

AN EFFICIENT SYNTHESIS OF 1,2-DITHIOLANES AND 1,2,4-TRITHIOLANES BY THE REACTION OF PHOSPHORUS YLIDES WITH ELEMENTAL SULFUR

Kentaro Okuma,* Kazuki Kojima, and Shinji Shibata

Department of Chemistry, Faculty of Science, Fukuoka University, Jonan-ku, Fukuoka 814-0180, Japan

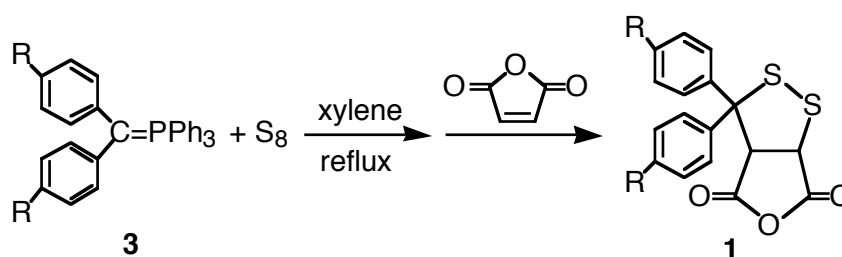
Abstract-Reaction of diarylmethylenetriphenylphosphoranes with elemental sulfur followed by the addition of maleic anhydride afforded 1,2-dithiolanes in good yields. When the reaction was carried out in the presence of adamantane-2-thione, two types of 1,2,4-trithiolane were formed. Thiation of thiobenzophenones with elemental sulfur also afforded the corresponding 1,2-dithiolanes.

The chemistry of cyclic polysulfides is of current interest.¹ 1,2-Dithiolanes (**1**) and 1,2,4-trithiolanes (**2**) are an important class of compounds because of their biological activity and structural interest.² The synthesis of **1** includes the oxidation of 1,3-dithiols,³ and the intramolecular cyclization of thiosulfine with double bond.⁴ 1,2,4-Trithiolanes **2** were prepared by the reaction of thiobenzophenone with *o*-chloranil,⁵ the reaction of thiobenzophenones with 1,1-diphenylethylene sulfide,⁶ the reaction of thiones with Lowesson reagents,⁷ the reaction of dialkyl ketones with hydrogen sulfide, elemental sulfur, and amines,⁸ and the fragmentation of 1,2,3-thiadiazoles.⁹ Recently, Senning and coworkers reported that reaction of α -chlorosulfonyl disulfides with morpholine afforded the corresponding dispirotrithiolanes.¹⁰ Previously, we have reported the synthesis of 1,2-dithiolanes **1** from Wittig reagents (**3**), elemental sulfur, and maleic anhydride.¹¹ Recently, we have reported that the reaction of pivalophenones with tetraphosphorus decasulfide afforded *cis*- and *trans*-3,5-di-*tert*-butyl-3,5-diaryl-1,2,4-trithiolanes, which equilibrated to give other isomers in refluxing toluene *via* thiopivalophenones and thiopivalophenone S-sulfides.¹² We report a synthesis of **1** and **2** from diarylmethylenetriphenylphosphoranes (**3**) and elemental sulfur.

Results and Discussion

Treatment of diphenylmethylenetriphenylphosphorane (**3a**) with excess sulfur in the presence of maleic anhydride resulted in the formation of 5,5-diphenyl-1,2-dithiolane-3,4-dicarboxylic acid anhydride (**1a**) in good yield. Reactions of other phosphoranes (**3b-d**) with elemental sulfur and maleic anhydride were carried out in a similar manner (Scheme 1, Table 1).

The reaction required relatively elevated temperature for completion. When the reaction was carried out in refluxing benzene, 50% of thiobenzophenone (**4a**) was remained unreacted.

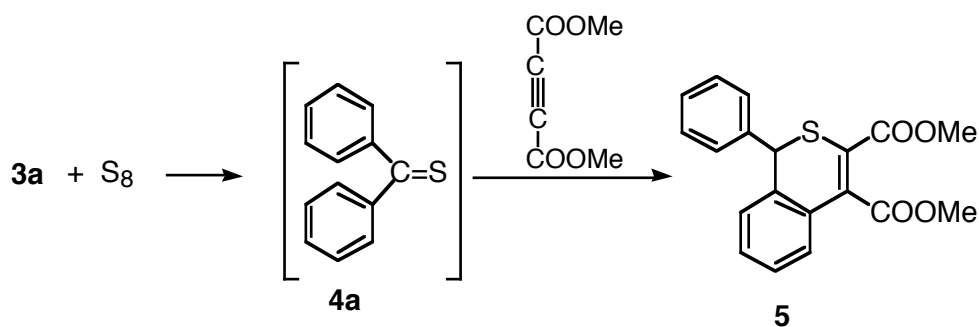


Scheme 1.

Table 1. Reaction of **3** with 7 Equivalents of Elemental Sulfur Followed by Maleic Anhydride in Xylene under Reflux

3	R	Conditions		1	Yield (%)
		Solvent	Time/day		
3a	H	Xylene	1	1a	74
3a	H	Toluene	1	1a	25
3b	Me	Xylene	1	1b	90
3c	MeO	Xylene	1	1c	79
3d	Cl	Xylene	1	1d	35
3d	Cl	Xylene	3	1d	60

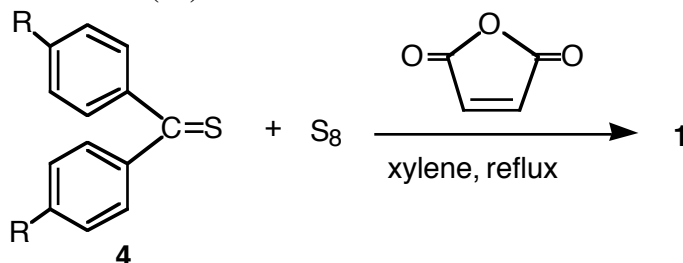
1,2-Dithiols were prepared by a cycloreversion and cycloaddition reaction of trithiolanes with Dimethyl acetylenedicarboxylate (DMAD) or by the reaction of ketone hydrazone with S_2Cl_2 followed by the addition of DMAD.^{6,13} Recently, we have reported the reaction of 4,4'-dimethylthiobenzophenone (**4b**: R=CH₃) with 2,5-norbornadiene; the initial [4+2] cycloaddition product was obtained without 1,3-prototropy.¹⁴ We tried the reaction of **3a** with elemental sulfur in the presence of DMAD in the hope of obtaining the [3+2] cycloadduct of thiosulfine with DMAD. However, only cyclic sulfide (**5**), a [4+2] cycloadduct of **4a** with DMAD was obtained, suggesting that, the reactivity of DMAD was quite different from that of maleic anhydride (Scheme 2).



Scheme 2.

Since **4a** is generally produced by the reaction of **3a** with elemental sulfur,¹⁵ we then tried the reaction of **4** with elemental sulfur in the presence of maleic anhydride. When 4,4'-dimethoxythiobenzophenone (**4c**) was treated with elemental sulfur in the presence of maleic anhydride, the cycloadduct (**1c**) was obtained in 30 % yield (Scheme 3, Table 2).

The lower yields for **1** is probably due to low concentration of activated sulfur. If activated sulfur plays an important role in this reaction, addition of triphenylphosphine could improve the yields of cycloadducts **1**. When the reaction of **4c** with excess sulfur was carried out in the presence of triphenylphosphine, the yield of adduct (**1c**) was increased to 65 %.

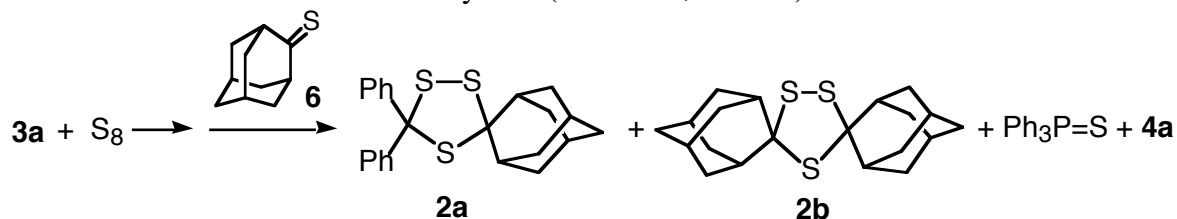


Scheme 3.

Table 2. Reaction of Thiobenzophenones (**4**) with Sulfur in the Presence of Maleic Anhydride in Xylene under Reflux

	R	Time/day	1	Yield (%)
4a	H	3	1a	13
4c	MeO	2	1c	30
4c	MeO	5	1c	48

Huisgen and Rapp reported the synthesis of 1,2,4-trithiolanes (**2**) by the reaction of thiobenzophenone-S-sulfides with adamantane-2-thione (**6**).⁶ To check the scope and limitation of the present methodology, we then tried the reaction of **3a** with elemental sulfur and **6** under these conditions in the hope of the formation of the corresponding **2**. Treatment of **3a** with elemental sulfur followed by the addition of **6** resulted in the formation of spiro-adamantane-1,2,4-trithiolanes (**2a**) and spiro-diadamantane-1,2,4-trithiolane (**2b**) in 15 % and 44 % yields, respectively. Thiobenzophenone (**4a**) and triphenylphosphine sulfide were also obtained in 35 % and 84 % yields (Scheme 4, Table 3).



Scheme 4.

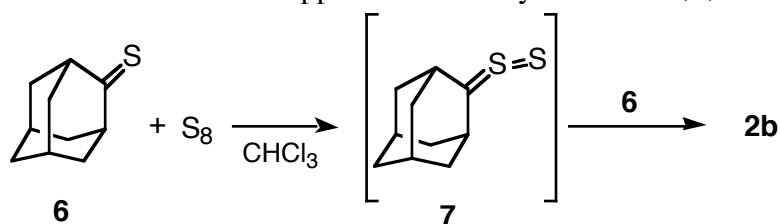
Table 3. Reaction of **2** with Sulfur in the Presence of Adamantane-2-thione in Toluene under Reflux

	R	Time/day	Products/ Yield (%)			
			2	4	2	4
3a	H	1	2a 15	2b 44	4a 35	
3c	MeO	2	2c 12	2b 38	4c 35	

Analogously, thiation of 4,4'-dimethoxythiobenzophenone (**4c**) by elemental sulfur and catalytic amount

of triphenylphosphine sulfide in chloroform followed by treatment with adamantane-2-thione led to the adamantane-spiro-1,2,4-trithiolanes (**2c**) (14 %) and (**2b**) (35 %) along with starting **4c** (45 %).

The above results suggest that initially formed thiosulfines reacted **6** to afford unsymmetrical trithiolanes (**2c**), which decomposed to give 4,4'-dimethoxythiobenzophenone and adamantane-2-thione S-sulfide (**7**). The obtained **7** further reacted with **6** to give the most stable symmetrical trithiolane (**2b**). To confirm this possibility, we then tried the reaction of elemental sulfur with **6** in the presence of catalytic amount of triphenylphosphine sulfide in chloroform. As expected, the corresponding trithiolane (**2b**) was obtained in 59 % yield. Thus, this method will be also applicable to the synthesis of 1,2,4-trithiolanes (Scheme 5).



Scheme 5.

In summary, we have succeeded in the synthesis of 1,2-dithiolanes from diarylmethylenetriphenylphosphorane, elemental sulfur, and maleic anhydride. We have also synthesized 1,2,4-trithiolanes from adamantane-2-thione, elemental sulfur, and thiobenzophenones.

ACKNOWLEDGMENT

This work was partly supported by a Grant-in-Aid for the Scientific Research from the Ministry of Education, Science, Sports, and Culture (No 02640415).

EXPERIMENTAL

General: Melting points are uncorrected. ^1H and ^{13}C NMR spectra were obtained with a JEOL FX-90Q or a JEOL GSX-400 spectrometer. Chemical shifts are given in ppm units downfield from tetramethylsilane. TLC analyses were performed using Merck silica gel 60 F254 aluminum plates. Gel-HPLC was performed on a JAI Model 908 by elution with chloroform.

Material: Thiobenzophenones (**4**) were prepared by the reaction of benzophenone with P_4S_{10} .¹⁶ Adamantane-2-thione (**6**) was prepared by a method in a literature.¹⁷

Reaction of Diphenylmethylenetriphenylphosphorane (3a) with Elemental Sulfur Followed by the Addition of Maleic Anhydride To a refluxing solution of **3a** (0.428 g, 1 mmol) in xylene (30 mL) was added elemental sulfur (0.224 g, 7.0 mg-atom) in one portion. After refluxing for 5 min, maleic anhydride (0.294 g, 3.0 mmol) was added in one portion and the solution was refluxed for 36 h. The reaction mixture was concentrated to give a dark brown oil, which was chromatographed over silica gel by elution from hexane-dichloromethane (1:1) to give triphenylphosphine sulfide (0.223 g, 76 %) and pale yellow crystals of 5,5-diphenyl-1,2-dithiolane-3,4-dicarboxylic acid anhydride (**1a**, 0.244 g, 74 %). **1a**: mp 86-88 °C (MeOH), ^1H NMR (400 M Hz, CDCl_3) δ = 4.61 (d, J = 8.0 Hz, 1 H, CH), 4.81 (d, J = 8.0 Hz, 1 H, CH), 7.20-7.42 (m, 10 H, Ph). Anal. Calcd for $\text{C}_{17}\text{H}_{12}\text{O}_3\text{S}_2$. C; 62.17, H; 3.68. Found. C; 62.27, H; 3.86. Other reaction was carried out in a similar manner. 3,3-di-*p*-tolyl-1,2-dithiolane-4,5-dicarboxylic acid anhydride (**1b**): mp 87-90 °C (MeOH). ^1H NMR (400 M Hz, CDCl_3) δ = 2.22 (s, 6 H, Me), 4.46 (d, J = 7.4 Hz, 1 H, CH), 4.67 (d, J = 7.4 Hz, 1H, CH), 7.00-7.22 (m, 8 H, Ar). HRMS: Found. 356.0545. Calcd for $\text{C}_{19}\text{H}_{16}\text{O}_3\text{S}_2$ (M^+) 356.0541. 5,5-di-*p*-methoxyphenyl-1,2-dithiolane-3,4-dicarboxylic acid anhydride (**1c**): mp 55-58°C. ^1H NMR (400 M Hz, CDCl_3) δ =3.77 (s, 3 H, MeO), 3.79 (s, 3 H, MeO), 4.54 (d, J = 7.3 Hz, 1 H, CH), 4.62 (d, J = 7.3 Hz, CH), 6.82 (br d, J =7.2 Hz, 4 H, Ar), 7.16 (d, J =7.2 Hz, 2 H, Ar), 7.24 (d, J =7.2 Hz, 2 H, Ar). ^{13}C NMR (100 MHz, CDCl_3) δ =53.65 (CH), 55.16 (OMe), 55.26 (OMe), 58.03 (CH), 79.89 (Ar_2C), 113.48, 113.57, 128.26, 129.21, 130.64, 134.13, 159.11,

159.24 (Ar), 166.10 (C=O), 167.54 (C=O). Anal. Calcd for $C_{19}H_{16}O_5S_2$. C; 58.75, H; 4.25. Found. C; 59.01, H; 4.53. 5,5-di-*p*-chlorophenyl-1,2-dithiolane-3,4-dicarboxylic acid anhydride (**1d**): mp 73-76 °C (MeOH). 1H NMR (400 MHz, for $C_{19}H_{16}O_5S_2$) δ = 4.61 (d, 1 H, J =7.4 Hz, CH), 4.70 (d, 1 H, J =7.4 Hz, CH), 7.10-7.42 (m, 10 H, Ar). ^{13}C NMR (100 MHz, for $C_{19}H_{16}O_5S_2$) δ = 53.11 (CH), 57.85 (CH), 79.14 (Ar₂C), 118.25, 128.26, 128.68, 128.82, 129.28, 130.14, 130.62, 134.38, 134.62, 136.47, 137.57, 140.29, 166.06, 168.79. HRMS: Found; 395.9448. Calcd for $C_{17}H_{10}O_3^{35}Cl_2S_2$ (M⁺) ; 395.9448.

Reaction of 3 with Elemental Sulfur followed by Addition of DMAD To a refluxing solution of **3a** (0.428 g, 1 mmol) in xylene (30 mL) was added elemental sulfur (0.224 g, 7.0 mg-atom) in one portion. After refluxing for 5 min, DMAD (0.57 g, 4.0 mmol) was added in one portion and the solution was refluxed for 16 h. The reaction mixture was concentrated to give a dark brown oil, which was chromatographed over silica gel by elution from hexane-dichloromethane (1:3) to give triphenylphosphine sulfide (0.228 g, 78 %) and colorless crystals of dimethyl 1-phenyl-1*H*-2-benzothiopyrane-3,4-dicarboxylate (**5**, 0.201 g, 56 %). mp 90-91 °C (MeOH) (lit.¹⁸ 91-92 °C). 1H NMR (CDCl₃) δ =3.77 (s, 3 H, OMe), 3.94 (s, 3 H, OMe), 5.21 (s, 1 H, CH), 6.95-7.50 (m, 9 H, Ph).

Reaction of Thiobenzophenone (4a) with Elemental Sulfur in the Presence of Maleic Anhydride

To a refluxing solution of **4a** (0.201 mg, 1.0 mmol) in xylene (20 mL) was added elemental sulfur (0.160 g, 5 mg-atom). After refluxing for 1 h, maleic anhydride (0.98 g, 10 mmol) was added to this blue solution and the solution was refluxed for 3 days. The reaction mixture was concentrated to give a dark brown oil, which was chromatographed over silica gel by elution from hexane-dichloromethane (1:1) to afford pale yellow crystals of **1a** (0.043 g, 13 %): mp 86-88 °C (MeOH).

Reaction of 4a with Elemental Sulfur Followed by Addition of Maleic Anhydride in the Presence of Catalytic Amount of Triphenylphosphine To a refluxing solution of **4a** (0.201 mg, 1.0 mmol) in xylene (20 mL) were added elemental sulfur (0.160 g, 5 mg-atom) and triphenylphosphine sulfide (0.029 g, 0.1 mmol). After refluxing for 1 h, maleic anhydride (0.98 g, 10 mmol) was added to this blue solution and the solution was refluxed for 24 h. The reaction mixture was concentrated to give a dark brown oil, which was chromatographed over silica gel by elution from hexane-dichloromethane (1:1) to afford pale yellow crystals of **1a** (0.213 g, 65 %): mp 86-88 °C (MeOH).

Reaction of 3a with Elemental Sulfur Followed by Addition of Adamantane-2-thione (6) To a refluxing solution of **3a** (0.428 g, 1 mmol) in toluene (20 mL) was added elemental sulfur (0.128 g, 4.0 mg-atom) in one portion. After refluxing for 30 min, **6** (0.165 g, 1.0 mmol) was added in one portion and the solution was refluxed for 24 h. The reaction mixture was concentrated to give a blue oil, which was chromatographed over silica gel by elution from hexane-dichloromethane (1:3) to give colorless crystals of 5',5'-diphenylspiro[adamantane-2,3'-(1,2,4)-trithiolane] (**2a**) (0.061 g, 15 %), dispiro[adamantane-2,3'-(1,2,4)-trithiolane-5',2'-adamantane] (**2b**) (0.080 g, 44 %), triphenylphosphine sulfide (0.252 g, 84 %), and benzophenone (0.064 g, 35 %). **2a**: mp 126-129 °C (THF-pentane) (lit.¹ 131-132 °C) 1H NMR (400 MHz, CDCl₃) δ =1.78 (br, 4 H, Ad-H), 1.86 (br s, 1 H, Ad-H), 1.97 (br d, 3 H, J = 16 Hz, Ad-H), 2.20 (br d, 2 H, J = 16 Hz, Ad-H), 2.27 (br d, 2 H, J = 16 Hz, Ad-H), 2.49 (br s, 2 H, Ad-H), 7.25-7.32 (m, 5 H, Ph), 7.60-7.63 (m, 5 H, Ph). **2b**: colorless crystals; mp 191-193 °C (THF-pentane) (lit.¹ 189-191 °C).

The reaction of **3c** with elemental sulfur and **6** was carried out in a similar manner. The reagents used in the preparation were: **3c** (0.481 g, 1.0 mmol), elemental sulfur (0.128 g, 4.0 mg-atom), **6** (0.165 g, 1.0 mmol) and toluene (20 mL). Flush chromatography followed by Gel-HPLC afforded 5',5'-di-*p*-methoxyphenylspiro[adamantane-2,3'-(1,2,4)-trithiolane] (**2c**) (0.061 g, 12 %), **2b** (0.080 g, 38 %), triphenylphosphine sulfide (0.252 g, 84 %), and **4c** (0.064 g, 35 %). **2c**: pale brown oil. 1H NMR (400 MHz, CDCl₃) δ =1.78 (br, 4 H, Ad-H), 1.85 (br s, 1 H, Ad-H), 1.96 (br d, 3 H, J = 16 Hz), 2.17 (br d, 2 H, J = 12 Hz, Ad-H), 2.27 (br d, 2 H, J = 12 Hz), 2.46 (br s, 2 H, Ad-H), 3.79 (s, 6 H, OMe), 6.81 (d, 4 H, J =9 Hz, Ar), 7.53 (d, 4 H, J = 9 Hz, Ar). ^{13}C NMR (100 MHz, CDCl₃) δ = 26.58, 26.74, 36.73, 37.77,

40.03, 55.26 (MeO) , 89.01, 93.49, 1 13.00 (meta, Ar), 130.31 (ortho, Ar), 134.36 (ipso, Ar), 158.79 (para, Ar). IR (KBr) ν (cm⁻¹): 2910, 2853, 1604, 1579, 1504, 1463, 1451, 1302, 1252, 1175, 1097, 1035, 961, 821. HRMS: Found; 456.1236. Calcd for C₂₅H₂₈O₂S₃ (M⁺); 456.1251.

Reaction of 4c with Elemental Sulfur Followed by Addition of 6 in the Presence of Catalytic Amount of Triphenylphosphine Sulfide To a solution of **4c** (0.050 g, 0.2 mmol) in chloroform (5 mL) were added elemental sulfur (0.016 g, 0.5 mg-atom) and triphenylphosphine sulfide (0.010 g, 0.03 mmol). After refluxing for 1 h, **6** (0.033 g, 0.2 mmol) was added in one portion and the solution was refluxed for 24 h and stirred for 15 days at rt. The reaction mixture was evaporated to give a blue oil, which was subjected to a preparative TLC by elution of hexane, hexane-dichloromethane (1:1), and dichloromethane to give **2c** (0.0091 g, 14 %). Trithiolane (**2b**) was also obtained (0.013 g, 35 %). Thioketone (**4c**) was recovered in 45 %.

Reaction of 6 with Elemental Sulfur in the Presence of Catalytic Amount of Triphenylphosphine Sulfide To a solution of **6** (0.066 g, 0.4 mmol) in chloroform (5 mL) were added elemental sulfur (0.016 g, 0.5 mg-atom) and triphenylphosphine sulfide (0.010 g, 0.03 mmol). After refluxing for 2 days, the reaction mixture was evaporated to give pale orange crystals, which was subjected to a preparative TLC by elution of hexane and hexane-dichloromethane (1:1) to afford colorless crystals of **2b** (0.043 g, 59 %).

REFERENCES

- 1 For a review, see "Progress in Heterocyclic Chemistry," Vol. 11, chapters 5.6 and 6.4, ed. by G. W. Gribble and T. L. Gilchrist, 1999, Pergamon. A. Ishii, T. Omata, K. Umezawa, and J. Nakayama, *Bull. Chem. Soc. Jpn.*, 2000, **73**, 729.
- 2 H. W. Brinkman, H. Copier, J. J. M. de Leuw, and S. B. Tjan, *J. Agr. Food Chem.*, 1972, **20**, 177. E. K. Adesogan, *J. Chem. Soc., Chem. Commun.*, **1974**, 906.
- 3 R. Sato, S. Saito, H. Chiba, T. Goto, and M. Saito, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 1647. M. Tazaki, S. Nagahama, and M. Takagi, *Chem. Lett.*, **1988**, 1339. H. Uneme, H. Mitsudera, T. Kamikado, Y. Kono, Y. Manabe, and M. Numata, *Biosci. Biotechnol. Biochem.*, 1992, **56**, 2023.
- 4 T. Saito, Y. Shundo, S. Kitazawa, and S. Motoki, *J. Chem. Soc., Chem. Commun.*, **1992**, 600.
- 5 M. M. Cambell and D. M. Evgenios, *J. Chem. Soc., Perkin Trans. 1*, **1973**, 2862.
- 6 R. Huisgen and J. Rapp, *J. Am. Chem. Soc.*, 1987, **109**, 902. R. Huisgen and J. Rapp, *Tetrahedron*, 1997, **53**, 939.
- 7 A. Ishii, J. Nakayama, M. -X. Ding, N. Kotaka and M. Hoshino, *J. Org. Chem.*, 1990, **55**, 2411.
- 8 F. Asinger, M. Thiel and G. Lipfert, *Liebigs Ann. Chem.*, 1959, **627**, 195. F. Asinger, W. Schäfer, K. Halcour, A. Saus and H. Triem, *Angew. Chem., Int. Ed., Engl.*, 1964, **3**, 19.
- 9 W. Winter, H. Buehl and H. Meier, *Z. Naturforsch. B. Anorg. Chem. Org. Chem.*, 1980, **35**, 1015.
- 10 F. A. G. El-Essay, S. M. Yassin, I. A. El-Sakka, A. F. Khatat, I. Soetofte, J. O. Madsen, and A. Senning, *J. Org. Chem.*, 1998, **63**, 9840. M. I. Hegab, F. M. E. Abdel-Megeid, F. A. Gad, S. A. Shiba, I. Soetofte, J. Moeller, and A. Senning, *Acta Chem. Scand.* 1999, **53**, 133.
- 11 K. Okuma, M. Shimasaki, K. Kojima, H. Ohta, and R. Okazaki, *Chem. Lett.*, **1993**, 1599.
- 12 K. Okuma, S. Shibata, Y. Koga, K. Shioji, and Y. Yokomori, *Chem. Commun.*, **2000**, 1535.
- 13 T. Machiguchi, M. Minoura, S. Yamabe, and T. Minato, *Chem. Lett.*, **1995**, 103.
- 14 K. Okuma, K. Shiki, T. Shiroka, K. Kojima, and K. Shioji, *Heterocycles*, 1997, **45**, 1281.
- 15 H. Staudinger and J. Meyer, *Helv. Chem. Acta*, 1919, **2**, 635.
- 16 N. Ramnath, V. Rameth, and V. Ramamurthy, *J. Org. Chem.*, 1983, **48**, 214.
- 17 J. W. Greidanus and W. J. Schwalm, *Can. J. Chem.*, 1979, **57**, 3715.