REACTION OF 5-HYDROXYIMINO-1,3-DIOXINE-4,6-DIONE (ISONITROSO MELDRUM'S ACID) WITH CARBODIIMIDES TO GIVE PARABANIC ACIDS#

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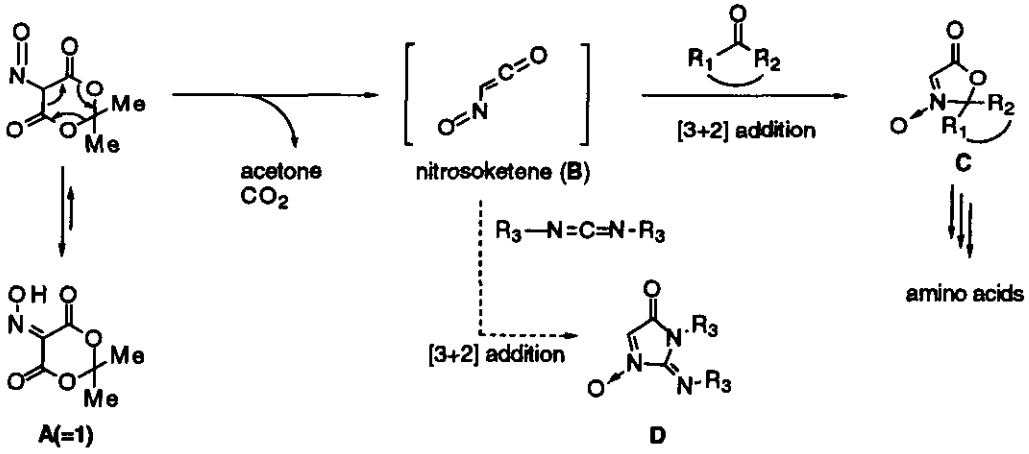
Abstract — Reaction of 5-hydroxyimino-1,3-dioxine-4,6-dione (isonitroso Meldrum's Acid) with carbodiimides gave cyanoformamide derivatives in quantitative yields, which cyclized to iminoparabanic acids and parabanic acids under basic and acidic conditions, respectively.

Previously, we reported that 5-hydroxyimino-1,3-dioxine-4,6-dione (isonitroso Meldrum's acid) (**A**=**1**), on heating, generated nitrosoketene (**B**) as a new reaction intermediate, which reacted with ketones to give cyclic nitrones (**C**).[1,2] The reaction involves the novel [3+2] cycloaddition of nitrosoketene to ketones, which act as $\pi 2$ components for the cycloaddition. We also reported that the nitrones (**C**: R_1-R_2 = chiral moiety) served as synthetic precursors for the chiral synthesis of nonproteinogenic amino acids.[3-5]

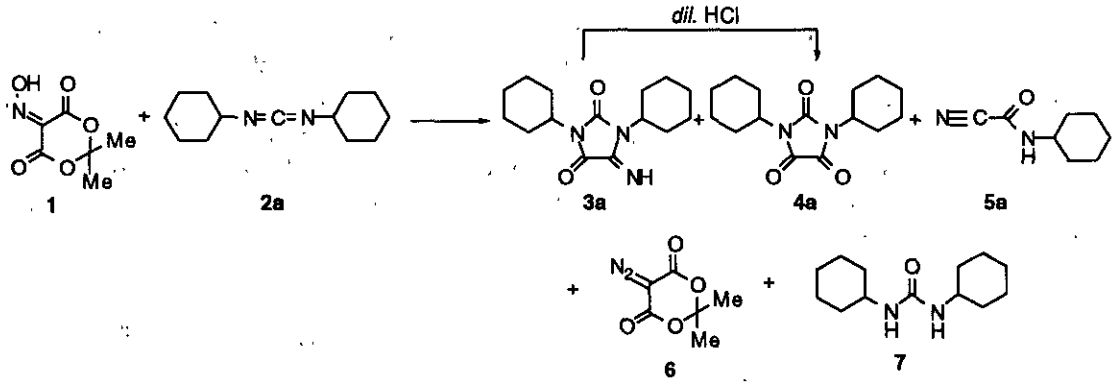


Scheme 1

Dedicated to the memory of the late Professor Shun-ichi Yamada.

In order to find a new $\pi 2$ component for this [3+2] cycloaddition and expecting a new heterocycle **D**, we examined the reaction of **1** with carbodiimides as $\pi 2$ components. However, we found that **1** reacted easily with carbodiimides at room temperature to give cyanoformamides in quantitative yields which cyclized to iminoparabanic acids or parabanic acids depending on the reaction conditions. This is the subject of this paper.

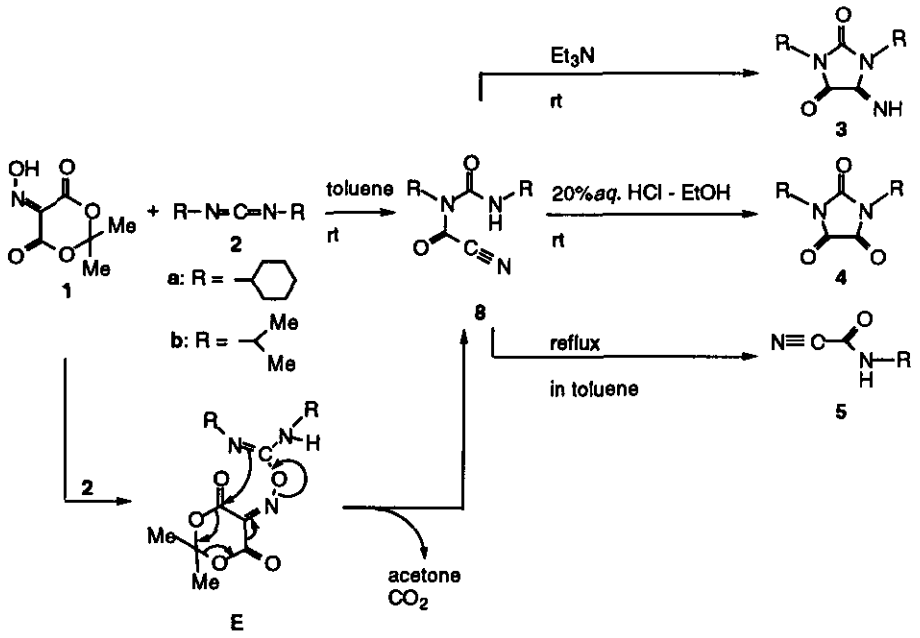
The reaction of **1** with ketones to form nitrones was carried out under the reflux in toluene because it was considered that heating was needed for the formation of nitrosoketene from **1**. Actually, it was confirmed by FTIR spectroscopy that nitrosoketene was generated at 80 °C in gaseous phase.[6] Therefore, we first tried the reaction of **1** with *N*,*N*'-dicyclohexylcarbodiimide (**2a**) in toluene under reflux. When **1** was heated with **2a** under reflux in toluene, five compounds (**3a**, **4a**, **5a**, **6**[7], and **7**) were obtained in 2, 2, 76, 2, and 9% yields, respectively. Although the former two compounds (**3a**) and (**4a**) could not be separated from each other, other compounds could be separated by silica gel column chromatography. The mixture of **3a** and **4a** was treated with *dil.* hydrochloric acid to give **4a** as a sole product.



Scheme 2

On the other hand, the reaction also proceeded in toluene at room temperature to give a cyanoformamide derivative (**8a**) in quantitative yield. The basic cyclization of **8a** using triethylamine afforded **3a** in 88% yield whereas **8a** cyclized to **4a** in the presence of 20% *aq*. HCl-EtOH in 88% yield. On the other hand, heating **8a** in toluene did not form the cyclized product such as **3a** or **4a**, but gave **5a** in 89% yield, concomitant with the elimination of the isocyanate. Similar reaction of **1** with *N*,*N*'-diisopropylcarbodiimide (**2b**) was also performed to give **8b** in quantitative yield. The cyclization of **8b** was again carried out in the presence of base and acid to form **3b** and **4b** in good yields, respectively. Also in this case, **8b** was heated in toluene to give **5b** in 71% yield.

Mechanism for the formation of **8** can be considered as follows: due to the strong acidity of **1**, this compound readily adds to the C=N bond of **2** to form the intermediate **E**, which eliminates acetone and carbon dioxide to give **8**.



Scheme 3

In conclusion, we have found that the carbodiimide does not behave as a $_{\pi}2$ component in the reaction with **1** but the reaction produces a cyanoformamide derivative (**8**) which readily cyclizes to the parabanic acid derivatives (**3**) and (**4**). The reaction would provides an efficient method for the synthesis of 1,3-disubstituted parabanic acid derivatives.[8]

EXPERIMENTAL SECTION

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.

Reaction of 5-Hydroxyimino-1,3-dioxine-4,6-dione (1) with *N,N'*-Dicyclohexylcarbodiimide (DCC: 2a)

A solution of **1** (865 mg, 5 mmol) and **2a** (1. 03 g, 5 mmol) in toluene (20 mL) was reflux for 2 h. After removal of the solvent *in vacuo*, the residue was submitted to silica gel (150 g) column chromatography. Elution with hexane-ethyl acetate (1:10, 1:1, and 1:0) gave a 1:1 mixture of **3a** and **4a**[8] (44 mg, 4%), **5a** (580 mg, 76%), **6**[9] (13 mg, 2%), and **7** (96 mg, 9%), respectively.

***N*-Cyanocarbonyl-*N,N'*-dicyclohexylurea (8a)**
A solution of **1** (1.73 g, 10 mmol) in toluene (40 mL) was added to a solution of **2a** (2.06 g, 10 mmol) in toluene (10 mL) with stirring under ice-cooling. After being stirred at rt for 45 min, the solvent was evaporated *in vacuo* at 20-30 °C to give **8a** (2.76 g, quant.). mp 133-135 °C, pale yellow prisms ($CHCl_3$-hexane). *Anal.* Calcd for $C_{15}H_{23}N_3O_2$: C, 64.96; H, 8.36; N, 15.15. Found: C, 64.60; H, 8.16; N, 15.13. High-resolution MS *m/z* Calcd for $C_{15}H_{23}N_3O_2$ (M^+): 277.1790. Found: 277.1801. IR ($CHCl_3$): 3600-3200 (br), 2249 (w), 1730 (s), 1675 (s) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 1.07-2.10 (20H, m, -C*H*$_2$-), 3.40-4.30 (2H, m, 2 x N-C*H*), 7.50-8.00 (1H, br, N*H*). ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 24.57, 24.84, 24.92, 25.38, 25.57, 26.17, 32.38, 33.85, 110.53, 150.38, 156.99.

***N*-Cyanocarbonyl-*N,N'*-diisopropylurea (8b)**
According to the procedure for the preparation of **8a**, **8b** (2.03 g, quant.) was obtained in almost quantitative yield from the reaction of **1** (1.73 g, 10 mmol) with **2b** (1.26 g, 10 mmol). mp 48-49 °C. Due to its ready cyclization to **3b** or **4b**, compound (**8b**) could not be recrystallized for futher purification. *Anal.* Calcd for $C_9H_{15}N_3O_2$: C, 54.81; H, 7.67; N, 21.30. Found: C, 54.39; H, 7.83; N, 20.86. High-resolution MS *m/z* Calcd for $C_9H_{15}N_3O_2$ (M^+): 197.1164. Found: 197.1188. IR ($CHCl_3$): 3425 (m), 3300 (br), 2249 (w), 1792 (w), 1738 (s), 1690 (s) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.25 (6H, d, *J* = 6.0 Hz, N'-CH(C*H*$_3$)$_2$), 1.56 (6H, d, *J* = 6.0 Hz, N-CH(C*H*$_3$)$_2$), 3.67-4.24 (1H, m, N'-C*H*(CH$_3$)$_2$), 4.41-4.94 (1H, m, N-C*H*(CH$_3$)$_2$), 7.08-7.74 (1H, br, N*H*).

1,3-Dicyclohexyl-4-iminoparabanic Acid (3a)
To a solution of **8a** (277 mg, 1.0 mmol) in $CHCl_3$ (5 mL) was added Et_3N (121 mg, 1.2 mmol). The solution was stirred at rt for 1 h. The solvent and Et_3N were evaporated *in vacuo* to give a crystalline substance, which was recrystallized from hexane to afford **3a** (244 mg, 88%) as colorless needles, mp 84-85 °C. *Anal.* Calcd for $C_{15}H_{23}N_3O_2$: C, 64.96; H, 8.36; N, 15.15. Found: C, 64.84; H, 8.44; N, 15.04. High-resolution MS *m/z* Calcd for $C_{15}H_{23}N_3O_2$ (M^+): 277.1790. Found: 277.1791. IR ($CHCl_3$): 3600-3200 (br), 1785 (w), 1735 (s), 1675 (s) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 1.20-2.22 (20H, m, -C*H*$_2$-), 3.95 (1H, tt, *J* = 12.5, 3.8 Hz, N-C*H*), 4.12 (1H, tt, *J* = 12.5, 3.8 Hz, N-C*H*), 8.75 (1H, s, C=NH). ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 24.90, 25.02, 25.82, 152.60, 154.00, 156.11.

1,3-Diisopropyl-4-iminoparabanic Acid (3b)
According to the procedure for the synthesis of **3a**, **3b** was obtained from **8b** in quantitative yield. Colorless oil. High-resolution MS *m/z* Calcd for $C_9H_{15}N_3O_2$ (M^+): 197.1164. Found: 197.1135. IR ($CHCl_3$): 3600-3200 (br), 1795 (m), 1735 (s), 1675 (s) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.44 (6H, d, *J* = 6.6, -C*H*$_3$), 1.49 (6H, d, *J* = 6.6, -C*H*$_3$), 4.0-4.9 (2H, m, 2 x N-C*H*), 8.78 (1H, s, C=NH). ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 19.52, 19.55, 44.50, 44.53, 152.12, 153.08, 155.86.

1,3-Dicyclohexylparabanic Acid (4a)
A solution of **8a** (277 mg, 1.0 mmol) in EtOH (2 mL) and 20% *aq.* HCl (2 mL) was

stirred for 12 h at rt. After removal of the solvent, the residue was submitted to silica gel (20 g) column chromatography. Elution with ethyl acetate-hexane (1:3) gave **4a** (244 mg, 88%) as colorless needles (EtOH-H_2O). mp 177-179 °C (*lit.*[8b], 174-175 °C). High-resolution MS *m/z* Calcd for $C_{15}H_{22}N_2O_3$ (M^+): 278.1630. Found: 278.1657. IR ($CHCl_3$): 1740 (s), 1730 (s) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 1.19-2.15 (20H, m, -C*H*$_2$-), 4.02 (2H, tt, *J* = 12.5, 3.8 Hz, 2 x N-C*H*). ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 24.80, 25.66, 29.55, 52.38, 153.46, 156.43.

1,3-Diisopropylparabanic Acid (4b)
A solution of **8b** (197 mg, 1.0 mmol) in EtOH (2 mL) and 20% *aq*. HCl (2 mL) was stirred for 12 h at rt. After removal of the solvent, the residue was submitted to silica gel (20 g) column chromatography. Elution with ethyl acetate-hexane (1:3) gave **4b** (184 mg, 93%) as colorless needles (EtOH-H_2O). mp 133-135 °C (*lit.*,[8b] 88-90 °C). High-resolution MS *m/z* Calcd for $C_9H_{14}N_2O_3$ (M^+): 198.1004. Found: 198.0966. IR ($CHCl_3$): 1740 (s), 1730 (sh) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.47 (12H, d, *J* = 6.6 Hz, 2 x N-CH(C*H*$_3$)$_2$), 4.18-4.74 (2H, m, 2 x N-C*H*(CH$_3$)$_2$). ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 19.22, 44.14, 153.55, 156.26.

***N*-Cyclohexylcyanoformamide (5a)**
A solution of **8a** (277 mg, 1.0 mmol) in toluene (10 mL) was refluxed for 3 h. After removal of the solvent, the residue was submitted to silica gel (20 g) column chromatography. Elution with ethyl acetate-hexane (1:7) gave **5a** (141 mg, 89%) as colorless prisms ($CHCl_3$-hexane). mp 81-82 °C. High-resolution MS *m/z* Calcd for $C_8H_{12}N_2O$ (M^+): 152.0949. Found: 152.0935. IR ($CHCl_3$): 3425 (m), 3300 (br), 2249 (w), 1695 (s) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.05-2.20 (10H, m, -C*H*$_2$-), 3.35-4.00 (1H, m, N-C*H*), 5.90-6.70 (1H, br, N*H*). ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 24.48, 25.14, 32.14, 50.12, 111.83, 142.62.

***N*-Isopropylcyanoformamide (5b)**
A solution of **8b** (197 mg, 1.0 mmol) in toluene (10 mL) was refluxed for 3 h. After removal of the solvent, the residue was submitted to silica gel (20 g) column chromatography. Elution with ethyl acetate-hexane (1:3) gave **5b** (77 mg, 71%) as a colorless oil. High-resolution MS *m/z* Calcd for $C_5H_8N_2O$ (M^+): 112.0637. Found: 112.0636. IR ($CHCl_3$): 3425 (m), 3310 (br), 2249 (w) , 1690 (s) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.25 (6H, d, *J* = 6.4 Hz, N-CH(C*H*$_3$)$_2$), 3.85-4.48 (1H, m, N-C*H*(CH$_3$)$_2$), 6.29-7.62 (1H, br, N*H*).

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