact, the reaction required 1,3-dithiane to complete the catalytic cycle efficiently.

We assume there is a plausible mechanism for the present cation-radical mediated cyclization of cyclopropanonethioacetal (**1**), though the mechanistic details are not yet clear (Figure 1). The single-electron oxidation of the sulfur atom on compound (**1**) by Fe^{3+} ion generated the cation radical intermediate (**A**). Fe^{2+} ion formed at this reaction stage was oxidized by air and regenerated Fe^{3+} ion to make the catalytic cycle of the oxidant. The next intermediate (**B**) was suspected to be the real transition state because the highest heat of formation energy was estimated by semi-empirical MO (PM3) calculations of the four plausible intermediates (**A** to **D**). [12] Once this radical species (**B**) was generated, the next step proceeded rapidly and formed the final intermediate (**D**) through the intermediate (**C**). 1,3-Dithian may contribute to the rapid reduction of **D** to produce the final product. As mentioned before, the stable nature of the radical cation form of the final intermediate (**D**) makes 1,3-dithian necessary as a mild reductant to complete the cyclization system.

To determine the scope and limitation of this radical-cation mediated cyclization, five types of allyl ethers were subjected to the reaction and the results are summarized in Table 2. Except for one case, the cyclization proceeded nicely and gave the corresponding bicyclo[3.3.0]octane derivatives in good yield (Entries 1-4). Unfortunately no cyclized product was obtained when isopropenyl ether (**1f**) was subjected to the reaction even though the reaction was carried out for 24 h (Entry 5). The stereochemistry of the cyclized products was determined by ^{1}H NMR, and it was found that only *cis*-fused compounds (**2)** were produced in all reactions. The stereochemistry was partially controlled at the α-position of dithioacetals and thermodinamically stable *cis-trans* compound (**2**) were obtained as major isomer for the reactions of **1b**, **1d**, and **1e** (Entries 1, 3, and 4).[13]

In conclusion, we have demonstrated an efficient synthesis of oxabicyclo[3.3.0]octane dithioacetal (**2**) *via* single electron transfer-mediated cyclization using a catalytic amount of $Fe(ClO_4)_3$ in the presence of 1 eq. of 1,3-dithiane as a mild reducing agent. This is the first example of a well-controlled and truly catalytic

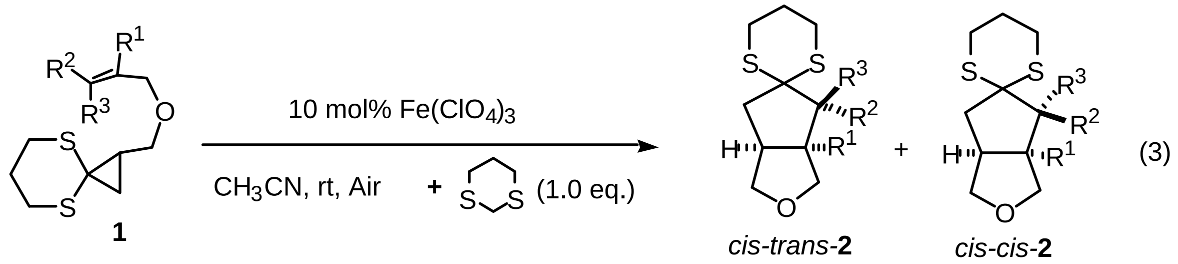

Table 2. Results of a single electron transfer-mediated cyclization of methylenecyclopropanonethiaoacetal **1**[a)]

Entry	Substrate	R^1	R^2	R^3	Reaction Time	Yield of **2** [b)]	Ratio of *cis-trans*-**2**/*cis-cis*-**2** [c)]
1	**1b**	H	CH_3	H	1.5 h	50%	94:6
2	**1c**	H	CH_3	CH_3	1.5 h	40%	----
3	**1d**	H	C_6H_5	H	2.0 h	57%	72:28
4	**1e**	H	*p*-BrC_6H_5	H	2.0 h	62%	88:12
5	**1f**	CH_3	H	H	24 h	0%	-----

a) All new compounds show analytical and spectral (^{1}H NMR, ^{13}C NMR, and IR) data consistent with the depicted structures. Stereochemistry established by NOE experiment. b) Isolated yield. c) The ratio was determined by chiral HPLC (OD); 0.46cm I.D.x25 cm, hexane /*i*-PrOH= 19:1, 1.0 mL/min, 30°C.

reaction system of cation radical-mediated intramolecular cyclization of cyclopropyl compounds, because dithioacetal moiety of **2** corresponds to the masked carbonyl group and serves as a versatile lead for further synthetic transformation. Hence the present reaction can undoubtedly allow us to evolve a smarter and more convenient synthesis of oxabicyclo ring systems. Further investigation into other ring systems and applications is ongoing.

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REFERENCES AND NOTES

*Dedicated to Professor Teruaki Mukaiyama on the occasion of his 73rd birthday.

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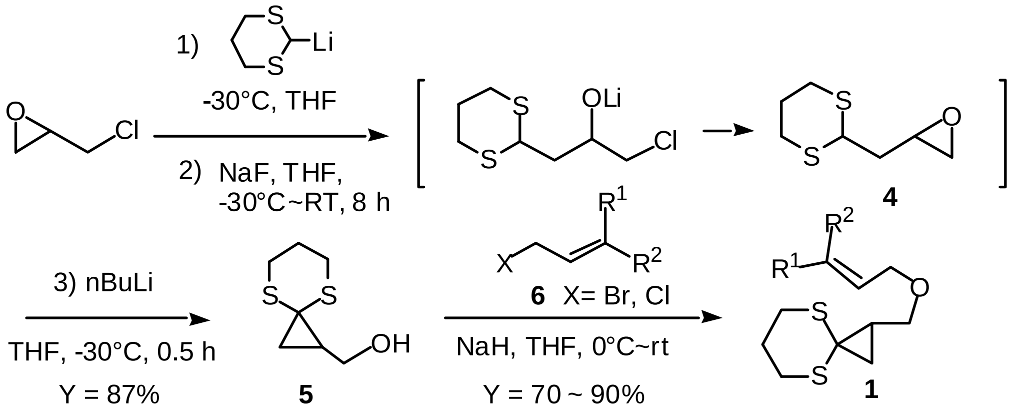
5. A preliminary account for the reaction of cyclopropanonetrimethylenethioacetal see. M. Nakamura, M. Toganoh, H. Ohara, and E. Nakamura, *Organic Lett*. **1999**, in press.
6. Reaction of lithio 1,3-dithiane with epichlorohydrin and subsequent treatment with sodium fluoride in tetrahydrofurane (THF) afforded glycidyl 1,3-dithiane (**4**), and further reaction with n-BuLi gave 2-hydroxymethyl-1,1-trimethylenedithiocyclopropane (**5)** in more than 85% yield. This alcohol was then treated with allyl bromide or allyl chloride in the presence of sodium hydride as base and provided the desired allyl ether (**1**) in good overall yield (Scheme 1).



Scheme 1. Simple synthesis of cyclopropane dithioacetal derivatives **1**

7. Representative procedure: To a stirred solution of **1a** (280 mg, 1.29 mmol) and 1,3-dithiane (156 mg, 1.29 mmol) in dry CH_3CN (5.2 mL) was added a solution of $Fe(ClO_4)_3$ in dry CH_3CN (1.30 mL, 0.1 M, 0.13 mmol) at rt under atmosphere, and the solution stirred at rt for 2.0 h. The reaction mixture was diluted with ether and filtered through a florisil short column. The solvent was removed under vacuum affording a brownish oil (430 mg). Silica gel flash column chromatography (hexane- ethyl acetate = 100:0 to 10:1) gave **2a** (190 mg, 68%) as a colorless oil. An acetonitrile solution of $Fe(ClO_4)_3$ was prepared as follows; an activated aluminum oxide (ICI-02084, neutral, Akt. I, 6.0 g) was placed in a flask equipped with a rubber septum under argon atmosphere and a CH_3CN (20 mL) solution of $Fe(ClO_4)_3nH_2O$ (70% as an anhydrous form, 1.012 g, 2.0 mmol) was added into the flask using a syringe, then the mixture was vigorously shaken for a few minutes. The resultant mixture was stand in a refrigerator for over night and the supernatant was used as 0.1 M $Fe(ClO_4)_3$ solution. This solution can be kept for several months without any loss of activity in a refrigerator. Physical constant and NMR data of **2a**: bp 90°C/ 2.5 Torr (Kugelrohr); Rf 0.38 (hexane/ethyl acetate = 4:1); ^1H NMR (200 MHz, δ, $CDCl_3$, J= Hz): 1.69 (2H, dd, J=13.3, 8.2), 1.92-2.03 (2H, m), 2.60 (2H, dd, J=13.3, 8.2), 2.78-2.96 (6H, m), 3.55 (2H, dd, J=8.2, 6.0), 3.68 (2H, d, J=8.2); ^{13}C NMR (50 MHz, $CDCl_3$, ppm): 25.66, 27.52, 28.64, 43.74, 47.18, 57.08, 73.63 ; IR(neat, cm^{-1}) 2955, 2847, 1421, 1363, 1239, 1178, 1083, 1044, 990, 910, and 782; Anal. Calcd for $C_{10}H_{16}OS_2$: C, 55.51; H, 7.49. Found: C, 56.18; H, 7.60.

8. 10-Membered thionomacrocycle (**3**) was obtained as the major by-product, and this was assumed to be produced by the reaction of oxygen with radical cation precursor of the final compound (**2a**) and subsequent ring expansion reaction. Physical constant and NMR data of **3**: mp 85°C (recrystallization from hexane/ ethyl acetate / dichloromethane); Rf 0.24 (hexane/ ethyl acetate = 2:1); ^{1}H NMR (500 MHz, δ, $CDCl_3$, J= Hz): 1.72-1.82 (1H, m), 1.85-1.94 (1H, m), 2.18 (1H, dd, J= 14.7, 10.8), 2.27-2.38 (1H, m), 2.45 (1H, t, J= 11.5), 2.52-2.72 (4H, m), 2.80 (1H, dt, J= 12.5, 4.6), 2.90-3.04 (1H, m), 3.29 (1H, dd, J= 9.0, 6.6), 3.35-3.47 (1H, m), 3.40 (1H, dd, J= 9.2, 4.6), 3.90 (1H, dd, J= 9.2, 7.6), 4.02 (1H, t, J= 8.2); ^{13}C NMR (50 MHz, $CDCl_3$, ppm): 27.50, 28.120, 28.121, 35.96, 42.26, 43.78, 48.83, 74.09, 74.15, 198.65 ; IR(neat, cm^{-1}) 2926, 2848, 1693, 1567, 1426, 1245, 1078, 1006, and 939; Anal. Calcd for $C_{10}H_{16}O_2S_2$: C, 51.69; H, 6.94. Found: C, 51.85; H, 6.87.
9. Five types of solvents, CH_3CN, DMF, THF, and trifluoroethanol, were tested to the reaction and dried CH_3CN was found to be the best.
10. For several examples of radical reaction using CAN as initiator, see (a) A. B. Paolobelli, F. Gioacchini, R. Ruzziconi, *Tetrahedron Lett*., **1993**, *34*, 6333. (b) A. B. Paolobelli, P. Ceccherelі, and F. *Pizzo, J. Org. Chem*., **1995**, *60*, 4954. (c) V. Nair, J. Mathew, and J. Prabhakaran, J. *Chemical Society Reviews*, **1997**, 127.
11. No stereoisomer was detected by capillary GC analysis (“Quadrex”bonded fused silica Methyl Silicone, ϕ0.25 mm x 25 m, N_2).
12. MacSpartan Plus was employed for MO (PM3) calculation. Calculation results (heat of formation): **A**: 189.98 Kcal/mol, **B**: 206.81 Kcal/mol, **C**: 188.32 Kcal/mol, **D**: 141.9 Kcal/mol.
13. MO (PM3) calculation results (heat of formation): *cis-trans*-**2b**: -40.78 Kcal/mol. *cis-cis*-**2b**: -38.80 Kcal/mol. The ratio of *cis-trans*-**2b** and *cis-cis*-**2b** was estimated by the difference in the heat of formation energy of these two isomers to be 96.5:3.5; this well agreed with the experimental result obtained (94:6). MO calculation suggests that *cis-trans*-**2d**, and *cis-trans*-**2e** are stable than the corresponding *cis-cis* isomers.