

MANGANESE(III)-BASED OXIDATIVE RADICAL CYCLIZATION OF TERMINAL ALKADIENES WITH *N,N'*-BIS(3-OXOBUTANOYL)- α,ω -ALKYLENEDIAMINES. FORMATION OF MACRODIAMIDES

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Abstract: $\alpha,\alpha,\omega,\omega$ -Tetraphenyl- α,ω -alkadienes reacted with *N,N'*-bis(3-oxobutanoyl)- α,ω -alkylenediamines in the presence of manganese(III) acetate at 100 °C under an argon atmosphere to give 11 to 22-membered macrocyclic diamides which had two fused dihydrofuran rings in a one-step procedure.

Many macrocyclic polyamides have been isolated from natural sources such as sea animals (1) and blue-green alga (2), and most of them have strong antitumor activities or very toxic characteristics. In order to synthesize a new class of macrocyclic diamides which might have potent functions or biological activities, we applied the manganese(III) acetate-mediated oxidative radical cyclization to terminal alkadienes and *N,N'*-bis(3-oxobutanoyl)alkylenediamines (3), and found that 11 to 22-membered macrocyclic diamides were easily obtained. Herein we briefly report the results of our study.

1,1,8,8-Tetraphenyl-1,7-octadiene **1_x** ($x = 4$; 0.5 mmol) and *N,N'*-bis(3-oxobutanoyl)-1,2-ethylenediamine **2_y** ($y = 2$; 1 mmol) were put in acetic acid (200 mL), and manganese(III) acetate (5 mmol) was added. The mixture was sufficiently degassed under reduced pressure using an ultrasonicator in order to exchange with an argon atmosphere, and then heated at 100 °C until the brown color of the Mn(III) disappeared. After the removal of the solvent, water (200 mL) was added and the aqueous solution was extracted with chloroform. The products were purified by silica-gel TLC (2% methanol/chloroform) to give 14-membered macrocyclic diamide **3₄₂** ($x = 4, y = 2$) which had two fused dihydrofuran rings in 43% yield (Table 1, entry 6). The structure determination of **3₄₂** was carried out using IR, NMR, FAB MS

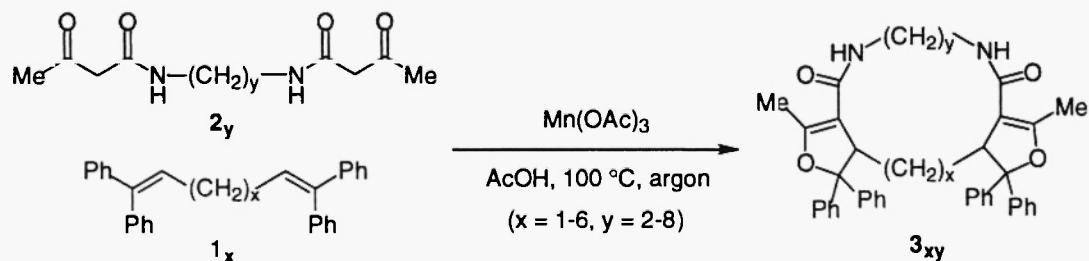


Table 1. Reaction of $\alpha,\alpha,\omega,\omega$ -Tetraphenyl- α,ω -alkadienes **1_x** with *N,N*'-Bis(3-oxobutanoyl)- α,ω -alkylenediamines **2_y** in the Presence of Manganese(III) Acetate^a

Entry	1_x x	2_y y	Reaction time min	Conversion of 1_x %	Product 3_{xy} Yield/% ^b	Ring size
1	1	2	20	68	21	11
2	2	2	30	84	32	12
3	2	3	30	81	27	13
4	2	4	40	80	20	14
5	3	2	30	78	34	13
6	4	2	20	76	43	14
7	4	3	30	86	34	15
8	4	4	19	90	33	16
9	4	5	30	86	31	17
10	4	6	20	84	26	18
11	4	7	12	70	24	19
12	4	8	21	81	23	20
13	5	2	16	74	29	15
14	6	2	30	72	31	16
15	6	4	20	67	29	18
16	6	8	21	71	18	22

^aThe reactions were carried out at a molar ratio of 1:2:10 for **1_x** (0.5 mmol):**2_y**:manganese(III) acetate in acetic acid (200 mL) at 100 °C under an argon atmosphere.

^bIsolated yield based on the amount of the alkadiene **1_x** used.

spectroscopies and elemental analysis (4).

We applied this reaction to other terminal alkadienes **1_x** ($x = 1\text{-}3, 5\text{-}6$) and *N,N*'-bis(3-oxobutanoyl)- α,ω -alkylenediamines **2_y** ($y = 3\text{-}8$) and obtained the corresponding 11 to 22-membered macrodiamides in the yields shown in Table 1. It was found that the longer the methylene chain length of **2_y**, the lower the yield of **3_{xy}**. The best result was obtained with the combination of **1₄** and **2₂**, and a 14-membered *macrodiamide* was formed in 43% yield (Entry 6), in contrast to the 17-membered *macrodilolide* in 86% yield for the use of **1₅** and butylene di(3-oxobutanoate) instead of **2_y** (3a). Although the yield of the macrodiamides **3_{xy}** was not so high, we guarantee that the procedure is simple and convenient for the preparation of 11 to 22-membered macrodiamides in one pot.

References and Notes

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- (4) **3₄₂**: Colorless microcrystals (from CHCl₃/EtOH); mp >300 °C; IR (KBr) δ 3600-3100 (NH), 1661 (C=O); ¹H NMR (DMSO-*d*₆) δ 7.60-7.17 (20H, m, 4 \times Ph), 7.11 (2H, brt, *J* = 4 Hz, 2 \times NH) which disappeared upon deuteration, 3.81 (2H, m, 2 \times CH), 3.56 (2H, m, CH₂), 2.98 (2H, m, CH₂), 2.16 (6H, s, 2 \times CH₃), 1.13 (4H, m, 2 \times CH₂), 0.63 (2H, m, CH₂), 0.40 (2H, m, CH₂); ¹³C NMR (DMSO-*d*₆) δ 164.2 (2C=O), 159.8 (2O-C=), 145.5, 140.6 (4 \times arom C), 127.9, 127.7, 127.5, 127.4, 126.8, 126.3, 125.9, 125.6 (20 \times arom CH), 110.6 (2>C=), 92.9 (2>C-O), 48.6 (2CH), 37.9 (2CH₂), 30.1 (2CH₂), 24.5 (2CH₂), 13.5 (2CH₃); FABMS *m/z* 639 (M+1). Anal. Calcd for C₄₂H₄₂N₂O₄: C, 78.97; H, 6.63; N, 4.39. Found: C, 79.08; H, 6.45; N, 4.21.
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Received on November 27, 1998