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Synthesis of heterocyclic propellanes using Mn(III)-based oxidative cyclization

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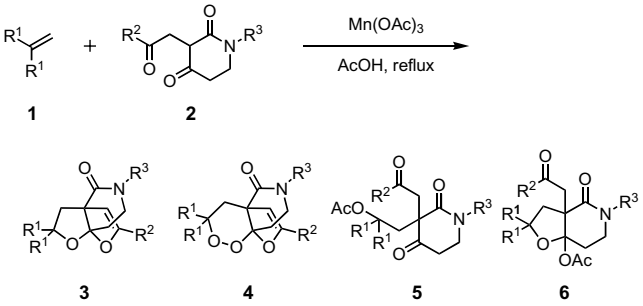
Abstract—The manganese(III)-based oxidative cyclization of 1,1-diarylethenes **1** with 3-(2-oxoethyl)piperidine-2,4-diones **2** was carried out in acetic acid at reflux temperature to selectively produce azadioxa[4.3.3]propellanes **3** in high yields. A similar cyclization with the 2-(2-oxoethyl)cycloalkane-1,3-diones **7** and 2-(3-oxopropyl)cycloalkane-1,3-diones **10** also gave the corresponding dioxapropellanes **8** and **11** in moderate to good yields.

Some biologically active furopyridinones are known as antifungal and antibacterial heterocycles.[1] For example, cladobotryal and an isomeric furopyridinone, which are metabolites of the fungus *Caldobotrium varium*, have an inhibitory effect on the growth of plant pathogens and moderate activity against some drug-resistant bacteria.[1a] Recently, we reported that the reaction of 1,1-disubstituted ethenes with 2-(2-oxoethyl)malonates in the presence of a stoichiometric amount of manganese(III) acetate in boiling acetic acid produced 2,8-dioxabicyclo[3.3.0]oct-3-enes via the cycloaddition-tandem cyclization.[2] The 2,8-dioxabicyclo[3.3.0]oct-3-ene skeleton is found in biologically and pharmacologically active compounds, such as the insect antifeedant clerodin isolated from *Clerodendrum infortunatum*.[3] The manganese(III)-based one-pot cycloaddition-tandem cyclization[4] is a useful method for constructing the 2,8-dioxabicyclo[3.3.0]oct-3-enes. In connection with the manganese(III)-based cycloaddition-tandem cyclization, we found the unique synthesis of heterocyclic propellanes having both furopyridinone and dioxabicyclo[3.3.0]octene frameworks using cyclic 1,3-dicarbonyls. Although small-ring propellanes are of significant theoretical interest,[5] [4.3.3]-, [4.4.3]-, [5.3.3]-, or [6.3.3]-propellanes are also attractive from the standpoint of their structures and syntheses.[6]

A mixture of 1,1-disubstituted ethene **1** (R^1 = Ph) and 3-(2-oxoethyl)piperidine-2,4-dione **2** (R^2 = Ph, R^3 = Bn)[7] was oxidized with manganese(III) acetate in acetic acid at reflux temperature. It was confirmed that the oxidation finished within 1 min since the brown color of the manganese(III) disappeared. After chromatographic separation,[8] four products were isolated (Scheme 1). The major product **3** had only one carbonyl carbon (δ 170.5 ppm) assigned to an amide, an extremely downfield shifted quaternary ketal carbon (δ 115.9 ppm), a quaternary carbon of the ring junction (δ 63.8 ppm), two characteristic sp^2 carbons due to a dihydrofuran ring (δ 156.3 and 99.0 ppm), and a quaternary carbon attached to the oxygen of tetrahydrofuran (δ 89.8 ppm) in the ^{13}C NMR spectrum. In addition, two



Scheme 1.

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methylenes of the piperidinedione remained unchanged, and an AB geminal quartet ($J = 13.4$ Hz) newly appeared at δ 3.59 and 2.97 ppm in the ^{1}H NMR spectrum, one of which shifted to high field because of the anisotropic effect for the alkenic double bond. Therefore, the structure was determined to be a 3-aza-7,12-dioxa[4.3.3]propellane **3** ($R^1 = R^2 = Ph$, $R^3 = Bn$) (Scheme 1).[9] The spectroscopic data of the minor product **4** were quite similar to those of the propellane **3** except for the ketal carbon at C-1, the quaternary carbon of the ring junction at C-6, and the quaternary carbon attached to the oxygen at C-4, which were slightly shifted upfield (4–9 ppm) in the ^{13}C NMR spectrum. The conclusive difference was the R_f value for the TLC and an extra oxygen in the FAB mass spectra as well as the combustion analysis.[10] Accordingly, the minor product **4** ($R^1 = R^2 = Ph$, $R^3 = Bn$) was apparently assigned as 8-aza-2,3,11-trioxa[4.4.3]propellane. The other minor products **5** and **6** were chromatographically inseparable, however, the acetate **5** could be isolated by fractional recrystallization from ethyl acetate–hexane. A similar reaction of other alkenes (R^1 = 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, and 4-FC_6H_4) with 3-(2-oxoethyl)piperidine-2,4-diones **2** (R^2 = 4-MeC_6H_4, 4-ClC_6H_4, R^3 = Me, Et, Pr, *i*-Pr, and Ph) was carried out and the desired propellanes **3** were obtained in moderate to good yields together with the corresponding azatrioxapropellanes **4** and the inseparable acetates **5** and **6** except for entries 2 and 3 in Table 1. The reaction of **1** having an electron-donating aryl group (R^1 = 4-Me–C_6H_4 and 4-MeO–C_6H_4) with **2** ($R^2 = Ph$, $R^3 = Bn$) exclusively gave the corresponding azadioxapropellanes **3** (entries 2 and 3). In contrast, when **1** bearing an electron-withdrawing aryl group (R^1 = 4-Cl–C_6H_4 and 4-F–C_6H_4) was used, the yield of the propellanes **3** decreased, while the yield of the acetates **5** and **6** increased (entries 4 and 5). The substituents R^2 and R^3 of **2** did not influence the product distribution (entries 6–11).

Since the azadioxapropellanes **3** and the acetates **5**, **6** must be formed from the same intermediate, a mixture

Table 1. Reaction of 1,1-diarylethenes **1** with 3-(2-oxoethyl)piperidine-2,4-diones **2** in the presence of manganese(III) acetate[a]

Entry	**1**	**2**		**1**:**2**:Mn(OAc)$_3$[b]	Time (min)	Product (yield %)[c]			
	R^1	R^2	R^3			**3**	**4**	**5**	**6**
1	Ph	Ph	Bn	1:1.2:3	1	53	9	13	13
2	4-Me–C_6H_4	Ph	Bn	1:1.3:3.5	1.5	90	4	—	—
3	4-MeO–C_6H_4	Ph	Bn	1:1.3:3	1	94	—	—	—
4	4-Cl–C_6H_4	Ph	Bn	1:1.6:4	1	28	10	39	19
5[d]	4-F–C_6H_4	Ph	Bn	1:1.5:3	1	37	6	16	17
6	Ph	4-Me–C_6H_4	Bn	1:1.5:3	1	51	6	20	14
7	Ph	4-Cl–C_6H_4	Bn	1:1.5:3	0.5	51	6	23	18
8	Ph	Ph	Me	1:1.5:3	1	57	8	18	14
9	Ph	Ph	Et	1:1.5:3	1	52	8	16	17
10	Ph	Ph	Pr	1:1.5:3	1	51	7	15	8
11	Ph	Ph	*i*-Pr	1:1.5:3	1	51	6	22	19
12	Ph	Ph	Ph	1:1.5:3	1	45	7	25	21

[a] The reaction of a diarylethene **1** (0.5 mmol) was carried out in glacial acetic acid (20 mL) at reflux temperature.
[b] Molar ratio.
[c] Isolated yield based on the amount of the alkene **1** used.
[d] The alkene **1** was recovered in 7%.

Table 2. Result of ten-minute continuous heating after the manganese(III)-based reaction of **1** with **2**[a]

Entry	**1**	**2**		**1**:**2**:Mn[b]	Yield (%)[c]	
	R^1	R^2	R^3		**3**	**4**
1	Ph	Ph	Bn	1:1.2:3	87	9
2	4-Cl–C_6H_4	Ph	Bn	1:1.6:4	73	10
3	4-F–C_6H_4	Ph	Bn	1:1.5:3	62	4
4	Ph	4-Me–C_6H_4	Bn	1:1.5:3	80	4
5	Ph	4-Cl–C_6H_4	Bn	1:1.5:3	93	6
6	Ph	Ph	Me	1:1.5:3	87	6
7	Ph	Ph	Et	1:1.5:3	78	11
8	Ph	Ph	Pr	1:1.5:3	93	4
9	Ph	Ph	*i*-Pr	1:1.5:3	86	4
10	Ph	Ph	Ph	1:1.5:3	90	4
11[d]	Ph	Ph	Bn	1:1.2:3	98	—

[a] The reaction of **1** (0.5 mmol) was carried out in boiling glacial acetic acid (20 mL). After finishing the oxidation, the mixture was continuously heated under reflux for 10 min.
[b] Molar ratio.
[c] Isolated yield based on the amount of the alkene **1** used.
[d] Before the oxidation, the mixture was degassed under reduced pressure for 30 min using an ultrasonicator followed by argon displacement, and freshly prepared manganese(III) acetate was used in the reaction.

of acetates **5** and **6** ($R^1 = 4\text{-Cl–}C_6H_4$, $R^2 = Ph$, $R^3 = Bn$) was heated under reflux in acetic acid for 10 min. As a result, the acetates **5** and **6** were converted into the corresponding propellane **3** in a 92% isolated yield. Therefore, the continuous heating for 10 min after finishing the oxidation resulted in the exclusive production of the azadioxapropellanes (Table 2).

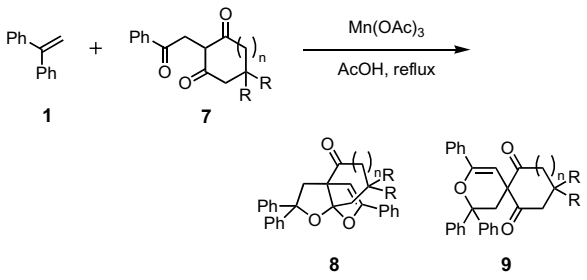
The formation of the trioxapropellanes **4** deserves comment. In our previous study, we reported the synthesis of azadioxabicyclo[4.4.0]decanones using the manganese(III)-catalyzed aerobic oxidation of 2,4-piperidinediones at ambient temperature.[11] The endoperoxide ring was derived from the molecular oxygen dissolved in the solvent.[12] In fact, when the reaction was carried out using a sufficient amount of manganese(III) acetate at elevated temperature under argon, the azadioxabicyclodecanones were not produced, while only azaoxabicyclo[4.3.0]nonanones were obtained.[11] Therefore, in order to avoid the formation of the minor product **4**, the complete degassing under reduced pressure for 30 min using an ultrasonicator followed by argon displacement before the oxidation and also the use of freshly prepared manganese(III) acetate could control the formation of **4** (Table 2, entry 11).

In order to examine the applicability of the manganese(III)-based propellane formation, the reaction using 2-(2-oxoethyl)cycloalkane-1,3-diones **7**[13] was carried out under similar oxidation conditions to give the desired propellanes **8** (Scheme 2 and Table 3). The ring size of the cycloalkanedione is bigger, the yield of the propellanes is lower, and the production of spiroalkanes was promoted (Table 3, entries 3 and 4).

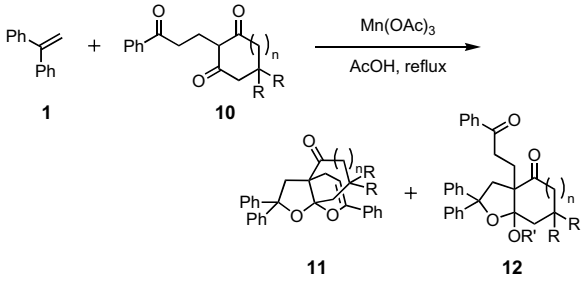
A similar reaction using 3-oxopropyl-substituted cycloalkanediones **10**[14] gave the desired propellanes **11** in moderate yields and also produced the [4.3.0]nonanes **12** as by-products (Scheme 3 and Table 4). In this case, the continuous heating after finishing the oxidation did not effectively increase the yield of **11**.

The manganese(III)-based oxidative cycloaddition-tandem cyclization could be explained by a similar mechanism for the reaction using the 2-(2-oxoethyl)malonates.[2,15] The manganese(III)-piperidinedione enolate complex **A** would be formed by the reaction of the piperidinediones **2** with manganese(III) acetate during the first stage (Scheme 4). It is known that the manganese(III)-enolate complex formation is the rate-determining step.[4,16] The enolate complex **A** easily oxidized the electron-rich alkenes **1** via a weak interaction between the complex **A** and the alkene **1** such as an electron donor–acceptor-like complex,[16] giving the corresponding tertiary carbon radicals **B**, which were rapidly oxidized by sufficient amounts of manganese(III) acetate under the stated conditions. As a result, the carbocations **C** would be formed and cyclize at the keto carbonyl oxygen of the piperidinediones to produce thermodynamically more stable carbocations **D**. The cations **D** would be allowed to intramolecuarlly cyclize at the carbonyl oxygen of the most appropriate position to finally produce the desired propellanes **3** by deprotonation. The by-products **5** and **6** were formed by the attack of the acetate ion on the cations **C** and **D**, however, the reaction should be reversible. The propellanes **3** could be solely obtained when the dissolved molecular oxygen in the solvent was completely removed by degassing before the oxidation and the heating of the reaction mixture was continued for 10 min after the oxidation.

In summary, we have accomplished the unique synthesis of heterocyclic propellanes using the manganese(III)-



Scheme 2.



Scheme 3.

Table 3. Mn(III)-based reaction of **1** with **7**[a]

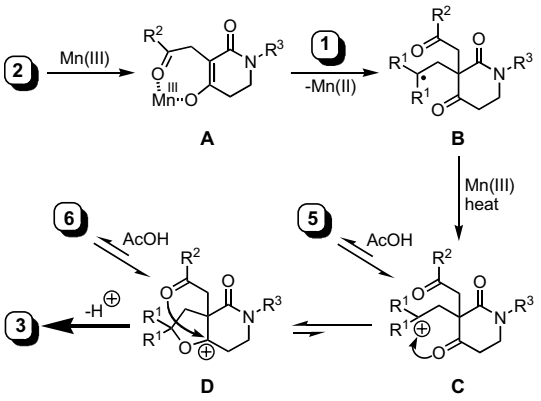
Entry	**7** R	*n*	**1**:**7**:Mn[b]	Time (min)	Yield (%)[c] **8**	**9**
1	Me	1	1:1.5:3	10	80	—
2	H	1	1:1.5:4	5	77	—
3	H	2	1:1.2:3	10	66	19
4	H	3	1:1.2:3	2	27	31

[a] The reaction of **1** (0.5 mmol) was carried out in boiling glacial acetic acid (20 mL).
[b] Molar ratio.
[c] Isolated yield based on the amount of the alkene **1** used.

Table 4. Mn(III)-based reaction of **1** with **10**[a]

Entry	**10** R	*n*	**1**:**10**:Mn[b]	Time (min)	Yield (%)[c] **11**	**12**
1	H	0	1:1.2:3	10	21	37 (R′ = H)
						34 (R′ = Ac)
2	Me	1	1:1.5:3.5	10	47	27
3	H	1	1:1.2:3	10	49	31

[a] The reaction of **1** (0.5 mmol) was carried out in boiling glacial acetic acid (20 mL).
[b] Molar ratio.
[c] Isolated yield based on the amount of the alkene **1** used.



Scheme 4.

based cycloaddition-tandem cyclization of 1,1-diarylethenes with 3-(oxoalkyl)piperidine-2,4-diones. The selective synthesis of interesting endoperoxide 8-aza-2,3,11-trioxa[4.4.3]propellanes is currently in progress.

Acknowledgements

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Supplementary data

Experimental details and full characterization of the propellanes **3** ($R^1 = R^2 = R^3 = Ph$), **4** ($R^1 = R^2 = R^3 = Ph$), **11** ($n = 1$, $R = H$) and by-products **5** ($R^1 = R^2 = Ph$, $R^3 = Bn$), **5** ($R^1 = R^2 = R^3 = Ph$), **6** ($R^1 = R^2 = R^3 = Ph$). Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.07.090.

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8. After the oxidation, the solvent was removed in vacuo, and the residue was triturated with water followed by extraction with chloroform (10 mL × 3). The combined extracts were dried over anhydrous magnesium sulfate, and then concentrated to dryness. The crude products were separated by TLC while eluting with chloroform.
9. Compound **3** ($R^1 = R^2 = Ph$, $R^3 = Bn$): $R_f = 0.22$ (chloroform); colorless oil; IR (neat) ν 1647 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (2H, m, arom. H), 7.40 (2H, m, arom. H), 7.39–7.12 (13H, m, arom. H), 7.00 (2H, m, arom. H), 6.84 (2H, m, arom. H), 5.19 (1H, s, H-9), 4.66 (1H, d, $J = 14.9$ Hz, Ph–CH_2), 4.44 (1H, d, $J = 14.9$ Hz, Ph–CH_2), 3.59 (1H, d, $J = 13.4$ Hz, H-10), 3.28 (1H, ddd, $J = 12.9$, 10.5, 2.9 Hz, H-4), 3.13 (1H, ddd, $J = 12.9$, 4.8, 3.9 Hz, H-4), 2.97 (1H, d, $J = 13.4$ Hz, H-10), 2.49 (1H, ddd, $J = 13.6$, 4.8, 2.9 Hz, H-5), 2.14 (1H, ddd, $J = 13.6$, 10.5, 3.9 Hz, H-5); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5 (C=O), 156.3 (C-8), 146.1, 144.4, 136.5, 129.2 (arom. C), 128.7, 128.6, 128.2, 127.74, 127.65, 127.5, 127.4, 126.8, 126.3, 125.4, 125.23, 125.16 (arom. *C*H), 115.9 (C-6), 99.0 and 98.9 (C-9), 89.8 (C-11), 63.8 (C-1), 50.1 (Ph–*C*H$_2$), 47.5 (C-10), 42.7 (C-4), 33.7 (C-5). FAB HRMS (acetone–NBA) calcd for $C_{34}H_{30}NO_3$ 500.2226 (M+1). Found 500.2229.
10. Compound **4** ($R^1 = R^2 = Ph$, $R^3 = Bn$): $R_f = 0.32$ (chloroform); colorless microcrystals (from diethyl ether); mp 166.5 °C; IR (neat) ν 1639 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (1H, m, arom. H), 7.43–7.12 (18H, m, arom. H), 5.13 (1H, s, H-13), 4.71 (1H, d, $J = 14.9$ Hz, Ph–CH_2), 4.37 (1H, d, $J = 14.9$ Hz, Ph–CH_2), 3.86 (1H, d, $J = 14.3$ Hz, H-5), 3.38 (1H, ddd, $J = 12.7$, 11.8, 2.8 Hz, H-9), 3.11 (1H, ddd, $J = 12.7$, 4.6, 3.5 Hz, H-9), 2.69 (1H, d, $J = 14.3$ Hz, H-5), 2.23 (1H, ddd, $J = 13.6$, 3.5, 2.8 Hz, H-10), 1.95 (1H, ddd, $J = 13.6$, 11.8, 4.6 Hz, H-10); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3 (C=O), 156.3 (C-12), 146.8, 143.7, 136.3, 129.3 (arom. C), 129.1, 128.7, 128.34, 128.27, 128.0, 127.7, 127.6, 127.1, 127.0, 125.42, 125.35, 125.2 (arom. *C*H), 111.8 (C-1), 100.5 and 100.4 (C-13), 86.0 (C-4), 54.7 (C-6), 50.6 (Ph–*C*H$_2$), 41.4 (C-9), 37.1 (C-5), 27.9 (C-10). Positive FAB MS (acetone–NBA) *m*/*z* 516 (M+1). Anal. Calcd for $C_{34}H_{29}NO_4$: C, 79.20; H, 5.67; N, 2.72. Found: C, 79.33; H, 5.60; N, 2.74.
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