

HETEROCYCLES, Vol. 78, No. 2, 2009, pp. 325 - 330. © The Japan Institute of Heterocyclic Chemistry
Received, 13th September, 2008, Accepted, 14th October, 2008, Published online, 16th October, 2008.
DOI: 10.3987/COM-08-11550

EFFECT OF A METAL SALT ON THIIRANATION OF 2'-ADAMANTYLIDENE-9-BENZONORBORNENYLIDENE WITH 4,4'-DITHIODIMORPHOLINE AND ACETIC ANHYDRIDE

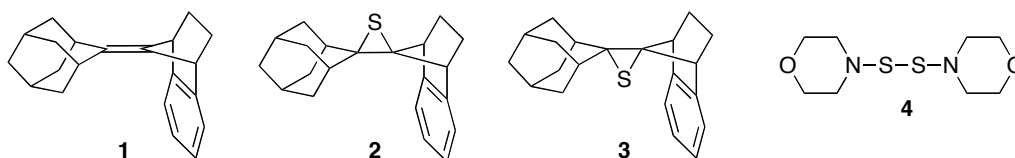
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Abstract – Using a solution of a metal salt, it was possible to decrease the quantity of Ac_2O used in the thiirane formation of 2'-adamantylidene-9-benzonorbornenylidene **1** with 4,4'-dithiodimorpholine **4** and Ac_2O . Thiirane formation in a 0.1 M Et_2O solution of LiClO_4 at $-15\text{ }^\circ\text{C}$ afforded thiiranes **2** and **3** in moderate yields without the decomposition of the thermally less stable **3**.

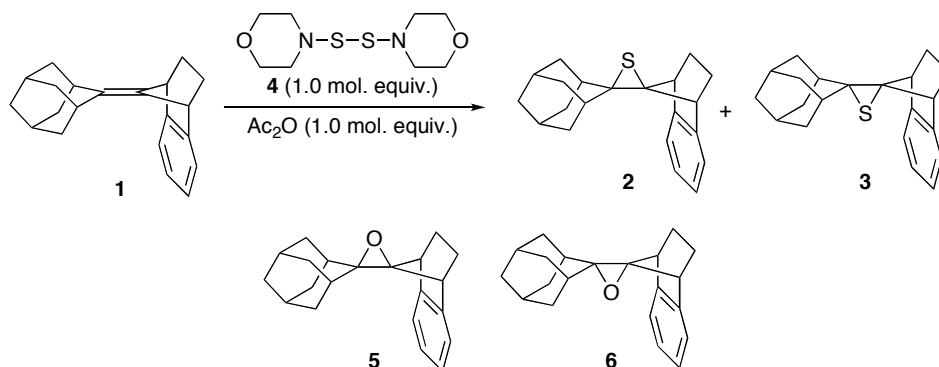
Thiiranes, as well as oxiranes and aziridines, can act as key intermediates in the syntheses of functional materials and biologically active compounds. Thus far, numerous methods, such as two-step synthesis from alkenes through oxiranes (a conventional laboratory method), for synthesizing thiiranes have been reported.¹ When using two-step synthesis, undesired polymerization of the resulting thiiranes occurred frequently.² On the other hand, thiirane formation of alkenes (episulfidation), i.e., direct synthesis of thiiranes from alkenes, is less common than oxirane formation (epoxidation) and aziridination of alkenes.³ There have been cases in which problems, such as the polymerization and decomposition of the resulting thiiranes, limitations of the alkenes used, and difficulty in synthesizing a sulfurating reagent, were faced during the thiirane formation. Development of a new method is required to overcome these problems. Recently, we indicated the possibility of using 2'-adamantylidene-9-benzonorbornenylidene **1**, which acts as a model alkene for investigating thiirane formation conditions.⁴ Until now, we investigated two novel thiirane formation methods with 4,4'-oligothiodimorpholines from the results of both thiirane formation of **1** to the corresponding thiirane **2** and **3**, and the decomposition of **3** to **1** and **2**.^{5,6} Thiirane **3** is thermally less stable than **2**; thus, the reaction of **3** at its C–S bond tends to produce **3** together with **1**. As a result, the method with 4,4'-dithiodimorpholine **4**, a commercially available, inexpensive vulcanizing agent, in Ac_2O at $-15\text{ }^\circ\text{C}$ was found to provide the best results.⁶ Although the thiirane formation proceeded with retention of the

configuration of the starting alkene, removal of excess Ac_2O from the reaction mixture by either vacuum distillation at $-15\text{ }^\circ\text{C}$ or hydrolysis with LiOH restricted the use of alkenes. A method of decreasing the quantity of Ac_2O used must be found. Here, we report the effect of a metal salt on the thiiraneation of **1** with **4** and Ac_2O .



LiClO_4 is highly soluble in many organic solvents, such as EtOH , Et_2O , and acetone, and is used as a weak Lewis acid in many organic reactions.⁷ A highly concentrated Et_2O solution of LiClO_4 is known to be a powerful reaction medium in organic synthesis.⁸ When this solution is used in the reaction, LiClO_4 not only acts as a Lewis acid, but also increases the polarity of the solvent. Therefore, some reactions that usually proceed only under drastic reaction conditions can proceed smoothly in this solution even at rt. Considering these effects, thiiraneation of **1** with **4** (1.0 molar equivalent) and Ac_2O (1.0 molar equivalent) in solutions of metal salts were examined (Scheme 1), and the results are summarized in Table 1. Thiiraneation of **1** with **4** and Ac_2O in an Et_2O solution of LiClO_4 (4.1 molar equivalent, 0.1 M) at $-15\text{ }^\circ\text{C}$ proceeded to give **2** and **3** in 20 and 29% yields, respectively, together with **1** in 42% yield (Entry 1). When thiiraneation was performed in CH_2Cl_2 at rt in the absence of LiClO_4 , a small quantity of **3** was formed together with the recovery of **1** (Entry 2).⁶ In the presence of 12-crown-4, which is known to capture Li^+ ions efficiently,⁹ **1** was recovered (Entry 3). Increasing the concentration of LiClO_4 in the solution tended to increase the yields of the thiiranes slightly, but formed oxirane **5** (Entries 4 and 5). In the absence of Ac_2O , a quantitative recovery of **1** was observed (Entry 6). These results suggest that Ac_2O is activated by the action with LiClO_4 as a Lewis acid, and then reacts with **4** to form a true thiiraneation reagent. When the solvent was changed from Et_2O into AcOEt and acetone, consumption of **1** increased, but oxirane **6** was obtained in addition to **5** (Entries 7 and 8). In these cases, AcOEt and acetone, both of which have a basic carbonyl-oxygen atom, may react with LiClO_4 instead of Ac_2O , and then with **4** to form the thiiraneation reagent. The oxiranes **5** and **6** must be produced by the oxidation of **1** with the perchlorate ion ClO_4^- .¹⁰ The reaction of **1** with Ac_2O and LiBF_4 in CH_3CN at $-15\text{ }^\circ\text{C}$ proceeded to give small quantities of **2** and **3** (Entries 9 and 10). Increasing the reaction temperature to rt resulted in the formation of **2** and **3** in moderate to good yields (Entries 11–14). Using THF and AcOEt as solvent showed the progress of thiiraneation, and production of **2** was greater than that of **3** (Entries 15 and 16). When LiOTf was used, the ratio of **2** to **3** decreased significantly, compared to using LiClO_4 and LiBF_4 (Entries 17 and 18). $\text{Mg}(\text{OTf})_2$ seems to be more efficient for activating Ac_2O than LiOTf (Entries 19 and 20). From the results as shown in entries 1, 10, 18, and 20, the efficiency of the reaction medium in the thiiraneation of **1** seemed to increase in the order of LiBF_4 in CH_3CN < LiOTf in CH_2Cl_2 < LiClO_4 in Et_2O

< Mg(OTf)₂ in CH₂Cl₂.



Scheme 1

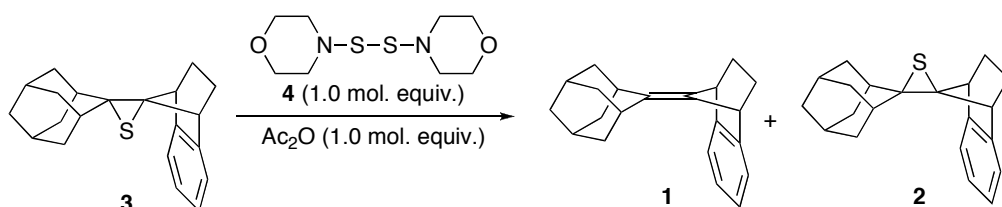
Table 1. Reactions of **1** with **4** and Ac₂O in a Metal Salt Solution^a

entry	metal salt/solvent (conc., M)	conditions	yield (%)				
			2	3	5	6	1
1	LiClO ₄ /Et ₂ O (0.1) ^b	-15 °C, 45 h	20	29	—	—	42
2 ^c	none/CH ₂ Cl ₂	rt, 45 h	—	3	—	—	92
3	LiClO ₄ /Et ₂ O (0.1) ^b	12-crown-4, ^d -15 °C, 45 h	—	—	—	—	96
4	LiClO ₄ /Et ₂ O (1.0) ^e	-15 °C, 45 h	31	30	8	—	20
5	LiClO ₄ /Et ₂ O (2.0) ^f	-15 °C, 45 h	35	40	7	—	8
6	LiClO ₄ /Et ₂ O (2.0) ^f	-15 °C, 45 h ^g	—	—	—	—	98
7	LiClO ₄ /AcOEt (2.0) ^f	-15 °C, 45 h	43	19	15	10	9
8	LiClO ₄ /acetone (2.0) ^f	-15 °C, 45 h	40	20	4	9	16
9	LiBF ₄ /CH ₃ CN (2.4x10 ⁻²) ^d	-15 °C, 168 h	5	5	—	—	83
10	LiBF ₄ /CH ₃ CN (0.1) ^b	-15 °C, 168 h	3	4	—	—	87
11	LiBF ₄ /CH ₃ CN (2.4x10 ⁻³) ^h	rt, 120 h	8	25	—	—	59
12	LiBF ₄ /CH ₃ CN (2.4x10 ⁻²) ^d	rt, 120 h	18	56	—	—	15
13	LiBF ₄ /CH ₃ CN (4.9x10 ⁻²) ⁱ	rt, 96 h	23	63	—	—	4
14	LiBF ₄ /CH ₃ CN (0.1) ^b	rt, 43 h	25	63	—	—	4
15	LiBF ₄ /THF (0.1) ^b	rt, 120 h	29	5	—	—	58
16	LiBF ₄ /AcOEt (0.1) ^b	rt, 120 h	34	9	—	—	49
17	LiOTf/CH ₂ Cl ₂ (2.4x10 ⁻²) ^d	-15 °C, 72 h	2	17	—	—	73
18	LiOTf/CH ₂ Cl ₂ (0.1) ^b	-15 °C, 72 h	3	28	—	—	61
19	Mg(OTf) ₂ /CH ₂ Cl ₂ (2.4x10 ⁻²) ^d	-15 °C, 72 h	3	28	—	—	62
20	Mg(OTf) ₂ /CH ₂ Cl ₂ (0.1) ^b	-15 °C, 72 h	18	54	—	—	17

^a**4** (1.0 mol. equiv.), Ac₂O (1.0 mol. equiv.). ^b4.1 mol. equiv. ^cRef. 6. ^d1.0 mol. equiv. ^e41 mol. equiv. ^f82 mol. equiv. ^gIn the absence of Ac₂O. ^h0.1 mol. equiv. ⁱ2.0 mol. equiv.

Reactions of **3** with **4** (1.0 molar equivalent) and Ac₂O (1.0 molar equivalent) in solutions of metal salts were examined (Scheme 2), and the results are summarized in Table 2. Decomposition of **3** did not occur in the Et₂O solution of LiClO₄ (4.1 molar equivalent, 0.1 M) at -15 °C and in CH₂Cl₂ at rt (Entries 1 and 2). When the concentration of LiClO₄ in Et₂O was increased to 1.0 M, isomerization to **2** and slight decomposition to **1** were observed (Entry 3). Oxirane **5**, in addition to **1** and **2**, was obtained by the reaction in the 2.0 M solution, but the recovery of **3** increased in comparison with that in the 1.0 M solution (Entry 4). Changing Et₂O into AcOEt or acetone decreased both the consumption of **3** and formation of **2** (Entries 5 and 6). The reaction in the Et₂O solution of LiBF₄ (4.1 molar equivalent, 0.1 M)

at $-15\text{ }^{\circ}\text{C}$ resulted in the quantitative recovery of **3**, whereas that at rt gave **1** and **2** (Entries 7 and 8). The decompositions of **3** in both the LiClO_4 and LiBF_4 solutions tended to produce **2** rather than **1**. This tendency is similar to that of the reaction of **3** with **4** (1.0 molar equivalent) and acid anhydride (1.0 molar equivalent) in CH_2Cl_2 .⁶ On the other hand, an approximately 1:1 to 1:2 mixture of **1** and **2** was obtained in the decompositions in metal-triflate solutions (Entries 9–11). From the results shown in entries 1, 7, 9, and 10, the order of ability as the reaction medium in the decomposition of **3** seemed to be LiOTf in $\text{CH}_2\text{Cl}_2 \approx \text{Mg}(\text{OTf})_2$ in $\text{CH}_2\text{Cl}_2 < \text{LiBF}_4$ in $\text{CH}_3\text{CN} \approx \text{LiClO}_4$ in Et_2O . Therefore, thiirane in the 0.1 M Et_2O solution of LiClO_4 at $-15\text{ }^{\circ}\text{C}$ produced the best results, because the thiirane gave **2** and **3** in moderate yields without the decomposition of the thermally less stable **3**.



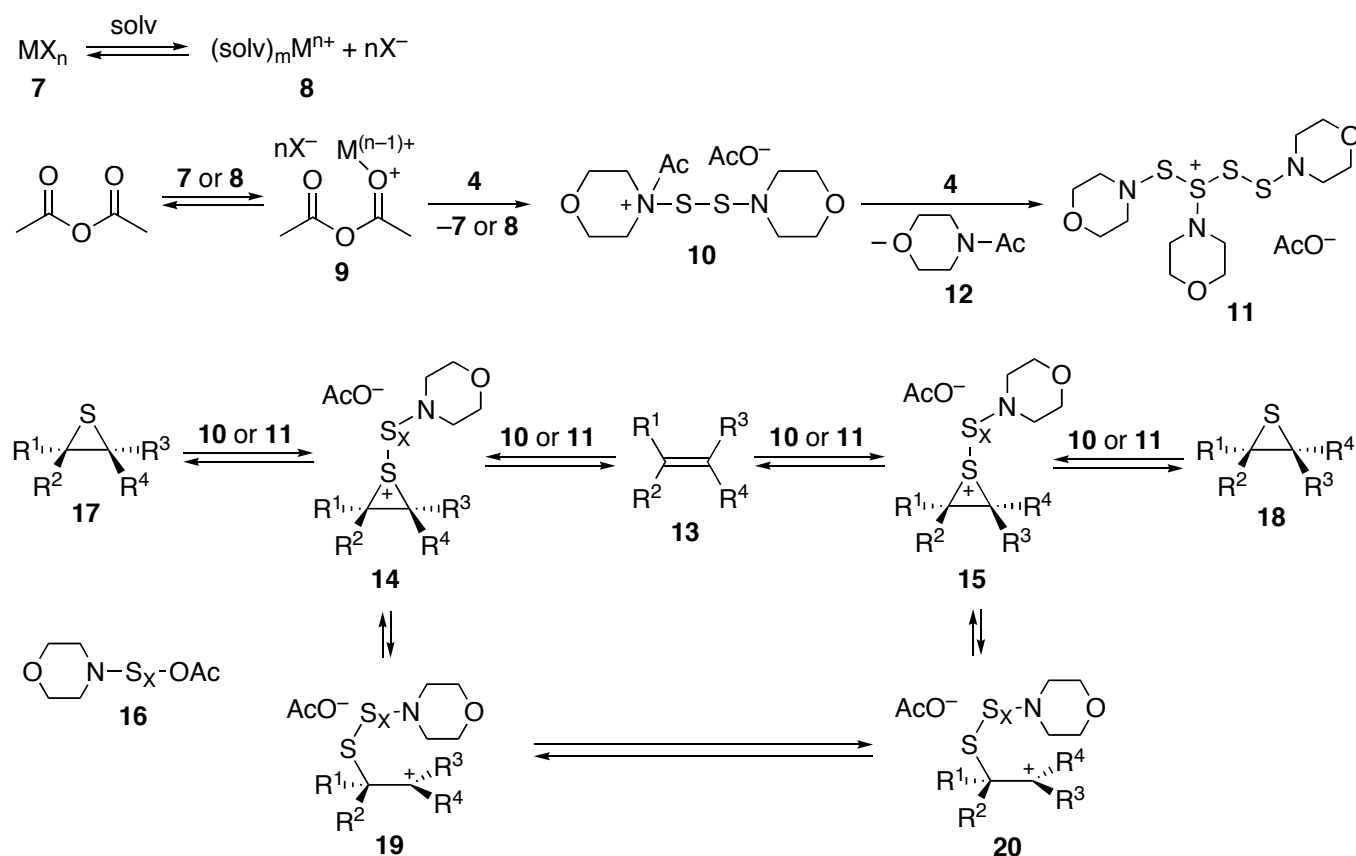
Scheme 2

Table 2. Reactions of **3** with **4** and Ac_2O in a Metal Salt Solution^a

entry	metal salt/solvent (conc., M)	conditions	yield (%)			
			1	2	5	3
1	$\text{LiClO}_4/\text{Et}_2\text{O}$ (0.1) ^b	$-15\text{ }^{\circ}\text{C}$, 45 h	—	—	—	94
2 ^c	none/ CH_2Cl_2	rt, 45 h	—	—	—	quant.
3	$\text{LiClO}_4/\text{Et}_2\text{O}$ (1.0) ^d	$-15\text{ }^{\circ}\text{C}$, 45 h	2	84	—	4
4	$\text{LiClO}_4/\text{Et}_2\text{O}$ (2.0) ^e	$-15\text{ }^{\circ}\text{C}$, 45 h	3	44	14	29
5	$\text{LiClO}_4/\text{AcOEt}$ (2.0) ^e	$-15\text{ }^{\circ}\text{C}$, 45 h	—	18	—	69
6	$\text{LiClO}_4/\text{acetone}$ (2.0) ^e	$-15\text{ }^{\circ}\text{C}$, 45 h	—	22	—	71
7	$\text{LiBF}_4/\text{CH}_3\text{CN}$ (0.1) ^b	$-15\text{ }^{\circ}\text{C}$, 168 h	—	—	—	quant.
8	$\text{LiBF}_4/\text{CH}_3\text{CN}$ (0.1) ^b	rt, 48 h	5	63	—	32
9	$\text{LiOTf}/\text{CH}_2\text{Cl}_2$ (0.1) ^b	$-15\text{ }^{\circ}\text{C}$, 168 h	14	24	—	60
10	$\text{Mg}(\text{OTf})_2/\text{CH}_2\text{Cl}_2$ (2.4×10^{-2}) ^f	$-15\text{ }^{\circ}\text{C}$, 168 h	14	20	—	66
11	$\text{Mg}(\text{OTf})_2/\text{CH}_2\text{Cl}_2$ (0.1) ^b	$-15\text{ }^{\circ}\text{C}$, 168 h	17	16	—	67

^a**4** (1.0 mol. equiv.), Ac_2O (1.0 mol. equiv.). ^b4.1 mol. equiv. ^cRef. 6. ^d41 mol. equiv. ^e82 mol. equiv. ^f1.0 mol. equiv.

A possible mechanism of the thiirane of **1** and the decomposition of **3** is as follows. A metal salt **7** is solvated by coordination to the basic atom in the solvent to form **8**. The M^+ ion from **7** or **8** coordinates the carbonyl-oxygen atom in Ac_2O to give ammonium salt **10**, which then reacts with **4** to form sulfonium salt **11**. The salts **10** and **11** must act as a thiirane reagent. Reaction of **13** with **10** or **11** gives thiirane salts **14** and **15**, which then extrude **16** to give **17** and **18**, respectively. The decomposition of **3** to **2** proceeds through the thiirane salts **14** and **15** and carbenium salts **19** and **20**, and that to **1** is a reverse process of thiirane. The processes among **13**–**15** and **17**–**20** are reversible, and therefore, the ratio of **1**, **2**, and **3** may be determined by both the Lewis acidity of the metal salt and the polarity of the concentrated solution of the metal salt.



Scheme 3

In summary, we studied the effect of a metal salt on the thiiranium of **1** with **4** and Ac_2O . As a result, the 0.1 M Et_2O solution of LiClO_4 at -15°C was used as a reaction medium for successful thiiranium of **1**. Further work is in progress in applying this thiiranium to other alkenes.

ACKNOWLEDGEMENTS

This work was supported by Grants-in-Aid for Scientific Research from Japan Society for the Promotion of Science.

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 - Typical procedures for thiiranon of **1** with **4** and Ac₂O in a metal–salt solution: To a Et₂O solution of a metal salt (3.0 mL) was added **1** (20.1 mg, 73 μmol) and **4** (17.2 mg, 73 μmol). After the mixture was cooled to –15 °C, Ac₂O (6.8 μL, 73 μmol) was added dropwise to the mixture. After stirring for 45 h at the same temperature, the reaction was quenched by the addition of ice water. After the mixture was diluted with Et₂O, the organic layer was separated, washed with H₂O three times, dried over MgSO₄, and evaporated under reduced pressure. The residue was chromatographed on a column of silica gel and the column was eluted with hexane to give a mixture of **1**, **2**, and **3**, and with CH₂Cl₂/hexane (1:5) to give a mixture of oxiranes **5** and **6**. The product ratios were estimated by ¹H NMR.
 - F. A. Cotton, G. Wilkinson, C. A. Murillo, and M. Bochmann, *Advanced Inorganic Chemistry*, 6th ed., Wiley-Interscience, New York, 1999, p. 103.
 - 5**: colorless crystals (from CH₂Cl₂/MeOH), mp 202.5–203.0 °C; ¹H NMR (300.1 MHz) δ 1.01–1.11 (m, 2H), 1.28–1.37 (m, 2H), 1.52–1.73 (m, 9H), 1.85–1.92 (m, 1H), 1.93–2.04 (m, 2H), 2.95–3.03 (m, 2H), 7.10–7.22 (m, 4H); ¹³C NMR (50.3 MHz) δ 25.2, 26.8, 27.1, 34.48, 34.54, 36.5, 36.8, 42.9, 72.1, 86.8, 120.8, 126.9, 144.9; IR (KBr) 3055, 2995, 2976, 2932, 2909, 2846, 1504, 1460, 1446, 1351, 1280, 1238, 1143, 1102, 1066, 1003, 958, 938, 927, 881, 851, 836, 769, 752, 686, 641, 613 cm⁻¹; Anal. Calcd for C₂₁H₂₄N₂O: C, 86.25; H, 8.27. Found: C, 86.22; H, 8.35. **6**: colorless crystals (from CH₂Cl₂/MeOH), mp 198.0–198.5 °C; ¹H NMR (300.1 MHz) δ 1.29–1.37 (m, 2H), 1.67–2.06 (m, 14H), 2.11–2.21 (m, 2H), 3.05–3.12 (m, 2H), 7.09–7.17 (m, 2H), 7.18–7.26 (m, 2H); ¹³C NMR (50.3 MHz) δ 25.2, 27.0, 27.3, 33.6, 34.8, 36.7, 37.5, 43.7, 79.2, 79.4, 121.6, 126.1, 145.2; IR (KBr) 3035, 2994, 2946, 2913, 2846, 1446, 1140, 1106, 1011, 957, 924, 837, 757, 728, 642 cm⁻¹; Anal. Calcd for C₂₁H₂₄N₂O: C, 86.25; H, 8.27. Found: C, 86.01; H, 8.31.
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