



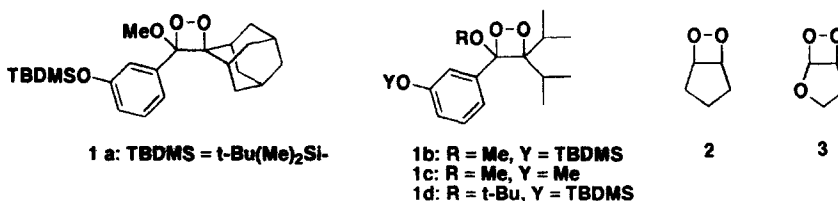
## Synthesis of 5-Alkyl-1-aryl-4,4-dimethyl-2,6,7-trioxabicyclo[3.2.0]heptanes as a Chemiluminescent Substrate with Remarkable Thermal Stability

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**Abstract:** Various 1-aryl-4,4-dimethyl-2,6,7-trioxabicyclo[3.2.0]heptanes were synthesized and their thermal stabilities and F<sup>-</sup>-induced chemiluminescent properties were examined. Among the bicyclic dioxetanes synthesized here, one bearing a tert-butyl or a 9-methylfluorenyl at the 5-position exhibited remarkable thermal stability. © 1997 Elsevier Science Ltd.

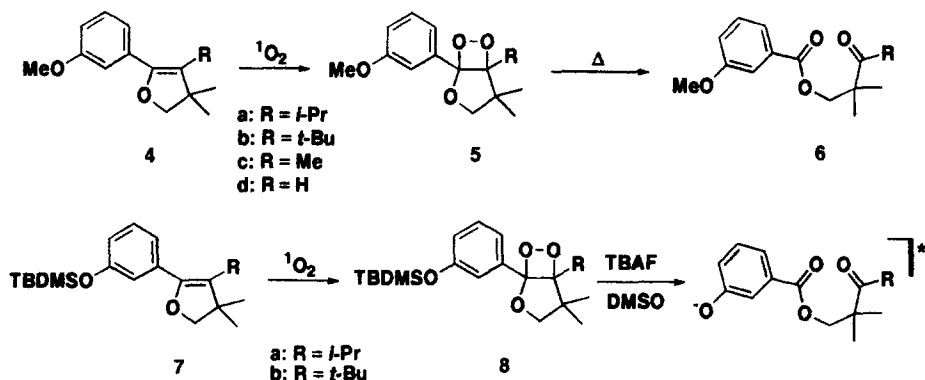
Dioxetanes bearing a fluorescent electron donor display chemically initiated electron exchange luminescence (CIEEL).<sup>1)</sup> The phenomenon has now been exploited for the synthesis of highly efficient chemiluminescent substrates<sup>2-5)</sup> represented by an adamantylidenedioxetane (**1a**)<sup>2b)</sup> and diisopropyldioxetanes (**1b - 1d**).<sup>5)</sup> Use of an adamantylidene as a substituent of dioxetanes for designing a new chemiluminescent substrate with further thermal stability is, however, limited. The latter (**1b-d**) seem to be also limited to design of a new stable chemiluminescent substrate, because steric repulsion between vicinal bulky substituents acts rather to twist the dioxetane ring and to destabilize it, as observed for **1d**.<sup>5a)</sup> On the other hand, it has been reported that, among 3,4-polymethylene-1,2-dioxetanes, a trimethylene analogue **2** decomposes with the highest activation energy, which is attributed to prevention of twisting of the dioxetane ring by the fused five-membered ring through decomposition process.<sup>6)</sup> This fact prompted us to attempt the synthesis of 1-aryl-2,6,7-trioxabicyclo[3.2.0]heptanes which possesses a structure constructed by joining a methoxyl to a methyne of vicinal isopropyl in **1b** and **1c**, though rather simple 2-oxa analogues (**3**) of **2** reported recently seem to be labile and decompose slowly even at room temperature.<sup>7)</sup>



A bicyclic dioxetane **5a** is a target molecule led directly from **1c** in accord with our concept. Singlet oxygenation of 4-isopropyl-3,3-dimethyl-2,3-dihydrofuran **4a**<sup>8)</sup> in CH<sub>2</sub>Cl<sub>2</sub> at -78 °C afforded a dioxetane **5a** as a colorless oil in 83.2 % yield.<sup>9)</sup> The dioxetane **5a** decomposed quantitatively to a ketoester **6a** in refluxing xylene-d<sub>10</sub>. The rates of decomposition of **5a** were measured at 100 - 140 °C, and the half-life (t<sub>1/2</sub>) of **5a** at

25 °C was estimated to be 13.7 y. The results showed that fusion of a methoxyl with a vicinal isopropyl of **1c** improves significantly the thermal stability of a dioxetane; **1c**:  $t_{1/2} = 1.28$  y.<sup>5a)</sup>

A dioxetane **5b** bearing a tert-butyl, in place of an isopropyl at the 5-position, was similarly synthesized by singlet oxygenation of the corresponding dihydrofuran **4b**. **5b** was obtained as pale yellow granules (mp 93.0 - 93.5 °C) in a 87.8 % isolated yield and exhibited remarkable thermal stability ( $t_{1/2} = 50$  y at 25 °C). Next, singlet oxygenation of a trimethyldihydrofuran **4c** was carried out to afford a dioxetane **5c** in a 80.8 % yield. It is noteworthy that the "ene" reaction, which is a reaction mode of singlet oxygen competitive to the 1,2-addition, was scarcely observed for **4c** though it bears an allylic methyl formally susceptible to the "ene" reaction.<sup>10)</sup> The dioxetane **5c** was also stable enough for handling at room temperature though less stable than **5a** and **5b**. The activation parameters of first-order thermal decomposition of these dioxetanes are summarized in Table 1, which shows that thermal stabilities of **5a** - **c** increase as a substituent at the 5-position become bulkier; **5b** > **5a** > **5c**. Singlet oxygenation of a 4,4-dimethyldihydrofuran **4d** with no substituent at the 5-position gave a mixture of the corresponding dioxetane **5d** and a ketoester **6d** (**5d** : **6d** = 1 : 1), and **5d** could not be isolated in pure form.<sup>11)</sup> These results suggest that the thermal stability of **5** depends significantly on a repulsive non-bonding interaction between methyl(s) at the 4-position and a substituent at the 5-position, as expected.



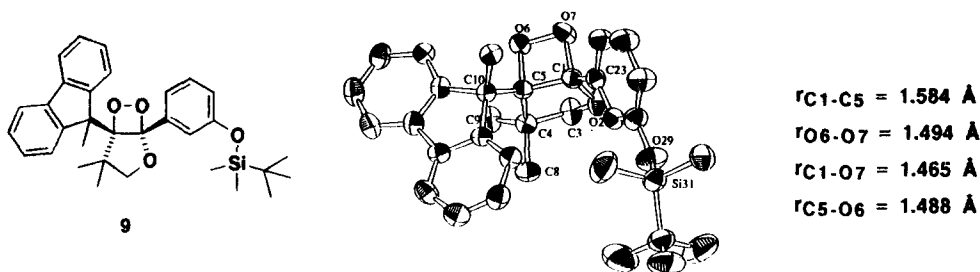
The present results disclosed that bicyclic dioxetanes **5**, especially **5b**, possess remarkable thermal stability. Thus, as the second stage, we synthesized bicyclic dioxetanes **8a** and **8b** bearing a *m*-(tert-butyldimethylsiloxy)phenyl instead of a *m*-methoxyphenyl and examined their F<sup>-</sup>-induced chemiluminescent properties. Singlet oxygenation of a dihydrofuran **7a** and **7b** gave the respective dioxetanes **8a** (84.4 %) and **8b** (96.2 %). Dioxetanes **8a** and **8b** were so stable thermally ( $t_{1/2}$  at 25 °C: 5.9 y for **8a** and 22.1 y for **8b**) as to surpass the thermal stability of adamantylidenedioxetane **1a** ( $t_{1/2} = 3.8$  y at 25 °C).<sup>2b)</sup> When a solution of **8a** in DMSO ( $10^{-6}$  mol dm<sup>-3</sup>, 1 ml) was added to a solution of tetrabutylammonium fluoride (TBAF) in DMSO ( $10^{-3}$  mol dm<sup>-3</sup>, 2ml) at 25 °C, intense light emission was observed ( $\lambda_{\max} = 467$  nm,  $\Phi_{\text{CL}} = 0.12$ ,<sup>12)</sup>  $t_{1/2} = 6.7$  s).<sup>13)</sup> Similar treatment of **8b** with TBAF in DMSO afforded light with  $\lambda_{\max} = 469$  nm,  $\Phi_{\text{CL}} = 0.17$ ,  $t_{1/2} = 4.4$  s. The chemiluminescent properties of **8a** and **8b** were similar to those of an adamantylidene analogue **1a** [ $\lambda_{\max} = 465$  (lit;[2b] 470) nm,  $\Phi_{\text{CL}} = 0.25$ [2b],  $t_{1/2} = 5.0$  (lit;[2b] 5) s]. These results showed that dioxetanes (**8**) are efficient chemiluminescent substrates, and suggested that the decomposition rate of a dioxetane induced by charge (electron) transfer from a fluorescent electron donor to the dioxetane ring is little dependent on thermal stability of the parent dioxetanes.

**Table 1. Activation parameters of dioxetanes 5, 8, and 9.**

		$E / \text{kcal mol}^{-1}$	$\Delta H / \text{kcal mol}^{-1}$	$\Delta S / \text{e.u.}$	$t_{1/2} / \text{y at } 25^\circ\text{C}$
5a		30.1	29.5	2.9	13.7
5b		30.2	29.6	-0.1	49.8
5c		28.7	28.1	0.2	1.7
8a		27.1	26.5	-6.1	5.9
8b		27.7	27.1	-6.8	22.1
9		29.1	28.5	-3.9	55.6
1a <sup>ref 2b)</sup>		28.4	---	---	3.8

The present results showed that dioxetanes **5b** and **8b** which bear the most bulky substituent at the 5-position are the most stable thermally among 1-aryl-4,4-dimethyl-2,6,7-trioxabicyclo[3.2.0]heptanes synthesized here. The fact raised our hopes that introduction of a substituent bulkier than tert-butyl would give further stable dioxetanes. Thus, we synthesized a bicyclic dioxetane **9** bearing a 9-methylfluorenyl at the 5-position, as a representative experiment. As expected, **9** showed remarkable thermal stability ( $t_{1/2} = 56$  y at  $25^\circ\text{C}$ ). Treatment of **9** with TBAF in DMSO gave light with  $\lambda_{\text{max}} = 468$  nm,  $\Phi_{\text{CL}} = 0.05$ , and  $t_{1/2} = 2.7$  s.

The way in which the non-bonding interaction between substituents at the 4- and 5-position influences the stereochemistry of 1-aryl-2,6,7-trioxabicyclo[3.2.0]heptanes **5**, **8**, and **9** is an interesting subject of investigation. A single-crystal X-ray analysis of **9**<sup>14)</sup> displayed some characteristics of the structure shown as an ORTEP view, where the bond angle of C4-C5-C10 is  $121.7^\circ$ , the dihedral angle of C1-O7-O6-C5 is only  $8^\circ$ , and the bond angle of C5-C1-C23 is unexpectedly large ( $129.7^\circ$ ).



Finally, we should note that 1-aryl-2,6,7-trioxabicyclo[3.2.0]heptane is a skeleton flexible for structural modification, because introduction of various substituents other than alkyl presented here at the 4- and 5-position can be easily attained. The results will be presented in forthcoming communication.

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- 8) Olefins **4** were synthesized by the use of McMurry reaction of the corresponding ketoesters **6**.
- 9) <sup>1</sup>H NMR (300 MHz in CDCl<sub>3</sub>) δ 0.75 (d, J = 7.1 Hz, 3H), 0.90 (d, J = 6.7 Hz, 3H), 1.16 (s, 3H), 1.24 (s, 3H), 2.15 - 2.31 (m, 1H), 3.83 (s, 3H), 3.88 (d, J = 8.3 Hz, 1H), 4.57 (d with fine coupling, J = 8.3 Hz, 1H), 6.93 (ddd, J = 8.2, 2.6, 0.9 Hz, 1H), 7.11 (s with fine coupling, J = 7.7 Hz, 1H), 7.14 (d with fine coupling, J = 7.7 Hz, 1H), 7.32 (dd, J = 8.2, 7.7 Hz, 1H) ppm; IR (liq. film) 2972, 2892, 1604, 1588, 1234, 1046 cm<sup>-1</sup>; Mass (m/z, %) 278 (M<sup>+</sup>, 7), 246 (8), 231 (14), 222 (32), 152 (38), 135 (100).
- 10) <sup>1</sup>H NMR spectrum showed that the photolysate of **4c** included **5c** together with a slight amount of a ketoester **6c**. Considering the reported results<sup>7)</sup> that the "ene" reaction and 1,2-addition of singlet oxygen occur concurrently for 4,5-dimethyl-2,3-dihydrofuran, the results for **4c** suggest that an aryl at the 1-position of dihydrofuran affects most likely the side selectivity of singlet oxygen.
- 11) **5d** was decomposed gradually while the isolation process.
- 12) All the efficiencies(Φ<sub>CL</sub>) measured here were based on the value for the Φ<sub>CL</sub> of **1a**.<sup>2b)</sup>
- 13) For all the F<sup>-</sup>-triggerable dioxetanes **8** and **9**, TBAF induced luminescence occurred by a pseudo-first order process under the conditions described here, and the chemiluminescence spectra from **9** were identical to the fluorescence emission spectra of the corresponding spent reaction mixture.
- 14) Colorless crystals of **9** are triclinic, the space group is P1 with *a* = 10.543(5) Å, *b* = 18.427(6) Å, *c* = 7.817(2) Å, α = 91.01 (3) °, β = 102.34 (3) °, γ = 101.94(3), *V* = 1448.4 (9) Å<sup>3</sup>, *Z* = 2, and *d*<sub>calcd</sub> = 1.180 g / cm<sup>3</sup>.

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