ACETAL FORMATION BY METAL ION-MEDIATED DESULFURIZATION-CONDENSATION OF THIOKETONES WITH DIOLS AND PHENOLS

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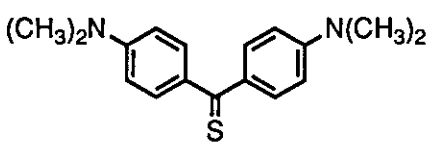
Abstract – The acetal formation of thioketones with several diols and phenols through metal ion-mediated desulfurization-condensation was investigated. The reactivities of 4,4'-bis(dimethylamino)thiobenzophenone, "thio-Michler's ketone" (TMK) and xanthene-9-thione (XT) toward α,ω-alkanediols [$HO(CH_2)_nOH$, n = 2~4] in the presence of silver trifluoroacetate and triethylamine were compared. The reaction of TMK with glycerol, *trans*- and *cis*-1,2-cyclohexanediols, α,α'-dihydroxy-*o*-xylene and biphenyl-2,2-diol in the presence of silver salt gave the corresponding acetals in good yields. On the other hand, copper(I) chloride, in place of silver(I) salt, was useful for catechol and pyrogallol to give their acetals, respectively. It was thus found that thioketones are new and versatile acetalizing reagents for diols and phenols.

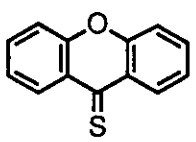
Divalent sulfur compounds have strong affinity with silver(I) ion. We have been trying to apply this interaction to the field of organic synthesis. In the previous paper[1] we reported on the silver(I) ion-mediated desulfurization-condensation between thiocarbonyl compounds and nucleophiles such as active methylene compounds, anilines, and ethylene glycol, and found that most reactions proceed smoothly at room

temperature under mild basic conditions to afford olefins, imines, and acetals in good yields. We also obtained condensation products which have been hardly obtainable from less reactive ketones or amides under acidic conditions.

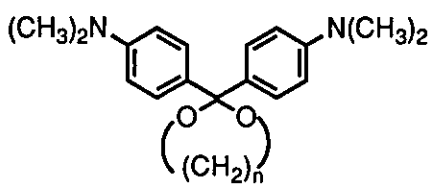
Here we wish to report on the acetal formation of thioketones with several diols and phenols by metal ion-mediated desulfurization-condensation and on the possibility as protecting agents for diols and phenols. It has been reported that even at room temperature the reaction of 4,4'-bis(dimethylamino)-thiobenzophenone, so-called thio-Michler's ketone[2] (TMK), with ethylene glycol gives 2,2-bis(4'-dimethylaminophenyl)-1,3-dioxolane (**1**) in the presence of triethylamine and silver trifluoroacetate in a good yield.[1] Thus we examined on the reaction of TMK with 1,3- propanediol and 1,4-butanediol under the same conditions as above mentioned and found that 2,2-bis(4'-dimethylaminophenyl)-1,3-dioxane (**3**) and -1,3-dioxepane (**5**) were obtained in 78 and 46% yields, respectively. The acetal formation of another thioketone, xanthene-9-thione (XT), with ethylene glycol, 1,3-propanediol and 1,4-butanediol was also examined and the results are shown in Table 1.



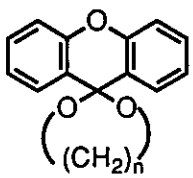
TMK



XT



1, 3, 5 **1**: n = 2
3: n = 3
5: n = 4



2, 4, 6 **2**: n = 2
4: n = 3
6: n = 4

The reactions of ethylene glycol with TMK and XT give acetals, 1,3-dioxolane (**1**) and (**2**), in good yields (Entries 1 and 2), 1,4-butanediol leads to the corresponding acetals, 1,3-dioxepanes (**5**) and (**6**), in moderate yields, respectively (Entries 6 and 7), and consequently the reactivities of TMK and XT toward them are similar to each other. On the other hand, while the reaction of 1,3-propanediol with XT gave no

1,3-dioxane derivative (4), the reaction with TMK afforded 3 in a good yield (Entries 3 and 5).

Table 1. Reaction of polymethylenediols with thioketones in the presence of silver trifluoroacetate.

Entry No.	$HO(CH_2)_nOH$ /n	Thioketone	Acetal	Yield / % [a]
1	2	TMK	1	76
2	2	XT	2	71
3	3	TMK	3	78
4	3	TMK	3	29 [b]
5	3	XT	4	0
6	4	TMK	5	46
7	4	XT	6	45

a) Based on the thioketone. b) CuCl was used instead of $AgOCOCF_3$.

This fact indicates that, owing to a steric repulsion between *peri*-hydrogens of xanthene ring and the hydrogens in the two hydroxymethyl groups of 1,3-propanediol, the formation of six-membered acetal ring must be seriously hindered, whereas, the steric repulsion on forming 3 would be avoided by free rotation of 4-dimethylaminophenyl group as shown in Figure 1. Five- or seven-membered ring closures affording 2 or 6 must be little affected on the repulsion. The desulfurization-condensation of TMK with 1,3-propanediol using copper(I) chloride was examined, but 3 was obtained in a low yield (Entry 4).

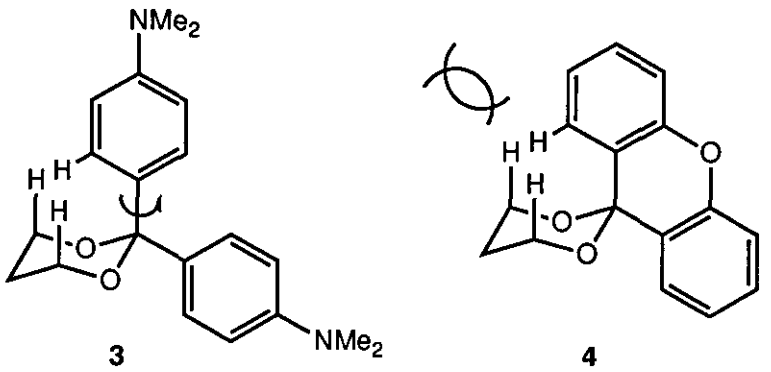
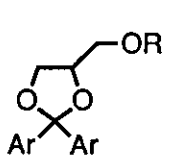
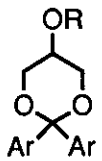


Figure 1. Steric repulsion of **3** and **4**

The reaction of TMK with glycerol afforded a single acetal (**7a**) although there is a possibility of formation of **7b**. The structures of **7a** were determined by ^{13}C nmr spectroscopy, that is, the signal of the acetal carbon of five-membered acetal(**1**) or six-membered acetal(**3**) appears at δ 110.1 or 101.7, respectively, and that of **7a** actually appeared at δ 110.7, and consequently **7a** was found to have 1,3-dioxolane structure as similar to **1**. This fact shows that five-membered ring closure takes place more preferentially than six-membered ring closure as in the case of acetone.[3] In addition, the acetate of **7a** (**7'a**) was also obtained directly in one pot by successive acetylation.



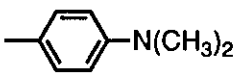
a



b

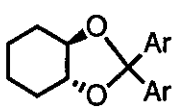
7 : R = H

7' : R = CH_3CO

Ar : 

The reaction of TMK with *trans*- and *cis*- 1,2-cyclohexanediols gave the acetals (**8**) and (**9**), respectively , and the yield of *cis* isomer (**9**) is higher than that of *trans* isomer (**8**) because of the easiness of ring closure as expected.[4]

α,α'-Dihydroxy-*o*-xylene and biphenyl-2,2-diol also afforded the acetals (**10**) and (**11**) in good yields inspite of rigid seven-membered ring closure.



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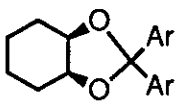

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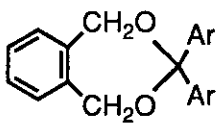
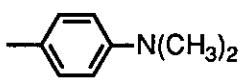
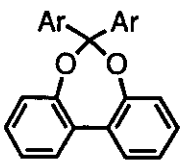


10

Ar : 



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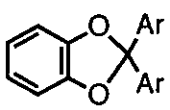
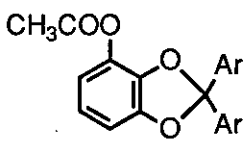


12



13

When TMK was treated with copper (I) chloride in the presence of triethylamine in refluxing acetonitrile, catechol afforded the acetal (**12**) in 66% yield. Pyrogallol did not afford product by silver salt, but on refluxing with TMK in the presence of copper(I) chloride, followed by treating with acetic anhydride, gave

the acetal monoacetate (**13**) in 54% yield. This fact indicates that copper(I) salt is useful for acetalization of phenols such as catechol and pyrogallol sensitive to silver(I) ion, inspite of poor efficiency for acetalization of 1,3-propanediol.

In addition, we examined the hydrolysis of **3** and **12** in order to use the reaction as a protecting agent for diols or phenols. On treatment with 1/10 M hydrochloric acid in methanol at room temperature, they were thoroughly hydrolyzed to give 1,3-propanediol or catechol and 4,4'-bis(dimethylamino)benzophenone, respectively.

In conclusion, we demonstrated that several diols and phenols easily afford acetal derivatives in good yields by means of metal ion-mediated desulfurization-condensation of thioketones under ambient basic conditions. The acetals thus obtained are usually crystalline and have a strong absorption in the uv region, so that it is easy to separate and purify them and to monitor the processes of the acetal formation and the deprotection. We also demonstrated that they are readily deprotected under mild acidic conditions.

EXPERIMENTAL

All of the melting points were uncorrected. ^{1}H and ^{13}C Nmr spectra were recorded on a Varian Gemini 300 spectrometer using TMS as an internal standard. The mass spectra were taken on a Shimadzu (GCMS-QP2000A) spectrometer. Ir spectra were measured on a JASCO (FT-IR5300) spectrophotometer using KBr disks.

Thioketones.

TMK was purchased from Tokyo Kasei Co., Ltd. and used without further purification. XT was derived from xanthone by refluxing with Lawesson's reagent in toluene and purified by recrystalizing from ethanol (mp 158 ℃, lit.,[5] 156 ℃).

Typical procedure for the reaction of thioketones with diols and phenols.

A typical experimental procedure for the reaction of TMK with 1,3-propanediol in the presence of $AgOCOCF_3$ was as follows: triethylamine (404 mg, 4 mmol) was added dropwise to a solution of TMK (284 mg, 1 mmol), 1,3-propanediol (91 mg, 1.2 mmol), and $AgOCOCF_3$ (553 mg, 2.5 mmol) in acetonitrile (5 ml) over 3 min. The reaction mixture was continuously stirred for an hour at room temperature. After evaporation of acetonitrile and triethylamine under reduced pressure, ethyl acetate was added to the residue, and Ag_2S was removed by suction. The resulting organic layer was passed through on

a silica gel column (Merk silica gel 60, hexane : AcOEt = 1:1) to afford **3** (254 mg, 78%). According to the above-mentioned method, acetals (**2**) and (**5** ~ **11**) were also obtained. Their characterization data were shown below.

Spiro[1,3-dioxolane-2,9'-xanthene] (2)

Colorless powder; yield 71%; mp 104 ~ 105 ℃ (isopropyl ether); ^{1}H nmr ($CDCl_3$) δ = 4.34 (4 H, s), 7.1 - 7.3 (4 H, m), 7.3 - 7.5 (2 H, m), 7.61 (2 H, dd, *J* =7.8 Hz, *J* =2.0 Hz); ^{13}C nmr ($CDCl_3$) δ = 68.3, 101.0 (acetal C), 116.7, 123.2, 125.9, 151.8; ms m/z; 240 (M^+); ir ν 1601, 1454, 1240, 1063, 941 cm^{-1}. Anal. Calcd for $C_{22}H_{28}N_2O_3$: C, 68.91; H, 7.10; N, 7.31. Found: C, 75.25; H, 4.99.

2,2'-Bis(4-dimethylaminophenyl)-1,3-dioxane (3)

Colorless powder; yield 78%; mp 143.5 ~ 144.5 ℃(isopropyl ether); ^{1}H nmr ($CDCl_3$) δ = 1.7 - 1.9 (2 H, m), 2.91 (12 H, s), 4.01 (4 H, t, *J* = 5.4 Hz), 6.6 - 6.8 (4 H, m), 7.2-7.4 (4 H, m), ^{13}C nmr ($CDCl_3$) δ = 25.9, 40.7, 61.6, 101.7 (acetal C), 112.3, 127.6, 130.8, 150.0; ms m/z 326 (M^+) ; ir ν 1608, 1523, 1181, 1105, 808 cm^{-1}. Anal. Calcd for $C_{20}H_{20}N_2O_2$: C, 73.59; H, 8.08; N, 8.58. Found: C, 73.54 ; H, 8.16 ; N, 8.61.

2,2'-Bis(4-dimethylaminophenyl)-1,3-dioxepane (5)

Colorless powder; yield 46%; mp 135 ~137 ℃ (isopropyl ether); ^{1}H nmr ($CDCl_3$) δ = 1.66 (4 H, br s), 2.89 (9 H, s), 3.05 (3 H, s), 3.70 (4 H, br s), 6.6 - 6.7 (4 H, m), 7.38 - 7.44 (3 H, m), 7.7 - 7.8 (1 H, br); ^{13}C nmr ($CDCl_3$) δ = 29.4, 40.2, 40.7, 63.1, 110.6 (acetal C), 112.1, 127.1, 132.3, 133.4, 149.6; ms m/z 340 (M^+); ir ν 2941, 1608, 1520, 1180, 1096, 808 cm^{-1}. Anal. Calcd for $C_{21}H_{28}N_2O_2$: C, 74.08; H, 8.29; N, 8.23. Found: C, 74.26; H, 8.21; N, 8.41.

Spiro[1,3-dioxepane-2,9'-xanthene] (6)

Colorless powder; yield 45%; mp 168 ℃(ethyl acetate); ^{1}H nmr ($CDCl_3$) δ = 1.6 - 1.8 (4 H, m), 3.64 - 3.68(1 H, m), 3.9 - 4.0 (3 H, m), 7.1 - 8.4 (8 H, m); ^{13}C nmr ($CDCl_3$) δ = 29.9, 30.0, 62.9, 65.3, 95.2 (acetal C), 117.1, 118.1, 122.7, 124.0, 125.4, 125.8, 126.8, 129.2, 134.9, 152.9; ms m/z 268 (M^+); ir ν 2943, 1451, 1231, 1090, 760 cm^{-1}. Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 75.95; H, 5.95.

2,2'-Bis(4-dimethylaminophenyl)-4-hydroxymethyl-1,3-dioxolane (7a)

Colorless oil; yield 83%. ^{1}H nmr ($CDCl_3$) δ = 1.91 (1 H, t, *J* = 6.4 Hz), 2.92 (6 H, s), 2.95 (6 H, s), 3.6 - 3.7 (1 H, m), 3.7 - 3.9 (1 H, m), 3.9 - 4.1 (2 H, m), 4.3 - 4.4 (1 H, m), 6.6 - 6.8 (4 H, m), 7.2 -

7.4 (4 H, m); ^{13}C nmr ($CDCl_3$) δ = 40.3, 63.2, 65.7, 76.3, 110.7 (acetal C), 111.6, 127.2, 127.3, 129.4, 129.8, 150.0, 150.2.

2,2'Bis(4-dimethylaminophenyl)-4-acetoxymethyl-1,3-dioxolane (7'a)

Glycerol (110 mg, 1.2 mmol) was treated with TMK(284 mg, 1 mmol) in the same manner as the typical procedure. After stirring for one hour and successive addition of acetic anhydride (122 mg, 1.2 mmol), the reaction mixture was allowed to stand overnight and worked up on a silica gel column to afford acetate of **7'a**. Colorless powder; yield 74%; mp 101 ~102 ℃ (isopropyl ether); ^{1}H nmr ($CDCl_3$) δ = 2.07 (3 H, s), 2.91 (6 H,s), 2.94 (6 H, s), 3.85 (1 H, dd, *J* = 8.1Hz, *J* = 5.8 Hz), 4.05 (1 H, dd, *J* = 8.1Hz, *J* = 7.0 Hz), 4.19 (2 H, d, *J* = 5.0 Hz), 4.2 - 4.4 (1 H, m), 6.6 - 6.8 (4 H, m), 7.2 - 7.4 (4 H, m); ^{13}C nmr ($CDCl_3$) δ = 20.9, 40.5, 65.0, 66.8, 73.7, 111.2 (acetal C), 111.8, 127.6, 127.7, 129.5, 129.8, 150.3, 150.5, 170.1; ms m/z 384 (M^+); ir ν 1736 (C=O), 1616, 1523, 1228, 821 cm^{-1}. Anal. Calcd for $C_{22}H_{28}N_2O_3$: C, 68.91; H, 7.10; N, 7.31. Found: C,68.92; H, 7.26; N,7.31.

4,4'-Bis(dimethylamino)benzophenone 1,2-*trans*-Cyclohexylene Acetal (8)

Colorless powder; yield 49%; mp 138 ℃ (isopropyl ether); ^{1}H nmr ($CDCl_3$) δ = 1.2 - 1.3 (2 H, m), 1.4 - 1.6 (2 H,m), 1.7 - 1.9 (2 H, m), 2.1 - 2.2 (1 H, m), 2.92 (12 H, s), 3.3 - 3.5 (2 H, m), 6.6 - 6.7 (4 H, m), 7.3 - 7.4 (4 H, m); ^{13}C nmr ($CDCl_3$) δ = 23.8, 28.9, 40.6, 80.6, 109.5 (acetal C), 111.8, 127.2, 132.3, 150.1; ms m/z 366 (M^+); ir ν 2949, 2868, 1613, 1522, 1080, 817 cm^{-1}. Anal. Calcd for $C_{23}H_{30}N_2O_2$: C, 75.38; H, 8.25; N, 7.64. Found: C, 75.56; H, 8.08; N, 7.57.

4,4'-Bis(dimethylamino)benzophenone-1,2-*cis*-Cyclohexylene Acetal (9)

Colorless powder; yield 84 %; mp 163~163.5 ℃ (AcOEt); ^{1}H nmr ($CDCl_3$) δ = 1.2 - 1.9 (8 H, m), 2.90 (6 H, s), 2.92 (6 H, s), 4.1 - 4.2 (2 H, m), 6.6 - 6.7 (4 H, m), 7.2 - 7.4 (4 H, m); ^{13}C nmr ($CDCl_3$) δ = 20.6, 27.9, 40.7, 74.1, 108.9 (acetal C), 111.87, 111.91, 127.2, 127.3, 132.5, 132.7, 150.0, 150.1; ms m/z 366(M^+); ir (KBr) ν 2930, 1614, 1522, 1192, 1078, 812 cm^{-1}. Anal. Calcd for $C_{23}H_{30}N_2O_2$: C, 75.38; H, 8.25; N, 7.64. Found: C, 75.62; H, 8.31; N, 7.62.

4,4'-Bis(dimethylamino)benzophenone 1,2-*o*-Xylene-α,α'-diyl Acetal (10)

Colorless powder; yield 80.5%; mp 173 ℃ (AcOEt); ^{1}H nmr ($CDCl_3$) δ = 2.90 (12 H, s), 4.77 (4 H, s), 6.6 - 6.7 (6 H, m), 7.0 - 7.3 (2 H, m), 7.4 - 7.5 (4 H, m); ^{13}C nmr ($CDCl_3$) δ = 40.6, 65.8, 105.4 (acetal C), 111.9, 126.2, 126.5, 131.26, 138.76, 149.9; ms m/z 388 (M^+); ir ν 1614, 1520, 1190, 1096, 818 cm^{-1}. Anal. Calcd for $C_{25}H_{28}N_2O_2$: C, 77.29; H, 7.25; N, 7.21. Found: C, 77.54; H, 7.30; N,

7.19.

4,4'-Bis(dimethylamino)benzophenone Biphenyl-2,2'diyl Acetal (11)

Colorless powder; yield 83 %; mp 197 ℃ (ethyl acetate); ^{1}H nmr ($CDCl_3$) δ = 2.91 (12 H, s), 6.6 - 6.8 (6 H, m), 7.1 - 7.2 (4 H, m), 7.3 - 7.5 (6 H, m); ^{13}C nmr ($CDCl_3$) δ = 40.5, 111.3, 118.1 (acetal C), 124.0, 124.9, 127.8, 128.3, 128.4, 129.7, 133.8, 150.1, 152.1; ms m/z 436 (M^+); ir ν 1610, 1521, 1186, 1163, 816 cm^{-1}. Anal. Calcd for $C_{29}H_{28}N_2O_2$: C, 79.79; H, 6.42; N, 6.42. Found: C, 79.73; H, 6.47; N, 6.39.

4,4'-Bis(dimethylamino)benzophenone 1,2-Phenylene Acetal (12)

Catechol (132 mg, 1.2 mmol) was treated with TMK (284 mg, 1 mmol) and silver trifluoroacetate (553 mg, 2.5 mmol) in the same manner as the typical procedure to afford 54 mg, 15% yield of **12** (colorless plates). On the other hand, on refluxing with TMK and copper(I) chloride (248 mg, 2.5 mmol) for one hour 238 mg, 66% yield of **12** was obtained. mp 155 ℃ (ethyl acetate); ^{1}H nmr ($CDCl_3$) δ =2.94 (12 H, s), 6.4 - 6.6 (4 H, m), 6.7 - 6.9 (4 H, m), 7.3 - 7.5 (4 H, m); ^{13}C nmr ($CDCl_3$) δ = 40.4, 108.4 (acetal C), 111.5, 121.1, 127.7, 128.0, 147.6, 150.8; ms m/z 360 (M^+); ir ν 1614, 1485, 1240, 1186, 810 cm^{-1}. Anal. Calcd for $C_{23}H_{24}N_2O_2$: C, 76.64; H, 6.71; N, 7.77. Found: C, 76.69; H, 6.71; N, 7.78.

4,4'-Bis(dimethylamino)benzophenone 3-Acetoxy-1,2-phenylene Acetal (13)

To a solution of TMK (284 mg, 1 mmol), pyrogallol (151 mg, 1.2 mmol), and copper(I) chloride (248 mg, 2.5 mmol) in acetonitrile (5 ml), triethylamine (455 mg, 4.5 mmol) was added. After refluxing for one hour, to the reaction mixture was added acetic anhydride (122 mg, 1.2 mmol), and then the resulting mixture was allowed to stand overnight and worked up in the same manner as the typical procedure to afford colorless powder of **13** (226 mg, 54%). Mp 143~145℃ (ethyl acetate); ^{1}H nmr ($CDCl_3$) δ = 2.30 (3 H, s), 2.92 (6 H, s), 2.94 (6 H, s), 6.6 - 6.8 (7 H, m), 7.3 - 7.5 (4 H, m); ^{13}C nmr ($CDCl_3$) δ = 20.8 ($\underline{C}H_3CO$), 40.4, 106.3 (acetal C), 111.6, 115.4, 119.8, 121.0, 127.4, 127.9, 128.0, 133.3, 139.1, 149.4, 151.0, 168.3 ($CH_3\underline{C}O$); ms m/z 418 (M^+); ir ν 1767 (C=O), 1614, 1526, 1188, 1059, 814 cm^{-1}. Anal. Calcd for $C_{25}H_{26}N_2O_4$: C, 71.75; H, 6.25; N, 6.69. Found: C, 71.95; H, 6.22; N, 6.70.

Hydrolysis of acetals (3) and (12)

To a solution of acetal (**3**) (100 mg, 0.307 mmol) in methanol (3 ml) was added 5 drops of 1/10 M hydrochloric acid. The mixture was stirred for 5 min at room temperature and then poured into excess amounts of water to afford 4,4'-dimethylaminobenzophenone (77 mg, 94%). Acetal(**12**)(100 mg, 0.278

mmol) was treated for one hour in the same manner as above to give 4,4'- dimethylaminobenzophenone (72 mg, 93%).

REFERENCES

1 I. Shibuya, Y. Taguchi, T. Tsuchiya, A. Oishi, and E. Katoh, *Bull. Chem. Soc. Jpn.*, 1994 , **67**, 3048 .

2 B. Gehauf and J. Goldenson, *Anal. Chem.*, 1950, **22**, 498 ; A. J. Christopher, *Analyst*, 1969, **94**, 397 ; G. Ackermann and H. Röder, *Talanta*, 1977, **24**, 99 .

3 A. N. Debelder, *Adv. Carbohydr. Chem. Biochem.*, 1977, **34**, 179 .

4 P. Lavallée, R. Ruel, L. Grenier, and M. Bissonnette, *Tetrahedron Lett.*, 1986, **27** , 679 .

5 C. Graebe and P. Röder, *Ber.*, 1899, **32**, 1688 .

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