METHYLATION OF 5-ISONITROSO-1,3-DIOXINE-4,6-DIONES WITH DIAZOMETHANE AND SOME REACTIONS OF ITS PRODUCTS[#]

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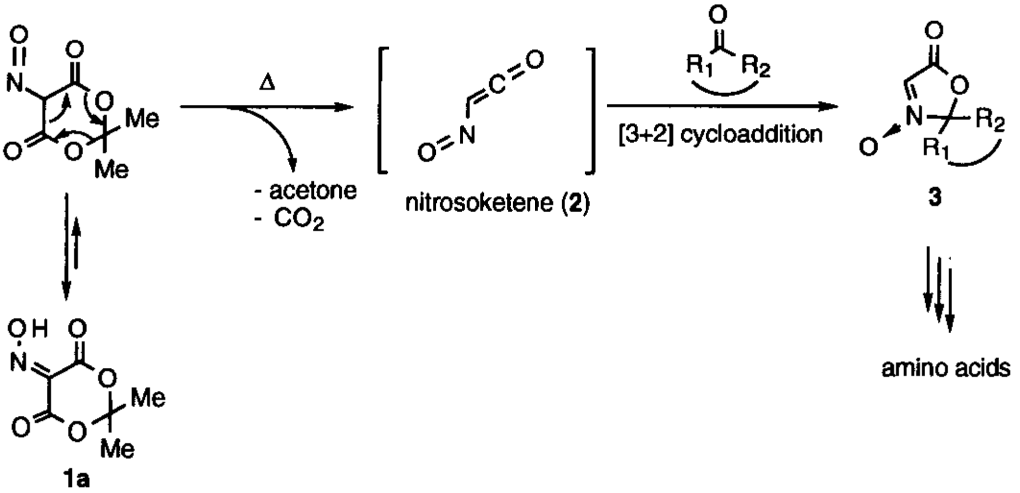
Abstract - Methylation of 5-isonitroso-1,3-dioxine-4,6-diones (**1**) with diazomethane afforded 5-methoxyimino-1,3-dioxine-4,6-diones (**4**) and 5-methylimino-1,3-dioxine-4,6-dione *N*-oxides (**5**) together with a cyclic nitrone (**7**) as a minor product. Compound (**5**) reacted with two molar equivalents of triphenylphosphine to give phosphonium betaines (**8**) whereas photoreaction of **5** formed novel spiro compounds (**9**) *via* oxaziridine intermediates (**G**).

A new reaction intermediate, nitrosoketene (**2**), has been recently developed by thermolysis of 5-isonitroso-2,2-dimethyl-1,3-dioxane-4,6-dione (**1a**: isonitroso Meldrum's acid) in our laboratory.[1-3] This intermediate readily underwent [3+2] cycloaddition with various ketones[4] to produce cyclic nitrones (**3**) which were found to be versatile reagents for the EPC (enantiomerically pure compound) synthesis of nonproteinogenic amino acids.[5-7]

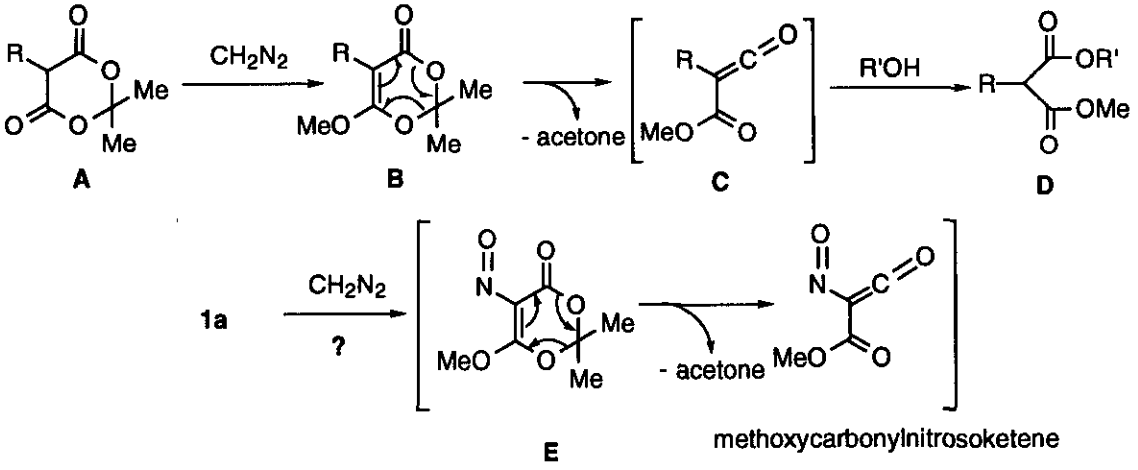


Scheme 1

[#] This paper is dedicated to the celebration of the 75th birthday of Prof. Koji Nakanishi of Columbia University.

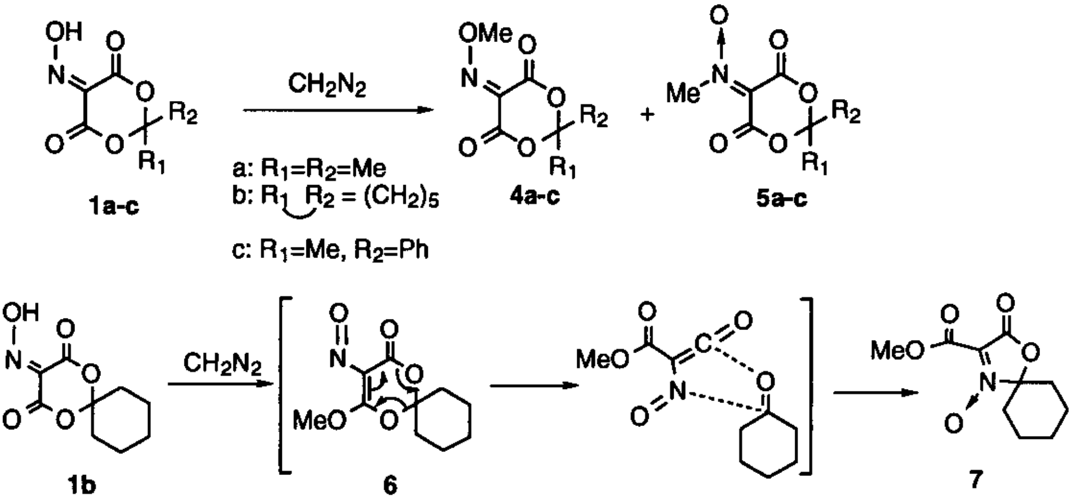
In connection with our continuing interest in the ketene chemistry directed towords the synthesis of new heterocycles, we studied the methylation of **1** with diazomethane expecting the formation of 6-methoxy-5-nitroso-1,3-dioxin-4-one derivatives(**E** and **6**) which would behave as a new ketene (methoxycarbonylnitrosoketene) precursor. However, we found that the reaction did not produce the desired derivatives (**E** and **6**) but 5-methoxyimino-1,3-dioxane-4,6-diones (**4**) and 5-methylimino-1,3-dioxane-4,6-dione *N*-oxides (**5**). We report here the synthesis of **5** and their reaction to give phosphonium betaines (**8**) and 7-methyl-7-aza-1,3,6-trioxaspiro[3.4]octane-4,8-diones (**9**).

Matoba and Yamazaki previously reported that the reaction of Meldrum's acid (**A**) with diazomethane followed by treatment with alcohols gave malonic acid mixed esters (**D**) in good yields.[8] They also proposed mechanism for this reaction as follows; 6-methoxy-2,2-dimethyl-1,3-dioxin-4-one (**B**) is initially formed by methylation and the dioxine **B** spontaneously undergoes cycloreversion to give methoxycarbonylketene (**C**) which reacts with alcohols to yield the mixed esters (**D**).



Scheme 2

Considering this reaction pathway, we examined the reaction of **1a** with diazomethane to obtain 6-methoxy-2,2-dimethyl-5-nitroso-1,3-dioxin-4-one (**E**) to be a ketene precursor. When **1a** was treated with diazomethane in ether at 0 °C, a known compound (**4a**)[9] and an unknown (**5a**) were obtained in high total yield. The nitrone structure of **5a** was confirmed by later reactions. In oder to trap the ketene generated from **E**, if formed, the reaction was carried out in acetone or alcohol. However, the products were **4a** and **5a**. Although the total yield of **4a** (39%) and **5a** (60%) was improved at lower temperature (-78 °C), the desired **E** was not detected. Next, we carried out the methylation of **1b,c** with diazomethane in ether at 0 °C. Three products (**4b**, **5b**, and **7**) were obtained from the reaction with **1b**. Compound (**7**) would be formed by cycloaddition of cyclohexanone with methoxycarbonylnitrosoketene generated from **6**. On the contrary, the reaction of **1c** with diazomethane afforded **4c** and **5c** in good yields.

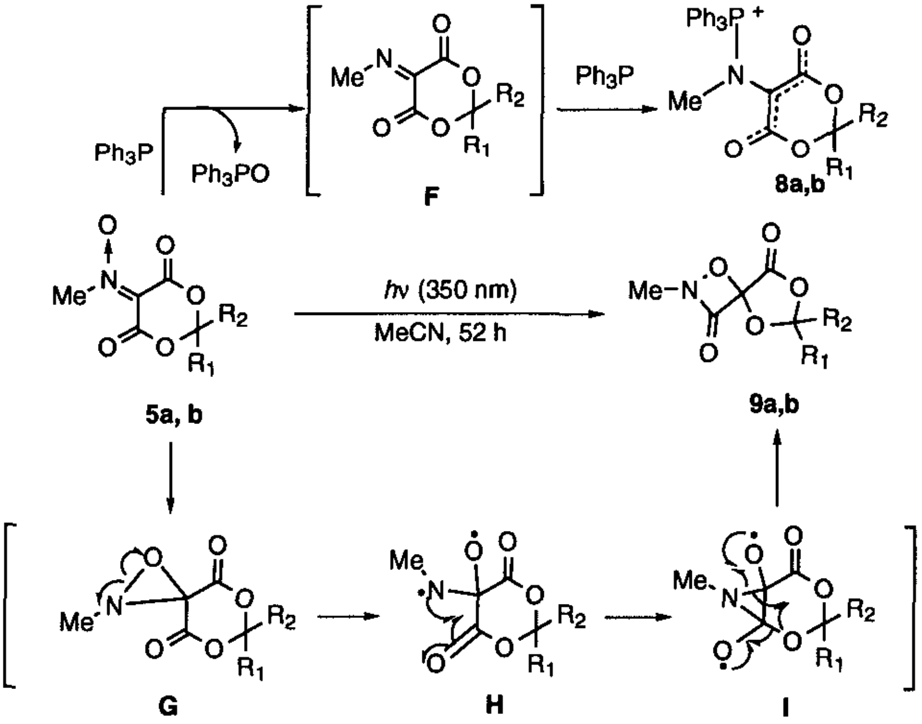


Scheme 3

To confirm the structure of **5**, **5a,b** were treated with triphenylphosphine. Two molar equivalents of triphenylphosphine reacted with **5a,b** at room temperature to give the corresponding betaines (**8a,b**) in almost quantitative yields, concomitant with the formation of triphenylphosphine oxide. Therefore, compound (**5a,b**) were initially deoxygenated by triphenylphosphine to form methylimino derivatives (**F**), which further reacted with triphenylphosphine to give betaines (**8a,b**). The structure of **8a,b** were determined by IR, ^{1}H-, and ^{13}C-NMR spectral data. The IR spectra of **8a,b** showed the week carbonyl absorptions at 1685 and 1680 cm^{-1}, respectively whereas the strong absorption was observed at 1607 cm^{-1} in both compounds due to the C=C bond. This phenomenon in the IR spectra was analogous to that of the corresponding ammonium betaine previously reported.[10] In the ^{1}H-NMR spectra of **8a,b**, the signals due to N-Me were observed at δ 2.99 and 2.93 as doublet patterns, respectively. The ^{13}C-NMR spectra of **8a,b** represented the carbonyl carbon (δ 165.6 and 165.5), 5-C (δ 84.7 and 84.8), and N-CH_3 (δ 38.3 and 38.5), respectively. The latter two signals were coupled with phosphorous atom in the off-resonance spectra.

A lot of literature is available concerning the photochemical reaction of nitrones.[11,12] In order not only to confirm the structure of **5** but also to develop new heterocycles, we investigated the photoreaction of **5a,b**. When **5a** was irradiated by 350 nm rays in acetonitrile at room temperature for 52 h, a spiro compound (**9a**) was obtained in 85% yield. The structure of **9a** was confirmed by IR, ^{1}H-, and^{13}C-NMR spectral data. The IR spectrum shows the carbonyl absorption bands due to oxazetidinone and dioxolone at 1775 and 1805 cm^{-1}, respectively. The ^{1}H-NMR spectrum represents the N-methyl protons at δ 3.01 whereas the ^{13}C-NMR spectrum shows the existence of two carbonyl carbons (δ159.3 and 161.4) and two quaternary carbons (δ 72.2 and 106.5). Similar photoreaction of **5b** gave **9b** in 90% yield. The spectral data of **9b** were analogous to that of **9a**. Mechanism for the formation of **9** can be considered as shown in Scheme 4: a oxaziridine **G** first would be formed by irradiation of **5**, which then undergoes radical cleavage to form **9** *via* **H** and **I**.

In conclusion, we have found that 5-isonitroso-1,3-dioxine-4,6-diones (**1**) were methylated with diazomethane to give the *O*-methylated (**4**) and the *N*-methylated (**5**) compounds. The nitrone (**5**) was treated with triphenylphosphine to give the novel betaine (**8**) whereas **5**, on irradiation, formed the novel spiro derivative (**9**) in high yields. Compound (**5**) seems to be a versatile synthon for the synthesis of heterocycles because **5** can be regarded as a Meldrum's acid derivative having a nitrone function. Further investigation of the reaction of **5** is in progress.



Scheme 4

EXPERIMENTAL

All melting points were determined on a Yanagimoto micro-hot stage and are uncorrected. IR spectra were measured on a JASCO-102 spectrophotometer and ^{1}H-NMR spectra were recorded on a JEOL JNM-PMX 60 SI, Hitachi R-3000, Varian Gemini-300L or JEOL GX-500 spectrometer with tetramethylsilane as an internal standard. High-resolution mass spectra were recorded on a JEOL JMS-DX-303 or JMS-AX-500 spectrometer. Wakogel (C-200) and Merck Kiesel-gel 60F 254 were employed for silica gel column and thin layer chromatography (TLC), respectively. *The ratios of solvent mixtures for chromatography are shown as volume / volume.*

Methylation of 5-Isonitroso-2,2-dimethyl-1,3-dioxane-4,6-dione (1a) with Diazomethane

To a solution of **1a** (346 mg, 2 mmol) in ether (30 mL) was added a solution of diazomethane in ether under ice-cooling until the evolution of N_2 gas ceased. After being stirred for 30 min, the solvent was evaporated *in vacuo*. The residue was submitted to silica gel (20 g) column chromatography. Elution with hexane - ethyl acetate (6:1) gave 5-methoxyimino-2,2-dimethyl-1,3-dioxane-4,6-dione (**4a**)(154 mg, 41%) and 2,2-dimethyl-5-methylimino-1,3-dioxane-4,6-dione *N*-oxide (**5a**)(155 mg, 41%).

4a: mp 81-82 °C (*lit.*,[9] mp 78 °C), colorless prisms (hexane-ethyl acetate). High-resolution MS *m/z* Calcd for $C_7H_9NO_5$ (M^+): 187.0481. Found: 187.0491. IR ($CHCl_3$): 1780 (sh), 1755 (s), 1565 (m) cm^{-1}. ^1H-NMR ($CDCl_3$, 500 MHz) δ: 1.76 (6H, s, $C(CH_3)_2$), 4.40 (3H, s, OCH_3). ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 28.01, 67.84, 105.85, 133.16, 151.15, 157.02.

5a: mp 56-57 °C, yellow prisms (ether-hexane). High-resolution MS *m/z* Calcd for $C_7H_9NO_5$ (M^+): 187.0481. Found: 187.0482. IR ($CHCl_3$): 1760 (sh), 1735 (s), 1500 (m) cm^{-1}. ^1H-NMR ($CDCl_3$, 500 MHz) δ: 1.75 (6H, s, $C(CH_3)_2$), 4.48 (3H, s, OCH_3). ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 27.76, 62.24, 104.83, 127.35, 154.71, 158.04.

Methylation of 3-Isonitroso-2,4-dioxo-1,5-dioxaspiro[5.5]undecane (1b) with Diazomethane

According to the procedure described above, **1b** (426 mg, 2 mmol) was treated with diazomethane in ether to give 3-methoxyimino-2,4-dioxo-1,5-dioxaspiro-[5.5]undecane (**4b**)(153 mg, 34%), 3-methoxycarbonyl-2-oxo-4-oxy-4-aza-1-oxa-spiro[5.4]dec-3-ene (**7**)(8.8 mg, 2%), and 3-methylimino-2,4-dioxo-1,5-dioxa-spiro[5.5]undecane *N*-oxide (**5b**)(216 mg, 48%).

4b: mp 105-106 °C, colorless prisms ($CHCl_3$ - hexane). *Anal.* Calcd for $C_{10}H_{13}NO_5$: C, 52.86; H, 5.77; N, 6.16. Found: C, 52.77; H, 5.54; N, 6.00. High-resolution MS *m/z* Calcd for $C_{10}H_{13}NO_5$ (M^+): 227.0794. Found: 227.0750. IR ($CHCl_3$): 1775 (sh), 1750 (s) cm^{-1}. ^1H-NMR ($CDCl_3$, 500 MHz) δ: 1.45-1.61 (2H, m, $-CH_2-$), 1.69-1.83 (4H, m, 2 x $-CH_2-$), 1.97-2.09 (4H, m, 2 x $-CH_2-$), 4.44 (3H, s, OCH_3). ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 22.12, 23.85, 36.94, 67.76, 106.72, 133.55, 151.23, 157.09.

5b: mp 165-167 °C, yellow needles ($CHCl_3$ - hexane). High-resolution MS *m/z* Calcd for $C_{10}H_{13}NO_5$ (M^+) and $C_4H_3NO_4$ ($M^+-C_6H_{10}O$) : 227.0794 and 129.0062. Found: 227.0766 and 129.0057. IR ($CHCl_3$): 1795 (s), 1735 (m), 1555 (s) cm^{-1}. ^1H-NMR ($CDCl_3$, 300 MHz) δ: 1.50-2.04 (10H, m, $-CH_2-$), 3.97 (3H, s, OCH_3).

7: mp 95 °C (decomp), pale yellow prisms ($CHCl_3$ - hexane). High-resolution MS *m/z* Calcd for $C_{10}H_{13}NO_5$ (M^+): 227.0794. Found: 227.0751. IR ($CHCl_3$): 1755 (sh), 1725 (s), 1495 (m) cm^{-1}. ^1H-NMR ($CDCl_3$, 500 MHz) δ: 1.42-1.58 (2H, m, $-CH_2-$), 1.70-1.80 (4H, m, 2 x $-CH_2-$), 1.94-2.08 (4H, m, 2 x $-CH_2-$), 4.51 (3H, s, OCH_3). ^{13}C-

NMR ($CDCl_3$, 125 MHz) δ: 22.14, 24.01, 36.33, 61.72, 105.39, 127.34, 154.37, 157.67.

Methylation of 5-Isonitroso-2-methyl-2-phenyl-1,3-dioxane-4,6-dione (1c) with Diazomethane

According to the procedure described above, **1c** (470 mg, 2 mmol) was treated with diazomethane in ether to give 5-methoxyimino-2-methyl-2-phenyl-1,3-dioxane-4,6-dione(**4c**)(72 mg, 29%) and 2-methyl-2-phenyl-5-methylimino-4,6-dione *N*-oxide (**5c**)(132 mg, 53%).

4c: mp 103-104 °C, colorless prisms (ether-hexane). High-resolution MS *m/z* Calcd for $C_{11}H_8NO_5$ (M^+- CH_3): 234.0402. Found: 234.0387. IR ($CHCl_3$): 1780 (sh), 1758 (s), 1562(m) cm^{-1}. ^1H-NMR ($CDCl_3$, 300 MHz) δ: 1.98 (3H, s, CH_3), 4.22 (3H, s, N-CH_3), 7.38-7.48 (5H, m, Ph). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 29.57, 67.57, 106.04, 125.21, 129.60, 130.28, 134.05, 140.88, 152.13, 157.98.

5c: mp 95-96 °C (decomp), pale yellow prisms (ether-hexane). High-resolution MS *m/z* Calcd for $C_{12}H_{11}NO_5$ (M^+): 249.0637. Found: 249.0632. IR ($CHCl_3$): 1770 (sh), 1738 (s), 1495 (m) cm^{-1}. ^1H-NMR ($CDCl_3$, 300 MHz) δ: 1.94 (3H, s, CH_3), 4.20 (3H, s, N-CH_3), 7.37-7.50 (5H, m, Ph). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 29.29, 60.72, 104.63, 124.71, 128.29, 129.52, 130.06, 140.85, 155.014, 158.52.

2,2-Dimethyl-5-methylimino-1,3-dioxane-4,6-dione Triphenylphosphonium Salt (8a)

A solution of **5a** (187 mg, 1 mmol) and triphenylphosphine (786 mg, 3 mmol) in benzene (10 mL) was stirred at rt for 24 h. After evaporation of the solvent, the residue was submitted to silica gel (100 g) column chromatography. Elution with ethyl acetate gave **8a** (404 mg, 90%) as pale yellow prisms ($CHCl_3$-hexane).

8a: mp 215-217 °C (decomp), colorless prisms (hexane-$CHCl_3$). *Anal.* Calcd for $C_{28}H_{28}NO_4P$: C, 69.28; H, 5.58; N, 3.23. Found: C, 69.11; H, 5.59; N, 3.24. High-resolution MS *m/z* Calcd for $C_{28}H_{28}NO_4P$ (M^+): 433.1443. Found: 433.1478. IR ($CHCl_3$): 1685 (w), 1607 (s) cm^{-1}. ^1H-NMR ($CDCl_3$, 300 MHz) δ: 0.88 (3H, br s, CH_3), 1.51 (3H, br s, CH_3), 3.00 (3H, d, *J* = 8.0 Hz, N-CH_3), 7.56-7.78 (9H, m, Ar), 8.02-8.18 (6H, m, Ar). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 23.93, 26.83, 38.32 (d, *J* = 12.6 Hz, N-Me), 84.65 (d, *J* = 9.2 Hz), 100.86, 122.05 (d, *J* = 103.1 Hz), 129.36 (d, *J* = 13.7 Hz), 134.15 (d, *J* = 2.3 Hz), 134.38 (d, *J* = 10.3 Hz), 165.63.

4-Methylimino-2,4-dioxo-1,5-dioxaspiro[5.5]undecane Triphenylphosphonium Salt (8b)

According to the procedure described above, **5b** (113.5 mg, 0.5 mmol) was treated with triphenylphosphine (393 mg, 1.5 mmol) to give **8b** (232 mg, 99%) as pale yellow prisms ($CHCl_3$-hexane).

8b: mp 202-204 °C (decomp), pale yellow prisms (hexane-$CHCl_3$). High-resolution MS *m/z* Calcd for $C_{28}H_{28}NO_4P$ (M^+): 473.1756. Found: 473.1716. IR ($CHCl_3$): 1680 (w), 1605 (s), 1575 (w) cm^{-1}. ^1H-NMR ($CDCl_3$, 500 MHz) δ: 0.93 (2H, br, -CH_2-), 1.33-1.54 (4H, br m, 2 x -CH_2-), 1.50 (2H, br, -CH_2-), 1.72 (2H, br, -CH_2-), 2.93 (3H, d, *J* = 8.1 Hz, N-CH_3), 7.52-7.66 (9H, m, Ar), 8.00-8.07 (6H, m, Ar). ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 22.36, 22.64, 24.97, 32.75, 35.61, 38.46 (d, *J* = 13.4 Hz, N-Me), 84.84 (d, J = 9.2 Hz), 101.43, 122.16 (d, J = 102.1 Hz), 129.32 (d, J = 12.4 Hz), 134.06 (d, J = 2.9 Hz), 134.40 (d, J = 11.4 Hz), 165.53.

2,2,7-Trimethyl-4,8-dioxo-7-aza-1,3,6-trioxaspiro[5.4]octane (9a)
A solution of **5a** (374 mg, 2 mmol) in acetonitrile (80 mL) was bubbled with argon gas for 30 min, and then irradiated by 350 nm ray for 52 h. After evaporation of the solvent, to the residue was added $CHCl_3$. After removal of the insoluble precipitate, the solution was evaporated again to give **9a** (318 mg, 85%) which was confirmed to be pure by ^1H- and ^{13}C-NMR spectra. However, **9a** could not be purified further by recrystallization due to its instability.
9a: amorphous solid. High-resolution MS m/z Calcd for $C_{10}H_{13}NO_5$ (M^+-CH_3): 172.0246. Found: 172.0260. IR ($CHCl_3$): 1807 (s), 1780 (s) cm^{-1}. ^1H-NMR ($CDCl_3$, 300 MHz) δ: 1.87 (3H, s, CH_3), 1.89 (3H, s, CH_3), 3.01 (3H, s, N-CH_3). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 27.32, 28.93, 42.44, 72.23, 106.54, 119.87, 159.33, 161.36.

2-Methyl-3,13-dioxo-2-aza-1,5,12-trioxadispiro[3.1.5.2]tridecane (9b)
According to the procedure described above, a solution of **5b** (227 mg, 1 mmol) in acetonitrile (100 ml) was irradiated for 52 h to give **9b** (204 mg, 90%) which was confirmed to be pure by ^1H- and ^{13}C-NMR spectra.
9b: mp 100 °C (dec.). High-resolution MS m/z Calcd for $C_{10}H_{13}NO_5$ (M^+): 227.0794. Found: 227.0829. IR ($CHCl_3$): 1805 (s), 1779 (s) cm^{-1}. ^1H-NMR ($CDCl_3$, 500 MHz) δ: 1.47-1.65 (2H, m, -CH_2-), 1.65-1.93 (4H, m, 2 x -CH_2-), 1.93-2.18 (4H, m, 2 x -CH_2-), 3.02 (3H, s, N-CH_3). ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 21.74, 22.53, 23.73, 35.79, 38.49, 42.49, 107.42, 119.87, 159.30, 161.28.

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