SYNTHESIS OF 2,3-DIALKOXY-1H-PYRROLE VIA REDUCTION OF DIOXOPYRROLINE WITH SODIUM HYDROSULFITE

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Abstract - Reduction of 1H-pyrrole-2,3-dione (3 and 7) with sodium hydrosulfite took place selectively in a 1,4-manner. Methylation of the product with diazomethane gave 1,5-dihydro-3-methoxy-2H-pyrrol-2-one (5 and 8) in good yield. Treatment of the methyl ether (5 or 8) with triethylxonium tetrafluoroborate caused ethylation of the lactam carbonyl with concomitant deprotonation to give 2,3-dialkoxy-1H-pyrole (9). This conversion provides a simple synthetic method of 2,3-dialkoxy-pyrroles.

The electrophilic property of 1H-pyrrole-2,3-dione (dioxopyrroline) has been shown by its vulnerability to protic solvents. The high reactivity of the ring system towards nucleophiles is attributable to its non-aromatic character. However, the reaction for other nucleophiles except protic solvent is seldom reported.

For reduction of dioxopyrroline, Andreichikov's group3 reported that reaction of 4-benzoyl-1-benzyl-5-phenyl-dioxopyrroline (1) with formamide happened to cause reduction giving 1,5-dihydro-3-hydroxy-2H-pyrrol-2-one (2) in good yield. In this paper we report conversion of dioxopyrrolines into 2,3-dialkoxy-1H-pyrroles via the reduction with hydrosulfite.

\[
\text{PhCO} \; \text{Ph} \; \text{N} \; \text{O} \; \text{Ph} \; \text{CH}_2\text{Ph} \xrightarrow{\text{HCONH}_2} \text{PhCO} \; \text{OH} \; \text{N} \; \text{O} \; \text{Ph} \; \text{CH}_2\text{Ph}
\]

Scheme 1
When a dioxane solution of N-nonsubstituted 4-ethoxycarbonyl-5-phenyldioxopyrrole (3a) was treated with an aqueous solution of large excess of sodium hydrosulfite (about 20 mole equivalent), reduction took place immediately to give a 1,5-dihydro-3-hydroxy-2H-pyrrol-2-one (4a). This was very unstable to air oxidation even in solid state regenerating the dioxopyrrole. Methylation of the crude product with diazomethane (CH₂N₂) gave the methyl ether (5a) in 28% yield, which was stable and fully characterized. The structure of 5a was clarified by spectral data, specially by analogy of the uv spectrum to the known 1,5-dihydro-3-hydroxy-5-methoxy-2H-pyrrol-2-one (6b). In the following experiments the product obtained from reduction of dioxopyrrole was characterized as the corresponding methyl ether after methylation with CH₂N₂.

\[
\begin{align*}
\text{EtOOC} & \quad \text{Na₂S₂O₄} \\
\text{N} & \quad \text{dioxane-H₂O} \\
\text{O} & \\
3 & \\
\text{R} & \\
a: \text{H} \\
b: \text{Me} \\
c: \text{Ph} \\
d: \text{CH₂Ph} \\
\text{EtOOC} & \quad \text{CH₂N₂} \\
\text{N} & \quad \text{Me} \\
4 & \\
\text{CH₂N₂} & \\
5 & \\
\text{R} & \\
a: \text{H} \\
b: \text{Et} \\
\text{EtOOC} & \quad \text{Na₂S₂O₄} \\
\text{N} & \quad \text{dioxane-H₂O} \\
\text{O} & \\
6 & \\
\text{Me} & \\
a: \text{H} \\
b: \text{Et} \\
\text{R} & \\
a: \text{Ph} \\
b: \text{COOEt} \\
\text{R} & \\
a: \text{Ph} \\
b: \text{COOEt} \\
\text{R} & \\
a: \text{H} \\
b: \text{Me} \\
\text{R} & \\
a: \text{Ph} \\
b: \text{COOEt} \\
\text{R} & \\
a: \text{Ph} \\
b: \text{COOEt} \\
\text{Me} & \\
6a: \text{H} \\
b: \text{Et} \\
\text{Me} & \\
7a: \text{Ph} \\
b: \text{COOEt} \\
\text{Me} & \\
8a: \text{Ph} \\
b: \text{COOEt} \\
\end{align*}
\]

Scheme 2

Reaction of N-methyl-, N-phenyl-, and N-benzyldioxopyrrolines (3b, 3c, and 3d) with large excess of sodium hydrosulfite in aqueous dioxane solution caused the same 1,4-reduction to give the 1,5-dihydro-3-methoxy derivatives (5b, 5c, and 5d) in good yield, respectively, as shown in Scheme 2. Reduction of 4-benzyldioxopyrrolines (7a and 7b) with sodium hydrosulfite similarly took place to give the dihydro derivatives (8a and 8b) in 58% and 63% yields, respectively. Thus, sodium hydrosulfite selectively reduced the dioxopyrrole ring in a 1,4-manner to yield 1,5-dihydro-3-hydroxy-2H-pyrrol-2-one regardless of substituent at 1, 4, and 5 positions. The reductant, sodium hydrosulfite, should be used in large excess to
avoid solvolitic change of the dioxopyrroline that could competitively take place in the medium. For example, treatment of 3b in ethanol with an aqueous solution of 1.5 molar eq. of sodium hydrosulfite gave the ethanol adduct (6b) as a major product (23%) along with the water adduct (6a) (1.5%) and the reduced product (5b) (15%). On the other hand, reduction of 3a in ethanol with 20 molar eq. of sodium hydrosulfite gave 5a in 50% yield, no solvolytic product being isolated from the latter reaction.

Reduction of the dioxopyrroline (3) with other reducing methods such as sodium borohydride in ethanol, tetra-n-butylammonium borohydride in dichloromethane, and lithium borohydride in THF gave, after methylation with CH$_2$N$_2$, the methyl ether (5) in 2-15% yield and no other characterizable products were isolated from their reaction mixture. For example, reduction of 3a and 3b with tetra-n-butylammonium borohydride in dichloromethane gave 5a and 5b in 8% and 16% yield, respectively. A major reason decreasing the yield in hydride reductions may be due to over reduction, although no evidence was available.

The 1,5-dihydro-3-methoxy-2H-pyrrol-2-ones (5 and 8) were readily converted into the 2,3-dialkoxy-1H-pyrroles (9). Treatment of 5 or 8 with triethyloxonium tetrafluoroborate (Meerwein reagent) in dichloromethane at room temperature gave the 2-ethoxy-3-methoxy-1H-pyrrole (9) in good yield as shown in Scheme 3. The formation of pyrrole is rationalized in terms of 1,5-hydride shift and/or deprotonation from the iminium ion (10) formed by O-ethylation of lactam carbonyl with Meerwein reagent.

Scheme 3

**EXPERIMENTAL**

Unless otherwise stated, the following procedures were adopted. All melting points were taken on a Yanagimoto micro hot-stage melting point apparatus and are uncorrected. Ir spectra were measured with a Hitachi 260-10 and are given in $\nu_{\text{max}}$ cm$^{-1}$. Uv spectra were measured with a Hitachi 200-10 spectrophotom...
tometer in dioxane and given in $\lambda_{\text{max}}$ nm ($\varepsilon$). Nmr spectra were taken on a JEOL FX-100 NMR spectrometer ($^1$H; 100 MHz, $^{13}$C; 25.0 MHz) in CDCl$_3$ using tetramethylsilane (TMS) as an internal standard. The chemical shifts are given in $\delta$ values. Low resolution mass spectra (LRms) and high resolution mass spectra (HRms) were determined with a JEOL JMS-D 300 spectrometer at 30 eV.

**Reduction of Dioxopyrroline (1) with Sodium Hydrosulfite (General Procedure)** A freshly prepared solution of sodium hydrosulfite (20 mol eq.) in hot water (50 ml) was added in one portion to a solution of dioxopyrroline (3 or 7) (1 g, 2.83-4.08 mmol) in dioxane (50 ml), and the resulting solution was stirred at room temperature for 30 min. After filtration of insoluble materials, the filtrate was concentrated in vacuo and extracted with CH$_2$Cl$_2$. The extract was washed with water, dried over Na$_2$SO$_4$, and concentrated in vacuo to afford a crystalline powder, which was dissolved in CH$_2$Cl$_2$ and methylated by the addition of an excess ethereal CH$_2$N$_2$ to give 5 or 8 after usual work-up procedure and purification by SiO$_2$ column chromatography.

**5a:** 528 mg (28%). Colorless prisms from acetone-ether, mp 130-132.5$^\circ$C. Ir (Nujol): 3180, 3080, 1730, 1710, 1640. $^1$H-Nmr: 1.09 (3H, t, $J=7$ Hz, CO$_2$CH$_2$CH$_3$), 4.06 (2H, q, $J=7$ Hz, CO$_2$CH$_2$CH$_3$), 4.28 (3H, s, OCH$_3$), 5.24 (1H, br s, NC$_2$Ph), 7.28 (5H, s, ArH). $^{13}$C-Nmr: 13.9 (q), 58.0 (d), 60.2 (q), 60.6 (t), 118.8 (s), 127.3 (dx2), 129.5 (d), 128.5 (dx2), 136.5 (s), 153.2 (s), 161.9 (s), 167.1 (s). Uv: 248 (11500). LRms ($m/z$): 261 (M+). Anal. Calcd for C$_{14}$H$_{11}$NO$_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.45; H, 5.65; N: 5.20.

**5b:** 713 mg (67%). Colorless prisms from AcOEt-hexane, mp 75-76$^\circ$C. Ir (Nujol): 1720, 1700, 1600. $^1$H-Nmr: 1.08 (3H, t, $J=7$ Hz, CO$_2$CH$_2$CH$_3$), 2.76 (3H, s, N-CH$_3$), 4.05 (2H, dq, $J=1$ and 7 Hz, CO$_2$CH$_2$CH$_3$), 4.33 (3H, s, OCH$_3$), 5.02 (1H, s, NCH$_2$Ph), 7.0-7.65 (5H, m, ArH). $^{13}$C-Nmr: 13.9 (q), 27.73 (q), 60.1 (q), 60.5 (t), 63.4 (d), 116.8 (s), 127.6 (d), 128.4 (dx2), 135.2 (s), 153.9 (s), 161.8 (s), 164.6 (s). Uv: 247 (12000). LRms ($m/z$): 275 (M+), 202 (base peak). HRms ($m/z$): Calcd for C$_{15}$H$_{17}$NO$_4$ (M+): 275.1154. Found: 275.1143

**5c:** 732 mg (70%). Colorless needles from AcOEt-hexane, mp 82-83$^\circ$C. Ir (KBr): 1688, 1649, 1600. $^1$H-Nmr (90 MHz): 1.14 (3H, t, $J=7$ Hz, CO$_2$CH$_2$CH$_3$), 4.11 (2H, q, $J=7$ Hz, CO$_2$CH$_2$CH$_3$), 4.35 (3H, s, OCH$_3$), 5.74 (1H, s, NCH$_2$Ph), 6.9-7.5 (5H, m, ArH), 7.21 (5H, s, ArH). $^{13}$C-Nmr: 14.0 (q), 60.3 (q), 60.8 (t), 62.4 (d), 117.3 (s), 122.7 (dx2), 125.8 (d), 127.7 (dx2), 128.5 (dx2), 128.8 (dx2), 136.3 (s), 152.5 (s), 161.8 (s), 163.8 (s). Uv: 225 (13800), 256 (11000), 286 (6200, sh). LRms ($m/z$): 337 (M+), 264 (base peak). HRms ($m/z$): Calcd for C$_{20}$H$_{19}$NO$_4$ (M+): 337.1311. Found: 337.1301.
5d: 581 mg (56%). Colorless needles from ether-hexane, mp 61-62°C. Ir (KBr): 1692, 1636. 1H-Nmr (90 MHz): 1.02 (3H, t, J=7 Hz, CO2CH2CH3), 3.50, 5.12 (each 1H, d, J=15 Hz, NCH3Ph), 4.00 (2H, dq, J=1 and 7 Hz, CO2CH2CH3), 4.36 (3H, s, OCH3), 4.92 (1H, s, NCH3Ph), 7.0-7.6 (10H, m, Ar-H). 13C-Nmr: 13.9 (q), 44.0 (t), 60.2 (q), 60.5 (l), 60.7 (d), 117.2 (s), 127.8 (d), 128.0 (dx3), 128.5 (dx2), 128.8 (dx4), 135.0 (s), 136.4 (s), 135.3 (s), 161.8 (s), 164.5 (s). Uv: 246 (12000). LRms (m/z): 351 (M+), 91 (base peak). HRms (m/z): Calcd for C21H19N04 (M+): 351.1470. Found: 351.1480.

8a: 714 mg (68%). Colorless needles from CHCl3, mp 177-178°C. Ir (KBr): 1696, 1626, 1603. 'H-Nmr (90 MHz): 3.95 (3H, s, OCH3), 6.06 (lH, s, NCHPh), 7.0-7.8 (15H, m, ArH). 13C-Nmr: 60.0 (q), 62.7 (d), 119.8 (s), 122.0 (d), 125.5 (d), 126.2 (d), 127.0 (dx2), 128.8 (dx3), 128.9 (dx3), 129.1 (dx3), 133.4 (d), 134.7 (s), 136.4 (s), 137.6 (s), 148.8 (s), 162.4 (s), 190.6 (s). Uv: 262 (14200), 322 (6400, sh). LRms (m/z): 369 (M*), 105 (base peak). HRms (m/z): Calcd for C24H19NO3 (M+): 369.1365. Found: 369.1395.

Reduction of 3a with Sodium Hydrosulfite in EtOH A freshly prepared solution of sodium hydrosulfite (14.3 g, 20 mol eq.) in hot water (50 ml) was added to a solution of 3a (1 g, 4.08 mmol) in EtOH (70 ml), and the resulting solution was stirred at room temperature for 2 h. After removal of insoluble materials, the filtrate was concentrated in vacuo to dryness to afford a crude gum. Methylation of this with CH2N2 in CH2Cl2 and chromatography of the product over SiO2 gave 5a (528 mg, 50%).

Reduction of 3b with Sodium Hydrosulfite in EtOH A freshly prepared solution of sodium hydrosulfite (0.62 g, 1 mol eq.) in hot water (5 ml) was added to a solution of 3b (1 g, 3.86 mmol) in EtOH (40 ml) and ether (40 ml) at room temperature. After 30 min, a solution of sodium hydrosulfite (0.3 g, 0.5 mol eq.) in hot water (0.5 ml) was further added to this mixture, and the mixture was stirred at room temperature for 30 min. After removal of insoluble materials by filtration, filtrate was diluted with CH2Cl2, washed with water, dried over Na2SO4, and concentrated in vacuo to give a crude product (652 mg). This was methylated with CH2N2 and the product was purified by MPLC eluting with AcOEt-hexane (1:2) to give the ethanol-adduct (6b) (285 mg, 23%) as a pale yellow oil.2 The reduced product
Reduction of 3a or 3b with Tetra-n-butylammonium Borohydride  

Tetra-n-butylammonium borohydride (530 mg, 0.5 mol eq. for 3a and 496 mg, 0.5 mol eq. for 3b) was added to a solution of 3a or 3b (1.0 g) in dry CH$_2$Cl$_2$ (40 ml) at -40°C with stirring. After 1 min, excess hydride was decomposed by addition of ice-water. The mixture was extracted with CH$_2$Cl$_2$. The organic extract was washed with brine, dried over Na$_2$SO$_4$, and concentrated in vacuo to afford the crude product which was treated with CH$_2$N$_2$. After a usual work-up, the product was filtered through a short SiO$_2$ column eluting with AcOEt-hexane (1:1), and the eluate was purified by MPLC [AcOEt-hexane (1:1)] to give 5a (86 mg, 8.0%) or 5b (169 mg, 16%).

Synthesis of 2,3-Dialkoxy-1H-pyrrole (9) (General Procedure)  

An excess triethyloxonium tetrafluoroborate (Et$_3$OBF$_4$) and anhydrous K$_2$CO$_3$ (50-100 mg) was added to a solution of 5 or 8 (80-300 mg) in dry CH$_2$Cl$_2$ (10-40 ml), and the resulting solution was stirred at room temperature under argon atmosphere for 15-48 h. The mixture was poured into 5% NaHCO$_3$ (20-40 ml), and the whole was extracted with CH$_2$Cl$_2$, washed with water, and dried over Na$_2$SO$_4$. After evaporation of the solvent in vacuo, the residue was purified by column chromatography on SiO$_2$ [elution with AcOEt-hexane (1:3) and (1:1)].

9a: 276 mg (76%) from 330 mg (1.26 mmol) of 5a. Colorless prisms from ether-hexane, mp 131-134°C.  

Ir (Nujol): 3180, 1660, 1610, 1590.  

1H-Nmr: 1.22, 1.37 (each 3H, t, J=7 Hz, OCH$_2$CH$_3$), 3.86 (3H, s, OCH$_3$), 4.22, 4.23 (each 2H, q, J=7 Hz, OCH$_2$CH$_3$), 7.1-7.6 (5H, m, ArH), 7.1 (1H, br s, NH).  

13C-Nmr: 14.1 (q), 15.4 (q), 60.0 (t), 62.5 (q), 69.8 (t), 104.6 (s), 125.4 (s), 127.7 (d), 128.0 (dx3), 128.7 (d), 129.8 (s), 132.4 (s), 134.8 (s), 164.2 (s).  


9b: 151 mg (69%) from 200 mg (0.73 mmol) of 5b as a colorless oil. Ir (Film): 1690, 1600, 1590.  

1H-Nmr: 1.00, 1.33 (each 3H, t, J=7 Hz, OCH$_2$CH$_3$), 3.13 (3H, s, NCH$_3$), 3.79 (3H, s, OCH$_3$), 4.01, 4.17 (each 2H, q, J=7 Hz, OCH$_2$CH$_3$), 7.1-7.4 (5H, m, ArH).  

13C-Nmr: 14.0 (q), 15.5 (q), 29.5 (q), 59.1 (t), 62.5 (q), 69.9 (t), 103.9 (s), 127.8 (dx2), 127.9 (s), 129.4 (s), 130.8 (dx3), 131.9 (s), 135.1 (s), 164.0 (s).  

Uv: 234 (10500), 300 (6100). LRms (m/z): 303 (M$^+$), 274 (base peak). HRms (m/z): Calcd for C$_{17}$H$_{21}$NO$_4$ (M$^+$): 303.1471. Found: 303.1472.
9c: 300 mg (85%) from 275 mg (0.82 mmol) of 5c as a dark orange oil. Ir (Film): 1707, 1613, 1601. 1H-Nmr: 1.17 (6H, t, J=7 Hz, OCH2CH3), 3.94 (3H, s, OCH3), 3.96, 4.15 (each 2H, q, J=7 Hz, OCH2CH3), 7.0-7.4 (5H, m, ArH), 7.15 (5H, s, ArH). 13C-Nmr: 14.0 (q), 15.1 (q), 59.5 (q), 62.3 (t), 70.6 (t), 105.3 (s), 127.2 (dx3), 127.3 (d), 127.9 (s), 128.4 (dx3), 130.5 (s), 131.2 (dx3), 131.4 (sx2), 135.8 (s), 164.0 (s). Uv: 240 (16800), 301 (6900). LRms (m/z): 365 (M+), 336 (base peak). HRms (m/z): Caled for C22H23NO4 (M+): 365.1627. Found: 365.1660.

9d: 62 mg (72%) from 80 mg (0.23 mmol) of 5d as a yellow oil. Ir (Film): 1707, 1613, 1601. 1H-Nmr: 1.05, 1.20 (each 3H, t, J=7 Hz, OCH2CH3), 3.87 (3H, s, OCH3), 4.07, 4.08 (each 2H, q, J=7 Hz, OCH2CH3), 4.81 (2H, s, N-C6H5-Ph), 6.8-7.4 (10H, m, ArH). 13C-Nmr: 14.0 (q), 15.4 (q), 46.1 (t), 59.2 (t), 62.6 (q), 69.7 (t), 104.6 (s), 126.3 (dx3), 127.1 (d), 127.7 (dx2), 128.0 (s), 128.3 (dx2), 129.3 (s), 131.0 (dx2), 131.8 (s), 135.4 (s), 138.0 (s), 163.9 (s). Uv: 232 (13200), 296 (5700). LRms (m/z): 379 (M+). HRms (m/z): Caled for C23H25N04 (M+): 379.1781. Found: 379.1781.

9e: 94 mg (84%) from 100 mg (0.27 mmol) of 8a as a yellow oil. Ir (CH2Cl2): 1752, 1640, 1601. 1H-Nmr: 1.13 (3H, t, J=7 Hz, OCH2CH3), 3.74 (3H, s, OCH3), 3.97 (2H, q, J=7 Hz, OCH2CH3), 6.8-7.9 (10H, m, ArH), 6.96 (5H, s, ArH). 13C-Nmr: 15.4 (q), 62.1 (q), 70.7 (t), 114.4 (s), 126.3 (s), 126.9 (d), 127.4 (dx2), 127.6 (dx2), 128.0 (d), 128.3 (dx3), 128.5 (dx2), 129.7 (s, dx2), 130.7 (s, dx2), 131.8 (d), 135.5 (s), 136.0 (s), 139.0 (s), 192.0 (s). Uv: 240 (18300), 278 (15200), 350 (2800, sh). LRms (m/z): 397 (M+), 368 (base peak). HRms (m/z): Caled for C26H23N03 (M+): 397.1676. Found: 397.1651.

9f: 147 mg (64%) from 215 mg (0.59 mmol) of 8b as light yellow prisms from ether-hexane, mp 38-39°C. Ir (Film): 1715, 1667, 1599. 1H-Nmr: 0.66, 1.16 (each 3H, t, J=7 Hz, OCH2CH3), 3.73, 4.11 (each 2H, q, J=7 Hz, OCH2CH3), 3.75 (3H, s, OCH3), 7.2-8.1 (10H, m, ArH). 13C-Nmr: 13.3 (q), 15.2 (q), 60.0 (t), 62.7 (q), 70.2 (t), 109.8 (s), 122.6 (s), 127.9 (dx2), 128.3 (dx3), 128.5 (dx3), 129.4 (d), 130.4 (s), 133.0 (d), 136.3 (s), 138.3 (s), 139.8 (s), 159.2 (s), 192.7 (s). Uv: 250 (18900), 279 (14100). LRms (m/z): 393 (M+). HRms (m/z): Caled for C23H23NO5 (M+): 393.1574. Found: 393.1554.

REFERENCES

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