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RUTHENIUM TETROXIDE OXIDATION OF *N,N'*-DIBOC HEXAHYDROPYRIDAZINES

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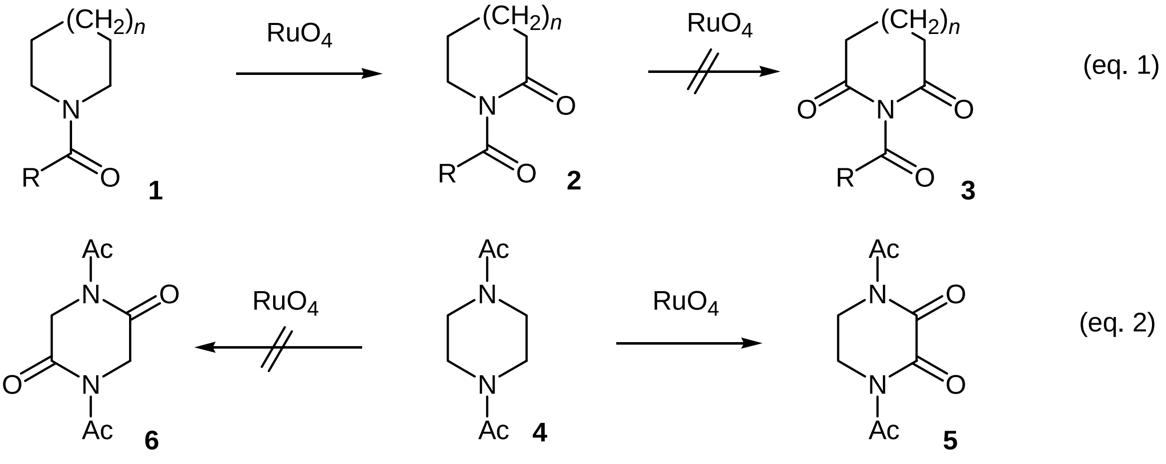
Abstract - The ruthenium tetroxide (RuO_4) oxidation of the 3-substituted *N,N'*-diBochexahydropyridazines gave the 6-oxohexahydropyridazines in good to high yields, whereas the oxidation of the unsubstituted ones also gave the 3,6-dioxo derivatives. The 3,6-*cis*-disubstituted pyridazines were essentially oxidized to give the 3-hydroxypyridazines; no oxidation of the *trans*-derivative occurred.

INTRODUCTION

RuO_4 is an effective multipurpose oxidant[1] and has been widely used for the oxidation of various amines, alcohols, olefins and aromatic compounds in recent years. In the RuO_4 oxidation of the *N*-acyl amines, only the methylene moiety adjacent to the nitrogen atom is generally oxidized to afford the imides; the second and higher stages of oxidation never occur (eq. 1). There are many reports concerning both the

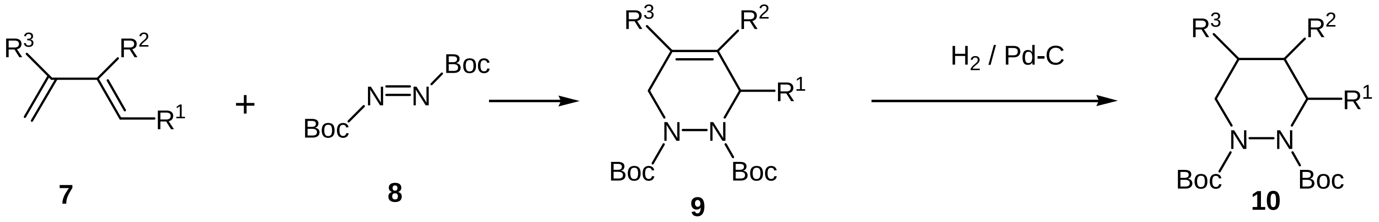


Scheme 1

transformation of cyclic and acyclic *N*-acyl amines into the corresponding lactams[2,3] and imides[4] including natural products[5] using a catalytic amount of RuO_2 hydrate and an appropriate co-oxidant by us[6] and other workers[7] in this field. However, to the best of our knowledge, only a few papers[8,9] have described the RuO_4 oxidation of the heterocycles containing two nitrogen atoms; the RuO_4 oxidation of *N,N'*-diacethylhexahydropyrazine (**4**)[8] gives the pyrazi-2,3-dione **5**, not pyrazi-2,5-dione **6** (eq. 2). We now report the result of the RuO_4 oxidation of the *N*-acylhexahydropyridazines, six-membered heterocycles containing two nitrogen atoms.

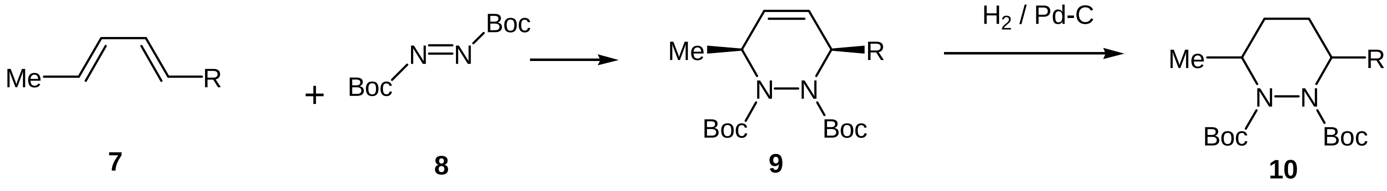
RESULTS AND DISCUSSION

In order to obtain the hexahydropyridazines, which are the substrates for the RuO_4 oxidation, the Diels-Alder (DA) reaction using the 1,3-dienes and azodicarboxylate was carried out. The hetero DA reaction between the 1,3-dienes **7a-h** and di-*tert*-butyl azodicarboxylate (**8**)[3] produced the corresponding adducts, the 6-unsubstituted 1,2-di-*tert*-butyl 1,2,3,6-tetrahydropyrydazine-1,2-carboxylates (**9**) in good to excellent yields except for the 1-methoxycarbonyl-1,3-diene (**7d**) having an electron withdrawing group (Scheme 2). Similarly, the reaction of 2,4-hexadiene (**7i**) and methyl hexa-2,4-dienate (**7j**) with **8** gave the 3,6-disubstituted *cis*-tetrahydropyrydazines **9i, j** in almost quantitative yields. The olefin moiety in **9** was hydrogenated by Pd-C in EtOH to give the hexahyropyridazine derivatives **10** in high yields as shown in Schemes 2 and 3. The methyl *cis*-ester **10j** was epimerized into the *trans*-ester **10k** by treatment with NaOMe in refluxing MeOH in 94% yield.



a: $R^1 = R^2 = R^3 = H$	a: 95%	a: 100%
b: $R^1 = Me, R^2 = R^3 = H$	b: 100%	b: 100%
c: $R^1 = Et, R^2 = R^3 = H$	c: 98%	c: 81%
d: $R^1 = CO_2Me, R^2 = R^3 = H$	d: 47%	d: 92%
e: $R^1 = H, R^2 = Me, R^3 = H$	e: 95%	e: 87%
f: $R^1 = H, R^2 = R^3 = Me$	f: 84%	f: 93%
g: $R^1 = R^2 = Me, R^3 = H$	g: 68%	g: 77%
h: $R^1 = Me, R^2 = H, R^3 = Me$	h: 89%	h: 83%

Scheme 2



i: R = Me

j: R = CO_2Me

9: i: 99%

j: 96%

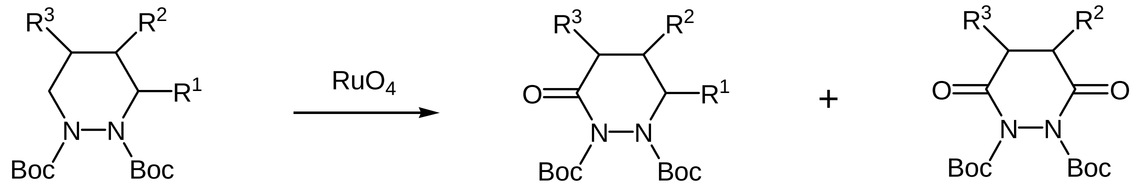
10: i: 92% (*cis*)

j: 81% (*cis*)

NaOMe → k: 94% (*trans*)

Scheme 3

Next, the RuO_4 oxidation of the hexahyropyridazines **10a-h** was carried out at room temperature according to our standard method[3] using a catalytic amount of RuO_2 hydrate and excess of 10% $NaIO_4$ in a double layer system of ethyl acetate-water. When the 3-substituted 6-unsubstituted pyridazines **10b-d, g, h** were oxidazed, the reaction smoothly proceeded to give the desired pyridazinones **11b-d, g, h** in good to excellent yields as the sole product. The oxidation of the pyridazines **10a, e, f** having no substituted at the C-3 and -6 positions in spite of the existence or absence of the functional groups at the C-4 and -5 positions, gave both the pyridazin-3-ones **11a, e, f** and 3,6-dioxo derivatives **12a, e, f** as shown in Scheme 4.

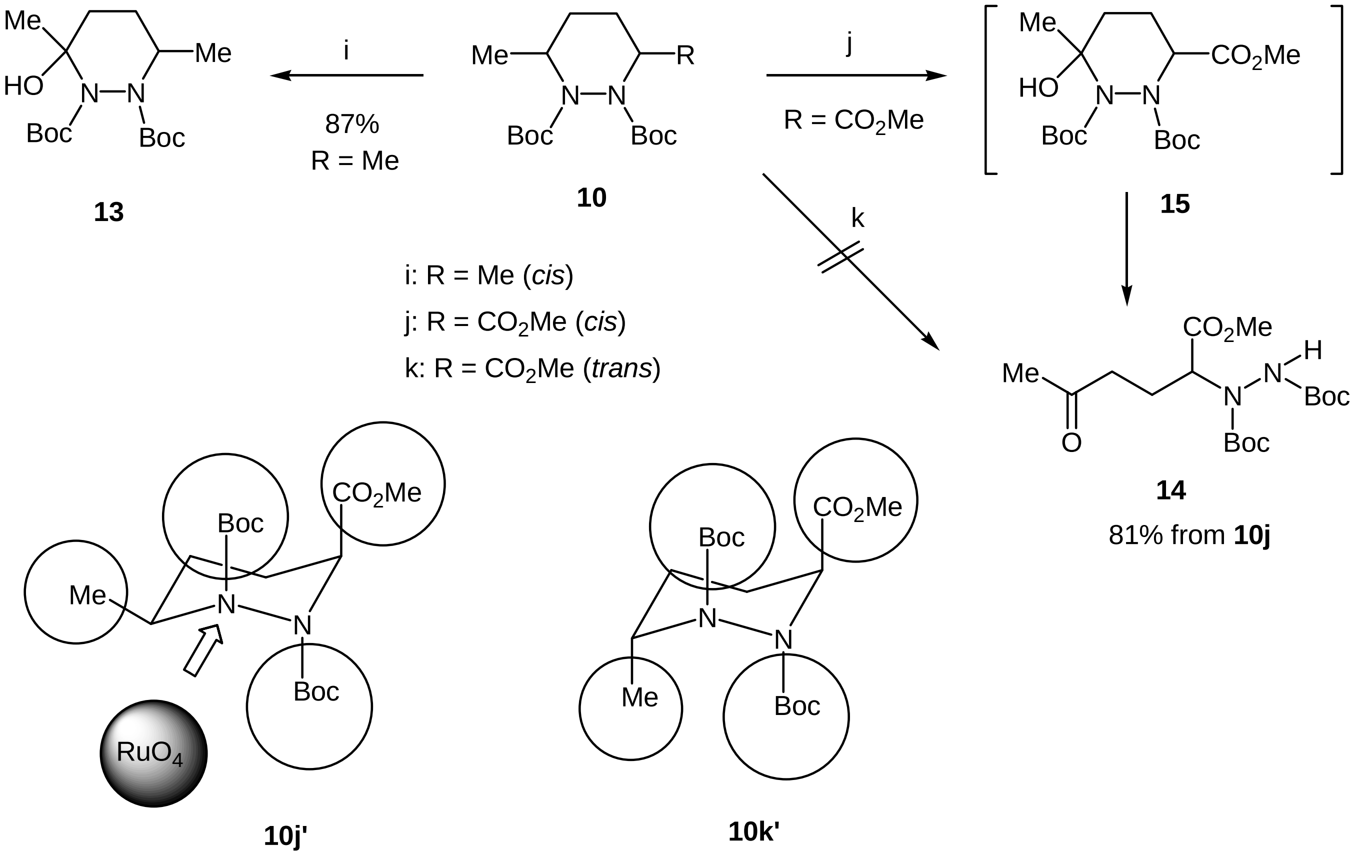


10	11	12
a: $R^1 = R^2 = R^3 = H$	a: 46%	a: 17%
b: $R^1 = Me$, $R^2 = R^3 = H$	b: 98%	b: 0%
c: $R^1 = Et$, $R^2 = R^3 = H$	c: 85%	c: 0%
d: $R^1 = CO_2Me$, $R^2 = R^3 = H$	d: 83%	d: 0%
e: $R^1 =H$, $R^2 = Me$, $R^3 = H$	e: 33%	e: 32%
f: $R^1 =H$, $R^2 = R^3 = Me$	f: 42%	f: 27%
g: $R^1 = R^2 = Me$, $R^3 = H$	g: 91%	g: 0%
h: $R^1 = Me$, $R^2 = H$, $R^3 = Me$	h: 78%	h: 0%

Scheme 4

On the other hand, the behavior of the 3,6-disubstituted pyridazines **10i-k** under the RuO_4 oxidation was different. The hemiaminal **13** was produced by the RuO_4 oxidation of *cis*-dimethylpyridazine **10i** in 87% yield as the sole product. In contrast, the oxidation of the methyl *cis*-ester **10j** under similar conditions resulted in the ring-opening reaction to give the hydrazine derivative **14** in 81% yield *via* the hemiaminal intermediate **15**, which is essentially the same type of oxidation product as **13**. However, the RuO_4

oxidation of the methyl *trans*-ester **10k** did not occur; the starting material was recovered. This distinction between the *cis* and *trans* carbon functionalities at the C-3 and C-6 positions of the chair-form conformation having two axial *N*-Boc groups with respect to the reactivity of the hexahyropyridazines **10i, j** towards the RuO_4 is explained in Scheme 5. During the RuO_4 oxidation of the methyl *cis*-ester **10j**, the reagent could slightly attack the nitrogen atom from the back side of the axial *N*-Boc group to oxidize the methyne carbon giving the hydroxypyridazine intermediate **15** as illustrated in **10j'**. However, RuO_4 could not approach the nitrogen atom of the methyl *trans*-ester **10k'** from any direction due to the steric hindrance of the two bulky Bocs, methyl and methoxycarbonyl groups, which are all axial. For that reason, no oxidized products were obtained.



Scheme 5

CONCLUSION

In summary, we have developed the RuO_4 oxidation of the *N,N'*-diacyl hexahydropyridazines. The results mentioned in this paper suggest that the RuO_4 oxidation of the six-membered species containing two nitrogen atoms smoothly proceeded, and is synthetically very useful for the preparation of the hexahydropyridazin-ones and -diones. A distinction between the oxidation of the *cis* and *trans* 1,2,3,6-tetrasubstituted hexahydropyridazines was also examined.

EXPERIMENTAL

Melting points were measured on a Yanagimoto micro melting point hot stage apparatus and are uncorrected. IR spectra were determined with a Horiba FT-720 spectrometer. Mass spectra (MS) and HRMS were recorded on a JEOL JMS-DX300 instrument. NMR spectra were determined with a JEOL EX-90A (90 MHz) or a JEOL JNM-GSX 400 (400 MHz) spectrometer in $CDCl_3$ using tetramethylsilane as internal standard and *J* values are given in Hz. Microanalyses were performed in the Microanalytical Laboratory in this Faculty.

Aza Diels-Alder reaction of 1,3-butadiene (7) with azodicarboxylate (8)

1,3-Butadiene (**7**, 33 mmol) was added to a solution of di-*tert*-butyl azodicarboxylate (**8**, 30 mmol) in CH_2Cl_2 (30 mL). The mixture was stirred at room temperature for 18-48 h, and then evaporated in vacuo. The resulting residue was purified by silica gel chromatography to give **9**. **9d** and **9j** were obtained by the reaction of **7d** and **7j** with **8** in refluxing benzene for 2-3 days.

Di-*tert*-butyl 1,2,3,6-Tetrahydropyridazine-1,2-dicarboxylate (9a)

Colorless prisms, mp 74-75 ˚C (from hexane) (lit.,[10] mp 73-75 ˚C).

Di-*tert*-butyl 3-Methyl-1,2,3,6-tetrahydropyridazine-1,2-dicarboxylate (9b)

Colorless oil. MS *m/z*: 298 (M^+). IR (neat) cm^{-1}: 1703 (C=O). ^{1}H-NMR δ: 1.22 (3H, d, *J* = 6.5 Hz, 3-Me), 1.44 (18H, s, *t*-Bu x 2), 3.29-3.85 (1H, m, 3-H), 3.95-4.83 (2H, m, 6-H_2), 5.37-5.87 (2H, m, 4- and 5-H). EI-HR-MS *m/z*: 298.1889 (Calcd for $C_{15}H_{26}N_2O_4$: 298.1893).

Di-*tert*-butyl 3-Ethyl-1,2,3,6-tetrahydropyridazine-1,2-dicarboxylate (9c)

Colorless oil. MS *m/z*: 312 (M^+). IR (neat) cm^{-1}: 1705 (C=O). ^{1}H-NMR δ: 0.73-1.37 (5H, m, 3-Et), 1.45 (18H, s, *t*-Bu x 2), 3.65 and 4.37 (each 1H, d, *J* = 16.5 Hz, 6-H_2), 4.07-4.57 (1H, m, 3-H), 5.50-6.05 (2H, m, 4- and 5-H). EI-HR-MS *m/z*: 312.2051 (Calcd for $C_{16}H_{28}N_2O_4$: 312.2049).

Di-*tert*-butyl 3-Methyl 1,2,3,6-Tetrahydropyridazine-1,2,3-tricarboxylate (9d)

Colorless prisms, mp 100-103˚C (from hexane). MS *m/z*: 342 (M^+). IR (KBr) cm^{-1}: 1759, 1697 (C=O). ^{1}H-NMR δ: 1.48 (18H, s, *t*-Bu x 2), 3.74 (3H, s, 3-COOMe), 3.56-3.92 and 4.24-4.52 (each 1H, br, 6-H_2), 5.07-5.40 (1H, br, 3-H), 5.87-6.01 (2H, br, 4- and 5-H). ^{13}C-NMR δ: 28.21 (q), 28.24 (q), 41.5 (t), 52.3 (q), 55.5 (d), 80.7 (s), 82.0(s), 122.3 (d), 125.5 (d), 153.9 (s), 154.4 (s), 169.1 (s). *Anal.* Calcd for $C_{16}H_{26}N_2O_6$: C, 56.13; H, 7.65; N, 8.18. Found: C, 56.12; H, 7.48; N, 8.26.

Di-*tert*-butyl 4-Methyl-1,2,3,6-tetrahydropyridazine-1,2-dicarboxylate (9e)

Colorless oil. MS *m/z*: 298 (M^+). IR (neat) cm^{-1}: 1709 (C=O). ^{1}H-NMR δ: 1.45 (18H, s, *t*-Bu x 2), 1.68

(3H, br s, 4-Me), 3.38-4.48 (4H, m, 3- and 6-H_2), 5.29-5.59 (1H, br, 5-H). EI-HR-MS *m/z*: 298.1890 (Calcd for $C_{15}H_{26}N_2O_4$: 298.1893).

Di-*tert*-butyl 4,5-Dimethyl-1,2,3,6-tetrahydropyridazine-1,2-dicarboxylate (9f)

Colorless prisms, mp 89-90 ˚C (from hexane). MS *m/z*: 312 (M^+). IR (KBr) cm^{-1}: 1720, 1709 (C=O). ^{1}H-NMR δ: 1.45 (18H, s, *t*-Bu x 2), 1.60 (6H, br s, 4- and 5-Me), 3.48 and 4.10 (each 2H, d, *J* = 16.4 Hz, 3- and 6-H_2). *Anal.* Calcd for $C_{16}H_{28}N_2O_4$: C, 61.51; H, 9.03; N, 8.97. Found: C, 61.54; H, 8.82; N, 8.98.

Di-*tert*-butyl 3,4-Dimethyl-1,2,3,6-tetrahydropyridazine-1,2-dicarboxylate (9g)

Colorless oil. MS *m/z*: 311 (M^+-1). IR (neat) cm^{-1}: 1703 (C=O). ^{1}H-NMR δ: 1.24 (3H, d, *J* = 6.3 Hz, 3-Me), 1.45 (18H, s, *t*-Bu x 2), 1.66 (3H, d, *J* = 1.5 Hz, 4-Me), 3.33-3.88 (1H, m, 3-H), 3.97-4.63 (2H, m, 6-H_2), 5.17-5.43 (1H, br, 5-H). EI-HR-MS *m/z*: 311.3961 (Calcd for $C_{16}H_{27}N_2O_4$: 311.3966).

Di-*tert*-butyl 3,5-Dimethyl-1,2,3,6-tetrahydropyridazine-1,2-dicarboxylate (9h)

Colorless oil. MS *m/z*: 312 (M^+). IR (neat) cm^{-1}: 1720, 1705 (C=O). ^{1}H-NMR δ: 1.12 and 1.17 (total 3H, intensity ratio 3:7, each d, *J* = 6.5 and 6.8 Hz, 3-Me), 1.45 (18H, s, *t*-Bu x 2), 1.66 and 1.80 (total 3H, intensity ratio 7:3, each br s, 5-Me), 2.32-3.44 (1H, m, 3-H), 3.50-4.89 (2H, m, 6-H_2), 5.24-5.95 (1H, m, 4-H). EI-HR-MS *m/z*: 312.2044 (Calcd for $C_{16}H_{28}N_2O_4$: 312.2049).

Di-*tert*-butyl *cis*-3,6-Dimethyl-1,2,3,6-tetrahydropyridazine-1,2-dicarboxylate (9i)

Colorless oil. MS *m/z*: 312 (M^+). IR (neat) cm^{-1}: 1726, 1711 (C=O). ^{1}H-NMR δ: 1.25 (3H, d, *J* = 6.7 Hz, 3-Me), 1.44 (18H, s, *t*-Bu x 2), 1.51 (3H, d, *J* = 6.7 Hz, 6-Me), 3.86-4.87 (2H, m, 3- and 6-H), 5.23-5.92 (2H, m, 4- and 5-H). EI-HR-MS *m/z*: 312.2042 (Calcd for $C_{16}H_{28}N_2O_4$: 312.2049).

Di-*tert*-butyl 3-Methyl *cis*-6-Methyl-1,2,3,6-tetrahydropyridazine-1,2,3-tricarboxylate (9j)

Colorless prisms mp 87-88 ˚C (from hexane). MS *m/z*: 356 (M^+). IR (KBr) cm^{-1}: 1734, 1709 (C=O). ^{1}H-NMR δ: 1.10-1.62 (21H, m, *t*-Bu x 2 and 6-Me), 3.71 (3H, s, 3-COOMe), 4.40-4.95 (2H, m, 3- and 6-H), 5.32-5.67 (1H, m, 5-H), 5.83-6.29 (1H, m, 4-H). *Anal.* Calcd for $C_{17}H_{28}N_2O_6$: C, 57.29; H, 7.92; N, 7.86. Found: C, 57.25; H, 7.71; N, 7.86.

Catalytic Hydrogenation of Tetrahydropyridazine (9): Hexahydropyridazine (10)

A mixture of **9** (5 mmol) and 10% Pd-C (175 mg) in MeOH (40 mL) was shaken in H_2 gas (1-5 atm) at room temperature until disappearance of the starting material (about 12-60 h). The mixture was filtered off, the filtrate was evaporated in vacuo. The obtained residue was purified by silica gel chromatography (AcOEt-hexane, 1:1~2:1) to give **10**.

Di-*tert*-butyl Hexahydropyridazine-1,2-dicarboxylate (10a)

Colorless prisms, mp 62-63 ˚C (from hexane). MS *m/z*: 286 (M^+). IR (KBr) cm^{-1}: 1697 (C=O). ^{1}H-NMR δ: 1.12-1.72 (4H, m, 4- and 5-H_2), 1.46 (18H, s, *t*-Bu x 2), 2.56-3.18 and 3.18-4.34 (each 2H, m, 3- and 6-H_2). *Anal*. Calcd for $C_{14}H_{26}N_2O_4$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.50; H, 8.98; N, 9.76.

Di-*tert*-butyl 3-Methylhexahydropyridazine-1,2-dicarboxylate (10b)

Colorless oil. MS *m/z*: 300 (M^+). IR (neat) cm^{-1}: 1701 (C=O). ^{1}H-NMR δ: 1.16 (3H, d, *J* = 6.8 Hz, 3-Me), 1.28-2.01 (4H, m, 4- and 5-H_2), 1.44 (18H, s, *t*-Bu x 2), 2.41-3.15 (1H, m, 3-H), 3.68-4.63 (2H, m, 6-H_2). EI-HR-MS *m/z*: 300.2051 (Calcd for $C_{15}H_{28}N_2O_4$: 300.2049).

Di-*tert*-butyl 3-Ethylhexahydropyridazine-1,2-dicarboxylate (10c)

Colorless oil. MS *m/z*: 314 (M^+). IR (neat) cm^{-1}: 1701 (C=O). ^{1}H-NMR δ: 0.99 (3H, t, *J* = 7.3 Hz, 3-CH_2*CH_3*), 1.46 and 1.47 (each 9H, s, *t*-Bu x 2), 1.25-1.52 and 1.59-1.85 (each 3H, m, 3-*CH_2*CH_3, 4-H and 4-H, 5-H_2), 2.82-3.04 (1H, m, 3-H), 3.85-4.19 (2H, m, 6-H_2). ^{13}C-NMR δ: 11.4 (q), 19.3 (t), 23.6 (t), 26.9 (t), 28.3 (q x 2), 43.4 (t), 54.9 (d), 80.2 (s), 80.6 (s), 154.8 (s), 155.4 (s). EI-HR-MS *m/z*: 314.2201 (Calcd for $C_{16}H_{30}N_2O_4$:314.2206).

Di-*tert*-butyl 3-Methyl Hexahydropyridazine-1,2,3-tricarboxylate (10d)

Colorless oil. MS *m/z*: 344 (M^+). IR (neat) cm^{-1}: 1738, 1703 (C=O). ^{1}H-NMR δ: 1.43 and 1.46 (each 9H, s, *t*-Bu x 2), 1.80-2.20 (4H, m, 4- and 5-H_2), 2.47-3.17 and 3.87-4.27 (each 1H, m, 6-H_2), 3.69 (3H, s, 3-COOMe), 4.75-5.07 (1H, m, 3-H). EI-HR-MS *m/z*: 344.1943 (Calcd for $C_{16}H_{28}N_2O_6$: 344.1947).

Di-*tert*-butyl 4-Methylhexahydropyridazine-1,2-dicarboxylate (10e)

Colorless oil. MS *m/z*: 300 (M^+). IR (neat) cm^{-1}: 1705 (C=O). ^{1}H-NMR δ: 0.87 (3H, d, *J* = 5.8 Hz, 4-Me), 1.03-1.80 (3H, m, 4-H and 5-H_2), 1.45 (18H, s, *t*-Bu x 2), 2.15-3.37 and 3.62-4.32 (each 2H, m, 3- and 6-H_2). EI-HR-MS *m/z*: 300.2040 (Calcd for $C_{15}H_{28}N_2O_4$: 300.2049).

Di-*tert*-butyl *cis*-4,5-Dimethylhexahydropyridazine-1,2-dicarboxylate (10f)

Colorless oil. MS *m/z*: 314 (M^+). IR (neat) cm^{-1}: 1722, 1705 (C=O). ^{1}H-NMR δ: 0.83 and 0.89 (each 3H, d, *J* = 5.9 and 6.3 Hz, 4- and 5-Me), 1.44 (18H, s, *t*-Bu x 2), 1.55-2.05 (2H, br, 4- and 5-H), 2.44-3.27 and 3.58-4.15 (each 2H, m, 3- and 6-H_2). EI-HR-MS *m/z*: 314.2209 (Calcd for $C_{16}H_{30}N_2O_4$:314.2206).

Di-*tert*-butyl *cis*-3,4-Dimethylhexahydropyridazine-1,2-dicarboxylate (10g)

Colorless oil. MS *m/z*: 314 (M^+). IR (neat) cm^{-1}: 1699 (C=O). ^{1}H-NMR δ: 1.02 (3H, d, *J* = 6.1 Hz, 4-Me), 1.19 (3H, d, *J* = 6.4 Hz, 3-Me), 1.35-2.23 (3H, m, 4-H and 5-H_2), 1.45 (18H, s, *t*-Bu x 2), 2.79-3.46 (1H, m, 3-H), 3.58-4.46 (2H, m, 6-H_2). EI-HR-MS *m/z*: 314.2205 (Calcd for $C_{16}H_{30}N_2O_4$:314.2206).

Di-*tert*-butyl *cis*-3,5-Dimethylhexahydropyridazine-1,2-dicarboxylate (10h)

Colorless oil. MS *m/z*: 314 (M^+). IR (neat) cm^{-1}: 1720, 1701 (C=O). ^{1}H-NMR δ: 0.96 (3H, d, *J* = 6.0 Hz, 5-Me), 1.17 (3H, d, *J* = 6.5 Hz, 3-Me), 1.29-2.01 (3H, m, 4-H_2 and 5-H), 1.45 (18H, s, *t*-Bu x 2), 3.03-3.56 and 3.89-4.47 (2H, m and 1H, m, 3-H and 6-H_2). EI-HR-MS *m/z*: 314.2210 (Calcd for $C_{16}H_{30}N_2O_4$:314.2206).

Di-*tert*-butyl *cis*-3,6-Dimethylhexahydropyridazine-1,2-dicarboxylate (10i)

Colorless oil. MS *m/z*: 314 (M^+). IR (neat) cm^{-1}: 1720, 1705 (C=O). ^{1}H-NMR δ: 1.21 (6H, d, *J* = 6.5 Hz, 3- and 6-Me), 1.48 (9H, s, *t*-Bu), 1.51 (9H, s, *t*-Bu), 1.41-1.77 (4H, m, 4- and 5-H_2), 3.47-3.99 and 4.15-4.73 (each 1H, m, 3- and 6-H). EI-HR-MS *m/z*: 314.2205 (Calcd for $C_{16}H_{30}N_2O_4$:314.2206).

Di-*tert*-butyl 3-Methyl *cis*-6-Methylhexahydropyridazine-1,2,3-tricarboxylate (10j)

Colorless oil. MS *m/z*: 358 (M^+). IR (neat) cm^{-1}: 1753, 1739, 1707 (C=O). ^{1}H-NMR δ: 1.28 and 1.31 (total 3H, intensity ratio 3:2, each d, *J* = 6.6 Hz, 6-Me), 1.33-1.52 (18H, m, *t*-Bu x 2), 1.52-1.69 and 1.69-1.88 (each 2H, m, 4- and 5-H_2), 3.76 (3H, s, 3-COOMe), 4.15-4.50 (2H, m, 3- and 6-H). ^{13}C-NMR δ: 19.4 and 19.9 (each q), 23.3 and 23.8 (each t), 24.4, 24.5 and 25.2 (each t), 28.0 and 28.1 (each q), 28.3 (q), 50.6 and 50.7 (each d), 51.9 and 52.1 (each d), 56.4, 56.8 and 58.2 (each q), 80.9 (s), 81.2 and 81.4 (each s), 153.4 (s), 154.8 and 155.8 (each s), 170.9 and 171.7 (each s). EI-HR-MS *m/z*: 358.2103 (Calcd for $C_{17}H_{30}N_2O_6$: 358.2104).

Di-*tert*-butyl 3-Methyl *trans*-6-Methylhexahydropyridazine-1,2,3-tricarboxylate (10k)

A mixture of **10j** (209 mg) and Na metal (178 mg) in MeOH (3 mL) was refluxed for 2 h. After cooling, the mixture was neutralized with citric acid monohydrate (1.0 g), and evaporated. AcOEt (100 mL) and water (30 mL) was added to the residue. The organic layer was washed with water (30 mL x 2), dried over Na_2SO_4 and evaporated in vacou. The obtained residue was chromatographed on silica gel eluted with AcOEt-hexane to give **10k** (197 mg, 94% yield).

Colorless oil. MS *m/z*: 358 (M^+). IR (neat) cm^{-1}: 1738, 1697 (C=O). ^{1}H-NMR δ: 1.17 (3H, d, *J* = 6.6 Hz, 6-Me), 1.18-1.28, 1.70-1.86 and 1.94-2.07 (1H, m, 1H, m and 2H, m, 4- and 5-H_2), 1.47 (9H, s, *t*-Bu), 1.48 (9H, s, *t*-Bu), 3.73 (3H, s, 3-COOMe), 4.11-4.24 and 4.27-4.44 (total 1H, intensity ratio 1:4, each m, 6-H), 4.55-4.64 and 4.86 (total 1H, intensity ratio 1:4, m and d, *J* = 6.2 Hz, 3-H). ^{13}C-NMR δ: 17.6 and 18.2 (each q), 21.2 and 21.9 (each t), 26.0 and 26.5 (each t), 28.2 (q), 28.3 (q), 49.0 and 49.4 (each d), 51.9 and 52.0(each d), 54.7 and 57.4 (each q), 80.2 (s), 81.3 and 81.4 (each s), 154.0 (s), 155.1 (s), 170.8 (s). EI-HR-MS *m/z*: 358.2199 (Calcd for $C_{17}H_{30}N_2O_6$: 358.2104).

RuO_4Oxidation under the Standard Conditions in a Double Layer System

A solution of a substrate (**10**, 12 mmol) to be oxidized in AcOEt (40 mL) was added to a mixture of $RuO_2{\cdot}xH_2O$ (120 mg) and 10% aqueous $NaIO_4$ solution (120 mL). The mixture was vigorously stirred in a sealed flask at 20 ˚C until disappearance of the starting material.

Di-*tert*-butyl 3-Oxohexahydropyridazine-1,2-dicarboxylate (11a)

Colorless oil. MS (FAB) *m/z*: 301 (MH^+). IR (neat) cm^{-1}: 1711 (C=O). ^{1}H-NMR δ: 1.47 (9H, s, *t*-Bu), 1.54 (9H, s, *t*-Bu), 1.81-2.53 (4H, m, 4- and 5-H_2), 3.15-3.35 and 4.27-4.43 (each 1H, m, 6-H_2). ^{13}C-NMR δ: 20.4 (t), 28.0 (q), 28.1 (q), 32.5 (t), 41.8 (t), 82.3 (s), 83.9 (s), 148.9 (s), 154.2 (s), 171.3 (s). HR-MS (FAB) *m/z*: 301.1768 (Calcd for $C_{14}H_{25}N_2O_5$: 301.1763).

Di-*tert*-butyl 3,6-Dioxohexahydropyridazine-1,2-dicarboxylate (12a)

Colorless needles, mp 128-130 ˚C (from isopropyl ether). MS (FAB) *m/z*: 315 (MH^+). IR (KBr) cm^{-1}: 1736, 1716 (C=O). ^{1}H-NMR δ: 1.54 (18H, s, *t*-Bu x 2), 2.78 (4H, s, 4- and 5-H_2). ^{13}C-NMR δ: 27.9 (q), 31.5 (t), 85.4 (s), 147.7 (s), 168.9 (s). *Anal.* Calcd for $C_{14}H_{22}N_2O_6$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.38; H, 7.03; N, 8.90.

Di-*tert*-butyl 3-Methyl-6-oxohexahydropyridazine-1,2-dicarboxylate (11b)

Colorless oil. MS (FAB) *m/z*: 315 (MH^+). IR (neat) cm^{-1}: 1790, 1753, 1712 (C=O). ^{1}H-NMR δ: 1.22 (3H, d, *J* = 7.0 Hz, 3-Me), 1.46 (9H, s, *t*-Bu), 1.53 (9H, s, *t*-Bu), 1.35-1.60 and 2.12-2.27 (each 1H, m, 4-H_2), 2.33-2.44 (2H, m, 5-H_2), 4.58-4.69 (1H, m, 3-H). ^{13}C-NMR δ: 19.8 (q), 27.9 (q), 28.1 (q), 28.7 (t), 33.0 (t), 49.1 (d), 82.1 (s), 83.5 (s), 149.3 (s), 153.8 (s), 172.0 (s). HR-MS (FAB) *m/z*: 315.1917 (Calcd for $C_{15}H_{27}N_2O_5$: 315.1920.

Di-*tert*-butyl 3-Ethyl-6-oxohexahydropyridazine-1,2-dicarboxylate (11c)

Colorless oil. MS (FAB) *m/z*: 330 (MH_2^+). IR (neat) cm^{-1}: 1790, 1752, 1716 (C=O). ^{1}H-NMR δ: 1.03, (3H, t, *J* = 7.3 Hz, 3-CH_2CH_3), 1.47 (9H, s, *t*-Bu), 1.54 (9H, s, *t*-Bu), 1.32-1.61 and 2.10-2.29 (3H, m and 1H, m, 3-CH_2CH_3 and 4-H_2), 2.29-2.44 (2H, m, 5-H_2), 4.32-4.45 (1H, m, 3-H). ^{13}C-NMR δ: 10.8 (q), 27.2 (t), 27.6 (t), 28.0 (q), 28.1 (q), 32.9 (t), 55.5 (d), 82.0(s), 83.5 (s), 149.2 (s), 154.6 (s), 172.2 (s). HR-MS (FAB) *m/z*: 330.2160 (Calcd for $C_{16}H_{30}N_2O_5$: 330.2155).

Di-*tert*-butyl 3-Methyl 6-Oxohexahydropyridazine-1,2,3-tricarboxylate (11d)

Colorless prisms, mp 107-108 ˚C (from hexane). MS *m/z*: 359 (MH^+). IR (KBr) cm^{-1}: 1790, 1743, 1712 (C=O). ^{1}H-NMR δ: 1.48 (9H, s, *t*-Bu), 1.54 (9H, s, *t*-Bu), 2.09-2.33 (2H, m, 4-H_2), 2.41-2.58 (2H, m, 5-H_2), 3.76 (3H, s, 3-COOMe), 4.87-5.03 and 5.12-5.26 (total 1H, intensity ratio 4:1, each m, 3-H). ^{13}C-NMR δ: 23.7 (t), 27.9 (q), 28.0 (q), 32.2 (t), 52.5 (q), 54.3 (d), 83.3 (s), 83.7 (s), 148.6 (s), 154.0 (s), 170.4 (s), 170.8 (s). *Anal.* Calcd for $C_{16}H_{26}N_2O_7$: C, 53.62; H, 7.31; N, 7.82. Found: C, 53.67; H, 7.21; N, 7.85.

Di-*tert*-butyl 5-Methyl-3-oxohexahydropyridazine-1,2-dicarboxylate (11e)

Colorless oil. MS *m/z*: 313 ($M-1^+$). IR (neat) cm^{-1}: 1712 (C=O). ^{1}H-NMR δ: 0.86-1.29 (3H, br, 5-Me), 1.46 (9H, s, *t*-Bu), 1.52 (9H, s, *t*-Bu), 1.89-2.78 (3H, m, 4-H_2 and 5-H), 3.11-4.51 (2H, br, 6-H_2). EI-HR-MS *m/z*: 313.1760 (Calcd for $C_{15}H_{25}N_2O_5$: 313.1763).

Di-*tert*-butyl 4-Methyl-3,6-dioxohexahydropyridazine-1,2-dicarboxylate (12e)

Colorless oil. MS *m/z*: 327 ($M-1^+$). IR (neat) cm^{-1}: 1724 (C=O). ^{1}H-NMR δ: 1.25 (3H, d, *J* = 6.3 Hz, 4-Me), 1.52 (18H, s, *t*-Bu x 2), 2.38-3.03 (3H, m, 4-H and 5-H_2). EI-HR-MS *m/z*: 327.1551 (Calcd for $C_{15}H_{23}N_2O_6$: 327.1556).

Di-*tert*-butyl *cis*-4,5-Dimethyl-3-oxohexahydropyridazine-1,2-dicarboxylate (11f)

Colorless oil. MS (FAB) *m/z*: 329 (MH^+). IR (neat) cm^{-1}: 1790, 1751, 1709 (C=O). ^{1}H-NMR δ: 0.89 (3H, d, *J* = 6.6 Hz, 5-Me), 1.06 and 1.13 (total 3H, intensity ratio 1:9, each d, *J* = 4.0 and 6.2 Hz, 4-Me), 1.46 (9H, s, *t*-Bu), 1.55 (9H, s, *t*-Bu), 2.47-2.61 (2H, m, 4- and 5-H), [2.80 and 2.89-2.98 (total 1H, intensity ratio 4:1, dd, *J* = 13.6, 3.7 Hz, m), 4.34-4.47 and 4.62 (total 1H, intensity ratio 1:4, m, dd, *J* = 13.6, 9.2 Hz), 6-H_2]. ^{13}C-NMR δ: 11.0 and 11.2 (each q), 16.1 and 16.4 (each q), 28.0 (q), 28.1 and 28.2 (each q), 33.2 and 33.8 (each d), 40.0 (d), 50.1 and 52.1 (each t), 82.2 (s), 83.8 and 83.9 (each s), 148.7 and 148.8 (each s), 153.0 and 153.6 (each s), 172.5 and 172.7 (each s). HR-MS (FAB) *m/z*: 329.2074 (Calcd for $C_{16}H_{29}N_2O_5$: 329.2076).

Di-*tert*-butyl *cis*-4,5-Dimethyl-3,6-dioxohexahydropyridazine-1,2-dicarboxylate (12f)

Colorless prisms, mp 100-101 °C (from isopropyl ether). MS (FAB) *m/z*: 343 (MH^+). IR (KBr) cm^{-1}: 1788, 1755 (C=O). ^{1}H-NMR δ: 1.16 (6H, d, *J* = 7.3 Hz, 4- and 5-Me), 1.47 (9H, br s, *t*-Bu), 1.54 (9H, s, *t*-Bu), 2.85-3.03 (2H, m, 4-, 5-H). ^{13}C-NMR δ: 10.5 (q), 27.9 (q), 41.2 (d), 85.3 (s), 147.9 (s), 171.3 (s). *Anal.* Calcd for $C_{16}H_{26}N_2O_6$: C, 56.13; H, 7.65; N, 8.18. Found: C, 56.15; H, 7.54; N, 8.19.

Di-*tert*-butyl *cis*-3,4-Dimethyl-6-oxohexahydropyridazine-1,2-dicarboxylate (11g)

Colorless prisms, mp 74-75 °C (from isopropyl ether). MS (FAB) *m/z*: 329 (MH^+). IR (KBr) cm^{-1}: 1786, 1716 (C=O). ^{1}H-NMR δ: 1.11 (3H, d, *J* = 5.6 Hz, 4-Me), 1.21 (3H, d, *J* = 6.4 Hz, 3-Me), 1.46 (9H, s, *t*-Bu), 1.51 (9H, s, *t*-Bu), 1.65-2.93 (3H, m, 4-H and 5-H_2), 3.80-4.27 (1H, m, 3-H). *Anal.* Calcd for $C_{16}H_{28}N_2O_5$: C, 58.52; H, 8.59; N, 8.53. Found: C, 58.61; H, 8.33; N, 8.55.

Di-*tert*-butyl *cis*-4,6-Dimethyl-3-oxohexahydropyridazine-1,2-dicarboxylate (11h)

Colorless prisms, mp 75-76 °C (from isopropyl ether). MS (FAB) *m/z*: 329 (MH^+). IR (KBr) cm^{-1}: 1786, 1707(C=O). ^{1}H-NMR δ: 1.15 (3H, d, *J* = 6.5 Hz, 4-Me), 1.19 (3H, d, *J* = 6.5 Hz, 6-Me), 1.46 (9H, s, *t*-Bu), 1.53 (9H, s, *t*-Bu), 1.92-2.88 (3H, m, 4-H and 5-H_2), 4.28-4.92 (1H, m, 6-H). *Anal.* Calcd for $C_{16}H_{28}N_2O_5$: C, 58.52; H, 8.59; N, 8.53. Found: C, 58.70; H, 8.45; N, 8.56.

Di-*tert*-butyl 3-Hydroxy-3,6-dimethylhexahydropyridazine-1,2-dicarboxylate (13)

Colorless prisms, mp 98-100 °C (from isopropyl ether). MS *m/z*: 330 (M^+). IR (KBr) cm^{-1}: 3475 (OH), 1741, 1689 (C=O). ^{1}H-NMR δ: 1.01-1.10, 1.34-1.57, 1.69-1.77 and 1.90-2.07 (1H, m, 1H, m, 1H, m and 1H, m, 4- and 5-H_2), 1.14 and 1.15 (total 3H, intensity ratio 3:2, each d, J = 6.6 and 6.2 Hz, 6-Me), 1.45, 1.47, 1.48 and 1.49 (total 18H, intensity ratio 1:2:3:2, each s, *t*-Bu x 2), 1.78 and 1.79 (total 3H, intensity ratio 3:2, 3-Me), 3.30-3.53 and 3.84 (total 1H, intensity ratio 3:2, br and s, OH), 4.07-4.19 and 4.34-4.46 (total 1H, intensity ratio 2:3, 6-H). ^{13}C-NMR δ: 19.4 and 19.9 (each q), 25.5 and 25.7 (each q), 26.7 and 27.2 (each t), 28.2 and 28.25 (each q), 28.31 and 28.4 (each q), 35.7 and 36.8 (each t), 49.3 and 51.7 (each d), 80.7 (s), 81.1 (s), 88.0 and 88.2 (each s), 154.28 and 154.34 (each s), 155.4 (s). *Anal.* Calcd for $C_{16}H_{30}N_2O_5$: C, 58.16; H, 9.15; N, 8.48. Found: C, 58.37; H, 8.83; N, 8.58.

Methyl 2-(1,2-Di-*tert*-butoxycarbonyl)hydrozino-5-oxohexanate (14)

Colorless oil. MS *m/z*: 374 (M^+). IR (neat) cm^{-1}: 3321 (NH), 1743, 1712 (C=O). ^{1}H-NMR δ: 1.46 (18H, s, *t*-Bu x 2), 1.83-2.02 and 2.18-2.34 (each 1H, m, 3-H_2), 2.15 (3H, s, 5-Me), 2.65-2.95 (2H, m, 4-H_2), 3.73 (3H, s, COOMe), 4.62-4.75 and 4.75-4.92 (total 1H, intensity ratio 3:7, each br, 2-H), 6.19-6.29 and 6.37-6.57 (total 1H, intensity ratio 3:7, each br, NH). ^{13}C-NMR δ: 22.4, 22.8 (t), 28.1 (q), 28.2 (q), 30.0 (q), 39.7, 39.8 (t), 52.4 (q), 59.2, 61.2 (d), 81.0 (s), 82.1 (s), 115.2 (s), 115.7 (s), 171.9 (s), 208.3 (s). EI-HR-MS *m/z*: 374.2049 (Calcd for $C_{17}H_{30}N_2O_7$: 374.2053).

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