ELSEVIER

Journal of Fluorine Chemistry 80 (1996) 91–94

JOURNAL OF FLUORINE CHEMISTRY

Addition reactions of dibromodifluoromethane promoted by sulfinatodehalogenation reagents

Fan-Hong Wu, Bing-Nan Huang, Long Lu, Wei-Yuan Huang

Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences Shanghai, 200032, China

Received 20 January 1996; accepted 18 June 1996

Abstract

The addition reaction of difluorodibromomethane with alkenes, alkynes and cyclic enol ethers promoted by sulfinatodehalogenation reagents, R_FI/sodium dithionite, Rongalite or thiourea dioxide under mild conditions are described.

Keywords: Difluorodibromomethane; Sulfinatodehalogenation reagents

1. Introduction

Since many difluoromethyl substituted compounds have been found to be biologically active in pharmaceuticals and agrochemicals, the introduction of the CF_2 group into organic molecules is of much interest [1–6]. More recently, the use of fluorinated building blocks, such as difluoro substituted methanes, gained increasing popularity [7,8]. It was reported that CF_2Br_2 reacted with alkenes to give the normal $BrCF_2$ containing adducts. However, these reactions required vigorous conditions [9–14]. $BrCF_2SO_2Br$ was reported as a mild and efficient bromodifluoromethylation agent in our laboratory [15]. Here we present a novel bromodifluoromethylation method via the addition of CF_2Br_2 with olefins, alkynes and cyclic enol ethers initiated by sulfinatodehalogenation reagents.

2. Results and discussion

In presence of sodium dithionite, Rongalite or thiourea dioxide, CF_2Br_2 reacted with terminal alkenes in aqueous acetonitrile solution at room temperature or with cooling by an ice bath to give the corresponding adducts in good yields (Table 1).

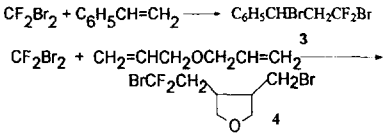
$$CF_2Br_2 + CH_2=CH-R \xrightarrow[CH_3CN/H_2O,0-5\ ^\circ C]{Na_2S_2O_4/NaHCO_3} BrCF_2CH_2CHBrR$$

$$CF_2Br_2 + CH_2=CH-R \xrightarrow[or\ (H_2N)_2C=SO_2]{HOCH_2SO_2Na} BrCF_2CH_2CHBrR$$

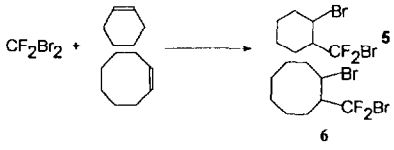
$$R = n-C_4H_9,\ \mathbf{1},\ n-C_6H_{13},\ \mathbf{2}$$

In the case of styrene, together with the addition product, oligomer containing fluorine resulted. When diallyl ether was utilized as a substrate, the tetrahydrofuran derivative was formed.

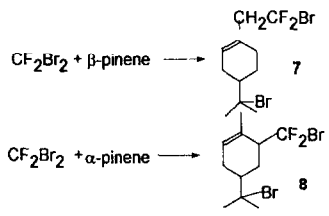
$$CF_2Br_2 + C_6H_5CH=CH_2 \rightarrow \underset{3}{C_6H_5CHBrCH_2CF_2Br}$$



Both cyclohexene and cyclooctene gave the addition products as a mixture of cis and trans isomers.



CF_2Br_2 reacted with α-pinene or β-pinene to give the corresponding addition-ring opening products.



PII S0022-1139(96)03503-8

Table 1
The addition reaction of CF_2Br_2 initiated by sulfinatodehalogenation reagents.

entry	reagent	substrate	adduct	yield (%)
1	Rongalite	1-hexene	1	85
2	Rongalite	1-octene	2	87
3	Rongalite	cyclohexene	5	70
4	Rongalite	styrene	3	50
5	thiourea dioxide	1-hexene	1	80
6	thiourea dioxide	cyclohexene	5	75
7	sodium dithionite	1-hexene	1	92
8	sodium dithionite	1-octene	2	88
9	sodium dithionite	cyclooctene	6	80
10	sodium dithionite	cyclohexene	5	75
11	sodium dithionite	diallyl ether	4	85
12	sodium dithionite	β-pinene	7	75
13	sodium dithionite	α-pinene	8	68
14	sodium dithionite	17	9	80
15	sodium dithionite	1-hexyne	10	55
16	sodium dithionite	1-heptyne	11	53
17	sodium dithionite	1-octyne	12	50
18	sodium dithionite	2,3-dihydrofuran	13	78
19	sodium dithionite	3,4-dihydro-2H-pyran	14	72
20	sodium dithionite	3,4-dihydro-2H-pyran (excess)	15	76

In the presence of sodium dithionite, CF_2Br_2 reacted with diethyl allylmalonate (**17**) to give the adduct **9**.

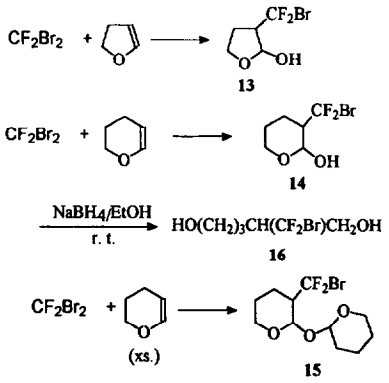
$$CF_2Br_2 + \underset{\mathbf{17}}{CH_2=CHCH_2CH(CO_2Et)2} \rightarrow \underset{\mathbf{9}}{BrCF_2CH_2CHBrCH_2CH(CO_2Et)}$$

The reaction of CF_2Br_2 with alkynes initiated by sodium dithionite gave the addition products as E and Z mixtures in moderate yields.

$$CF_2Br_2 + CH\equiv C-R \rightarrow BrCF_2CH=CBr-R$$

R = $(CH_2)_3CH_3$, **10**
= $(CH_2)_4CH_3$, **11**
= $(CH_2)_5CH_3$, **12**

Under conditions similar to those for polyfluoroalkyl iodides [16], CF_2Br_2 reacted with cyclic enol ethers, such as 2,3-dihydrofuran and 3,4-dihydro-2H-pyran to give the corresponding 2-(bromodifluoromethyl)hemiacetals (**13** and **14**) in good yields. Interestingly, CF_2Br_2 reacted with excess 3,4-dihydro-2H-pyran (2.5 eq.) to produce the corresponding bicyclic acetal **15** as a main product in good yield, while using excess 2,3-dihydrofuran only gave compound **13**. Compound **14** was very unstable and decomposed within 24 h at room temperature. It can be readily converted to 2-bromodifluoromethyl-1,5-pentadiol **16** in good yield through reduction with $NaBH_4$ in ethanol; **16** may be a useful fluorine-containing intermediate.



The addition of CF_2Br_2 with olefins and alkynes is supposed to proceed through a SET mechanism, as shown in Scheme 1 [17].

The reaction is initiated by the $SO_2^{-\cdot}$ radical anion which exist in the $Na_2S_2O_4$ solution. In the first step, $SO_2^{-\cdot}$ radical anion encountered with CF_2Br_2 and produces $CF_2BR^{\cdot}$ radical with the release of bromide anion and sulfurdioxide, then the produced $CF_2Br^{\cdot}$ radical attacks the olefin at the less hindered

$$S_2O_4^{2-} \rightleftharpoons SO_2^{\cdot-}$$

$$CF_2Br_2 + SO_2^{\cdot-} \longrightarrow {}^{\cdot}CF_2Br + Br^- + SO_2$$

$${}^{\cdot}CF_2Br + CH_2=CH-R \longrightarrow BrCF_2CH_2\dot{C}HR$$

$$BrCF_2CH_2\dot{C}HR + CF_2Br_2 \longrightarrow$$

$$BrCF_2CH_2CHBrR + {}^{\cdot}CF_2Br$$

Scheme 1. The mechanism of the addition reaction of CF_2Br_2 with alkenes promoted by sodium dithionite

side and yields a new $BrCF_2CH_2CHR\cdot$ radical, which gives the addition product by abstraction of a bromide from another molecule of CF_2Br_2 and producing a new $CF_2Br^{\cdot}$ radical to recycle the reaction.

In summary, the reaction provided a novel yet simple bromodifluoromethylation method for the synthesis of the precursor molecules containing the CF_2 group using CF_2Br_2 as the starting material.

3. Experimental

All boiling and melting points were uncorrected. IR spectra were recorded on an IR-440 spectrometer using films or potassium bromide pellets. ^{19}F NMR spectra were recorded on Varian EM-360L (56.4 MHz) or FX-90Q (84.6 MHz) spectrometers using TFA as external standard. Chemical shifts in ppm were positive for upfield shifts ($\delta_{CFCl3} = \delta_{TFA} + 76.8$ ppm). ^1H NMR spectra were recorded on an EM-360A (60 MHz) spectrometer using TMS as external or internal standard, or obtained on FX-90Q(90 MHz), Varian

XL-200 (200 MHz) or Bruker AC-300 (300 MHz) spectrometers. MS spectra were obtained on a Finnigan GC-MS-4021 spectrometer. The column chromatography was performed using silica gel H with petroleum ether and ethyl acetate as the eluent.

4. Typical procedure

The addition reaction of difluorodibromomethane with 1-hexene.

The mixture of CF_2Br_2 (2.10 g, 10 mmoL), 1-hexene (1.0 g, 15 mmoL), Rongalite (Sodium hydroxymethanesulphinate) (2.80 g, 18 mmoL), sodium bicarbonate (1.40 g, 16 mmoL), acetonitrile (6 mL) and water (2 mL) was stirred at room temperature for 12 h. CF_2Br_2 was converted completely as shown by ^{19}F NMR. The mixture was extracted with ether (3×20 mL). The ethereal layer separated was dried over anhydrous magnesium sulfate. After evaporation of the solvent, the resulted liquid could be vacuum distilled or chromatographed on a silica gel column using petroleum ether as eluent to give the adduct **1**, (2.50 g, 85%).

1: bp. 80–81 °C/23 mmHg υ_{max}: 2700–2900, 1190 cm^{-1}. $\delta_H(CDCl_3)$: 4.26 (1 H, m, CHBr), 3.5 (2 H, m, CH_2CF_2Br), 0.93–2.1 (9 H, m, other hydrogen atoms) ppm. δ_F ($CDCl_3$): 42.0 (2 F, m, CF_2Br) ppm. m/z(%): 296 (1.35), 294 (M^+, 1.75), 215 (M^+–Br, 1.28), 134 (M^+–Br_2, 27.30), 91.0 (28.46), 70 (100). Anal.: $C_7H_{12}Br_2F_2$ Calcd.: C 28.57 H 4.08 F 12.92 Found: C 28.80 H 4.42 F 12.6%.

2: δ_H(neat): 4.30 (1 H, m, CHBr), 3.0 (2 H, m, CH_2CF_2Br), 0.9–2.10 (13 H, m, other hydrogen atoms) ppm. $\delta_F(CDCl_3)$: 41.8 (2 F, m, CF_2Br) ppm.

3: $\delta_H(d_6$-acetone): 6.93 (5 H, m, C_6H_5), 4.92 (1 H, m, CHBr), 3.0 (2 H, m, CH_2CF_2) ppm. $\delta_F(d_6$-acetone): 43.8(2 F, m, CF_2Br) ppm.

4: υ_{max}: 2800–3000 (C–H), 1440, 1260, 1200(C–F), 1180, 950–930 cm^{-1}. δ_H ($CDCl_3$):2.0–3.0 (4 H, m), 3.20–4.40(6 H, m) ppm. $\delta_F(CDCl_3)$: 43.2(2 F, m, CF_2Br) ppm. m/z(%): 308 (M^++2, 0.7), 229 (M^+–Br, 7.5), 117 (16.8), 97 (5.5), 77 (6.9), 41 (6.3). Anal.: $C_7H_{10}Br_2F_2O$ (MW 308) Calcd.: C 27.30 H 3.27 F 12.34 Found: C 27.05 H 3.22 F 12.84%.

5: (E)/(Z) = 1.0 υ_{max}: 2800–3000 (C–H), 1460, 1300, 1200(C–F) cm^{-1}. $\delta_H(CDCl_3)$: (E): 4.18 (1 H, td, J_{HH} = 9 Hz, J_{HH} = 4 Hz, CHBr), (Z): 4.72(1 H, br, s, CHBr), (E) + (Z): 1.0–2.6 (9 H, m, other hydrogen atoms) ppm. $\delta_F(CDCl_3)$: (E): 41.23 (AB system), (Z): 48.50 (d, AB system), (m, 2 F, CF_2Br) ppm. m/z(%): 294 (0.04), 292 (0.11), 290 (M^+, 0.04), 211 (M^+–Br, 3.92), 131 (M^+–Br_2, 100), 111 (27.06), 91 (12.07), 77 (29.84), 52 (53.93).

6: $\delta_H(CDCl_3)$: 4.50 (1 H, m, CHBr), 1.0–2.6 (13 H, m, other hydrogen atoms) ppm. δ_F ($CDCl_3$): 47.3 (m, 2F, CF_2Br) ppm. m/z(%): 240(M^+–Br, 5.05), 238 (6.39), 160(M^+–Br_2, 54.36), 159 (54.13), 138 (45.80), 117 (34.82), 116 (21.18), 77 (64.14), 44 (100). Anal.: $C_9H_{14}Br_2F_2$ Calcd.: C 33.75 H 4.38 F 11.88 Found: C 34.16 H 4.24 F 12.20%

7: δ_H(neat): 4.5, 5.5 (1 H, m, C=C–H), 2.80 (2 H, m, CH_2CF_2Br), 1.60 (6 H, m, 2×CH_3), 2.20 (7 H, m, other hydrogen atoms) ppm. δ_F (neat): 41.8 (2 F, s, CF_2Br) ppm. m/z (%): 267 (65.97), 266 (50.80), 265 (M^+–Br,78.19), 211 (97.43), 209 (100), 141 (71.48), 79 (51.07), 59 (52.62), 43(60.45). Anal.: $C_{11}H_{16}Br_2F_2$ (MW 346) Calcd.: C 38.15 H 4.62 F 10.98 Found: C 38.70 H 4.90 F 11.50%.

8: $\delta_H(CDCl_3)$: 4.75,5.75 (1 H, m, C=C–H), 2.90(1 H, m, $CHCF_2Br$), 2.15–2.50 (2 H, m, CH_2), 1.65–2.0 (12 H, m, other hydrogen atoms) ppm. $\delta_F(CDCl_3)$: 39.0 (2 F, s, CF_2Br) ppm. m/z(%): 267 (38.88), 266 (24.29), 265 (M^+–Br, 44.55), 264 (20.11), 211 (94.98), 209 (100), 135 (46.42), 129 (58.14), 93 (93.39), 91 (48.11). Anal.: $C_{11}H_{16}Br_2F_2$ (MW 346) Calcd.: C 38.15 H 4.62 F 10.98 Found: C 38.22 H 4.52 F 11.34%.

9: $\delta_H(CCl_4)$: 4.10 (5 H, m, CHBr + CO_2CH_2), 3.50 (1 H, m, CH), 2.90 (2 H, m, CH_2CF_2Br), 2.20 (2 H, m, CH_2), 1.20 (6 H, t, 2×CH_3) ppm. $\delta_F(CCl_4)$: 41.8 (2 F, s, CF_2Br) ppm. m/z(%): 413 (1.73), 411 (3.43), 409 (M^+1,1.79), 329 (M^+–Br,9.78), 311 (9.77), 257 (17.07), 255 (18.59), 175 (39.00), 160 (100), 133 (25.89), 103 (17.10), 101 (20.93), 73 (18.15). Anal.: $C_{11}H_{16}Br_2F_2O_4$ (MW 410) Calcd.: C 32.20 H 3.90 F 9.27 Found: C 32.46 H 3.50 F 9.60%.

10: υ_{max}: 2800–3000 (C–H), 1740, 1720, 1650, 1470, 1320, 1200, 940–920, 680cm^{-1}. δ_H ($CDCl_3$): 6.36 (1 H, t, C=CH), 2.68 (2 H, t, CH_2), 1.20–1.60 (4 H, m, 2×CH_2), 0.90 (3 H, t, CH_3) ppm. $\delta_F(CDCl_3)$: (Z) 38.6 (2 F, d, $BrCF_2$, J = 11.8 Hz) (E) 40.1 (2 F, d, CF_2Br, J = 12.7 Hz) ppm. m/z(%): 295 (25.48), 293 (21.94), 213 (M^+–Br, 34.35), 211 30.81), 151 (15.97), 149 (24.35), 111 (52.58), 83 (M^+–CF_2Br_2, 25.84), 81 (23.71), 57 (100). Anal.: $C_7H_{10}Br_2F_2$(M 292) Calcd.: C 28.80 H 3.42 F 13.00 Found: C 28.64 H 3.52 F 13.20%.

11: υ_{max}: 2800–3000(C–H), 1740, 1640, 1460, 1200, 1080, 920 cm^{-1}. $\delta_H(CDCl_3)$: 6.35 (1 H, t, C=CH, J = 11.6 Hz), 2.68 (2 H, t, CH_2, J = 7.5 Hz), 1.68 (2 H, m, CH_2), 1.34 (4 H, m, 2×CH_2), 0.90 (3 H, t, CH_3) ppm. $\delta_F(CDCl_3)$: (Z) 37.8 (2 F, $BrCF_2$) (E) 39.8 (2 F, CF_2Br) ppm. m/z(%): 226 (M^+–Br,9.06), 149 (17.18),1 30 (26.79), 129 (22.21), 91 (100), 73 (30.90), 69 (20.10), 55 (23.16), 43 (17.59). Anal.: $C_8H_{12}Br_2F_2$ (MW 306) Calcd.: C 31.37 H 3.92 F 12.41 Found: C 31.00 H 4.00 F 12.22%.

12: υ_{max}: 2800–3000(C–H), 1740, 1640, 1460, 1200, 1100, 920 cm^{-1}. $\delta_H(CDCl_3)$: 6.32 (1 H, t, C=CH, J = 11.8 Hz), 2.68 (2 H, t, CH_2, J = 7.5 Hz), 1.65 (2 H, m, CH_2), 1.30 (6 H, m, 3×CH_2), 0.90 (3 H, t, CH_3) ppm. $\delta_F(CDCl_3)$: (Z) 38.6 (2F, $BrCF_2$) (E) 43.5 (2F, CF_2Br) ppm. m/z(%): 239 (M^+–Br, 11.68), 159(M^+–Br_2, 100), 139 (45.17), 117 (46.83), 103 (48.53), 95 (40.22), 69 (71.57), 55 (59.63), 43 (78.57). Anal.: $C_8H_{12}Br_2F_2$ (MW 306) Calcd.: C 33.75 H 4.38 F 11.88 Found: C 34.00 H 4.30 F 12.22%.

The addition reactions of CF_2Br_2 with 2,3-dihydrofuran and 3,4-dihydro-2H-pyran.

A mixture of sodium dithionite (9 g) and sodium bicarbonate (4.5 g) was added to a stirred solution of CF_2Br_2 (10.5 g, 50 mmol), 2,3-dihydrofuran or 3,4-dihydro-2H-pyran (50 mmol), acetonitrile (60 ml) and water (60 ml) at 5–10. The mixture was stirred for 4 h, diluted with water and extracted with ether (3×60 ml). The combined organic layer was dried with anhydrous sodium sulfate. After the removal of the solvent, the crude product was purified by column chromatography using petroleum ether and ethyl acetate (10:1) as eluents to give the pure product **13** or **14**.

13: υ_{max}: 3400 (O–H) cm^{-1}. $\delta_H(CDCl_3)$: 5.58 (1 H, dd, $^3J_{HH}=3.6$ Hz, $^3J_{HH}'=2.3$ Hz, CHO), 4.55 (1 H, d, $^3J_{HH}=3.6$ Hz, OH), 4.18–4.00 (2 H, m, CH_2O), 3.32–2.85 (1 H, m, $CHCF_2Br$), 2.48–1.82 (2 H, m, CH_2CH) ppm. $\delta_F(CDCl_3)$: 48.3 (2 F, d, $BrCF_2$) ppm. m/z: 217,215 (M^+–1), 201,199 (M^+–OH). Anal.: $C_5H_7BrF_2O_2$ Calcd.: C 27.67 H 3.25 F 17.51 Br 36.82 Found: C 27.69 H 3.29 F 17.52 Br 36.58%.

14: υ_{max}: 3400 (O–H) cm^{-1}. $\delta_H(CDCl_3)$:5.42 (1 H, d, $^3J_{HH}=2.6$ Hz, cis isomer, CHO), 4.82 (1 H, dd,$^3J_{HH}=6.4$ Hz, trans isomer, CHO), 4.20 (1 H, s, OH), 4.16–3.50 (2 H, m, CH_2O), 2.80–1.70 (5 H, m, $CHCF_2$, CH_2CH) ppm. $\delta_F(CDCl_3)$: 51.8–45.0 (AB, cis), 43.0 (2 F, s, $BrCF_2$, trans isomer) ppm. m/z: 331,329 (M^+-1), 215,213 (M^+-1), 215,213 (M^+–OH). Anal.: $C_6H_9BrF_2O_2$ Calcd.: C 31.19 H 3.93 F 16.45 Br 34.59 Found: C 31.02 H 4.01 F 15.99 Br 34.28%.

Compound **15** was prepared from the reaction of CF_2Br_2 (50 mmol) with 3,4-dihydro-2H-pyran (120 mmol) in a similar way.

15: υ_{max}: 1000–1200 (C–O,C–F) cm^{-1}. $\delta_H(CDCl_3)$: 5.42–4.95 (2 H, m, 2×CHO), 4.10–3.42(4H, m, 2×CH_2O), 2.85–1.45 (11 H, m, other hydrogen atoms) ppm. $\delta_F(CDCl_3)$: 51.8–45.4–52.3 (AB, cis), 43.2 (2 F, s, $BrCF_2$, trans isomer) ppm. m/z: 317,315 (M^++1), 235 (M^+–Br). Anal.: $C_{11}H_{17}BrF_2O_3$ Calcd.: C 41.92 H 5.44 F 12.06 Br 25.36 Found: C 41.32 H 5.51 F 11.91 Br 25.50%.

4.1. Preparation of compound **16**

Compound **14** (20 mmol) in ethanol (10 ml) was added dropwise at room temperature to a solution of $NaBH_4$ (1 g, 26 mmol) in 95% ethanol (15 ml). After 2 h of stirring, the reaction was quenched with NH_4Cl solution. Work up in the usual way and distillation under reduced pressure gave diol **16**.

16: bp. 110 °C/0.2 mmHg $\delta_H(CDCl_3)$: 4.00–3.50 (6 H, m, 2×CH_2OH), 2.35 (1 H, m, $CHCF_2Br$), 1.75 (4 H, m, other hydrogen atoms) ppm. $\delta_F(CDCl_3)$: 43.8 (2 F, s, CF_2Br) ppm. m/z(%): 235, 233 (M^++1), 215 (M^+–OH). Anal.: $C_6H_{11}BrF_2O_2$ Calcd.: C 30.92 H 4.76 F 16.30 Found: C 30.25 H 4.85 F 16.76%.

References

[1] R. Filler, T. Kobayashi, *Biomedical Aspects of Fluorine Chemistry*, Kondansha, 1982.
[2] J.T. Welch, *Tetrahedron, 34* (1987) 3123.
[3] J. Fried, E.A. Hallinau and M.J. Szwedo Jr., *J. Am. Chem. Soc., 106* (1984) 3871.
[4] M. Schlosser, *Tetrahedron, 34* (1987) 3.
[5] F. Tellier and R. Sanvertre, *Tetrahedron Lett., 33* (1992) 3643.
[6] P.Y. Kwok, F.W. Muellner, C.K. Chen and J. Fried, *J. Am. Chem. Soc., 109* (1987) 3684.
[7] T.S. Everett, *J. Chem. Educ., 64* (1987) 143.
[8] D.J. Burton and Z.Y. Yang, *J. Org. Chem., 56* (1992) 5125.
[9] D.J. Burton and L.J. Kehoe, *J. Org. Chem., 35* (1970) 1339.
[10] P. Tarrant and A.M. Lovelace, *J. Am. Chem. Soc., 76* (1954) 3466.
[11] P. Tarrant and E.C. Stump Jr., *J. Org. Chem., 29* (1964) 1198.
[12] I. Rico, O. Cantacuzene and C. Wakselman, *Tetrahedron Lett., 22* (1981) 3405.
[13] Y. Takeyama, Y. Ichinose, K. Oshima and K. Utimeto, *Tetrahedron Lett., 30* (1989) 3159.
[14] J. Chen and C.M. Hu, *J. Chem. Soc., Perkin Trans. I*, (1994) 1111.
[15] H.Z. Zhang and W.Y. Huang, *Chin. J. Chem., 10* (1992) 274.
[16] W.Y. Huang, Y. Xie and L. Lu, *Chin. J. Chem., 9* (1991) 167.
[17] T. Ozawa and M. Setaka, *Bull. Chem. Soc. Jpn., 44* (1971) 3473.