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TETRAHEDRON

A New and Novel Amide Bond Cleavage of *N*-Methoxymethyl-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones by Hydride Reduction via 3-Aza-Grob Fragmentation

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Abstract: A novel amide bond cleavage of *N*-methoxymethylpyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones by hydride reduction in high yield is described. MOM-protected dilactams **1** undergo ring-opening when treated with metal hydride via 3-aza-Grob fragmentation.

The pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones are key intermediates in the synthesis of pyrrolo[2,1-*c*][1,4]benzodiazepines (PBDs), an interesting group of antitumor antibiotics with significant biological activity.[1] These drugs show sequence selectivity and exhibit potent antitumor activity.[2-3] A variety of approaches have been developed for the synthesis of DNA-interactive PBDs.[4] Among them, hydride reduction of a cyclic dilactam seems to be a very straightforward method. Nevertheless, this method has been shown to have restrictions.[5]

The results reported here provide insights into the study of the hydride reduction of MOM-protected dilactams (**1**). Reduction of compounds of type **1** with lithium aluminum hydride in THF at -60 °C or with sodium borohydride in ethanol at 0 °C was carried out. Surprisingly, the corresponding imines or carbinolamines were not obtained but the overreduction products with a methyl group attached to the nitrogen (**4**) were formed (Scheme 1). The results presented in Table 1 show that the reactions occur in high yield whether electron donating or accepting groups are present in the aromatic ring of the PBD. The chemical shifts of the methyl protons are in the typical range (2.68~2.93 ppm). More impressively, some of them are coupled to the amino proton (entry a, c and e). This is often observed for a CH-NH-C- moiety (such as aromatic amines, enamines, etc.). For instance, the cross-peak (arrowhead) at 2D COSY of **4e** shown in figure 1 indicates that the methyl proton is coupled with the amino proton (coupling constant is 4.4 Hz). Single-crystal X-ray diffraction analysis of crystalline pyrrolidine **4c** (mp 166~168 °C) shown in figure 2 confirms our structure assignment for this series of compounds.[6]

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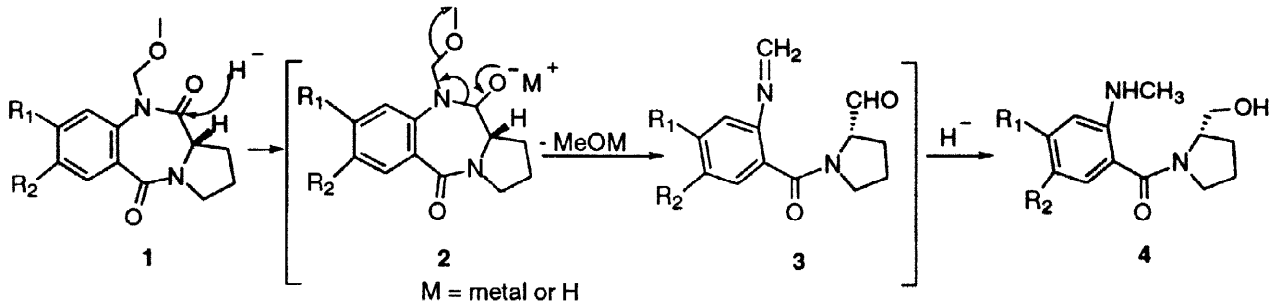


Scheme1. Hydride reduction of *N*-methoxymethylpyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones (**1**).

Table 1. Products (**4**) of hydride reduction of *N*-methoxymethylpyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones (**1**) via aza-Grob fragmentation.

entry	R_1	R_2	δ[a]	yield (%)
a	Cl	H	2.80 (d, 4.0 Hz)[b]	82
b	H	Cl	2.78 (s)	80
c	H	NO_2	2.93 (d, 5.1 Hz)	86
d	H	NH_2	2.75 (s)	72
e	NO_2	H	2.91 (d, 4.4 Hz)	85
f	NH_2	H	2.77 (s)	80
g	OCH_2Ph	OMe	2.68 (s)	75

a) chemical shifts of methyl group attached to nitrogen. δ was determined using a Varian Unity Plus 400 MHz ^{1}H-NMR. b) d: doublet; s: singlet.

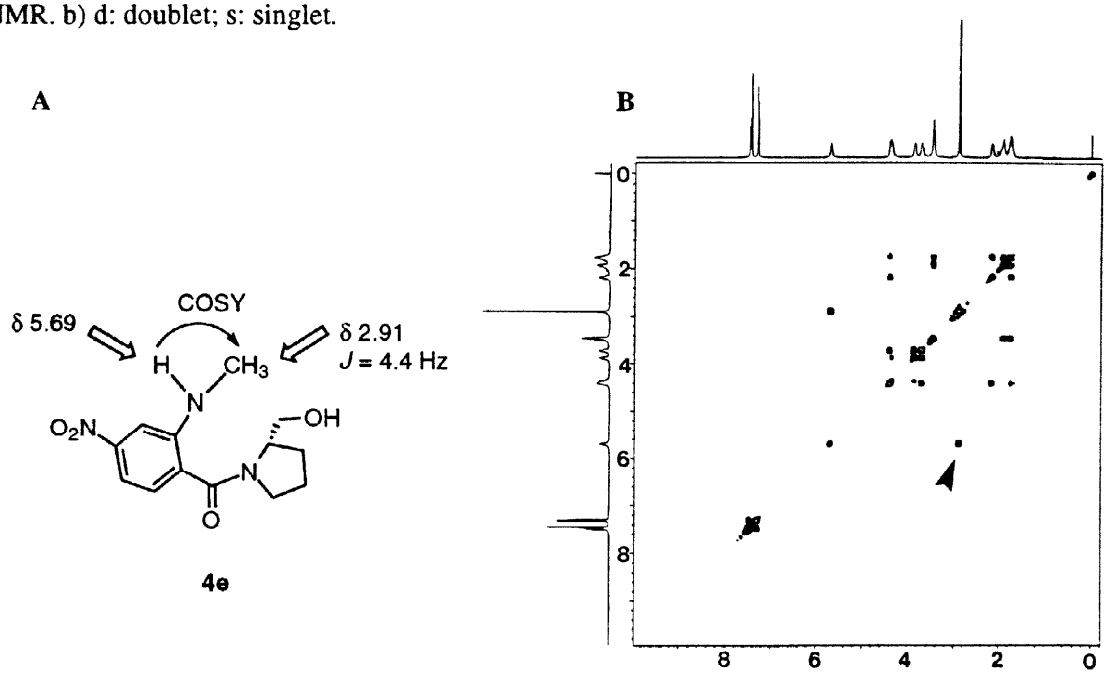


Figure 1. (A) The structure of pyrrolidine (**4e**). (B) 2D magnitude COSY contour plot of **4e**. Arrowhead denotes the scalar coupling between amino proton and methyl group.

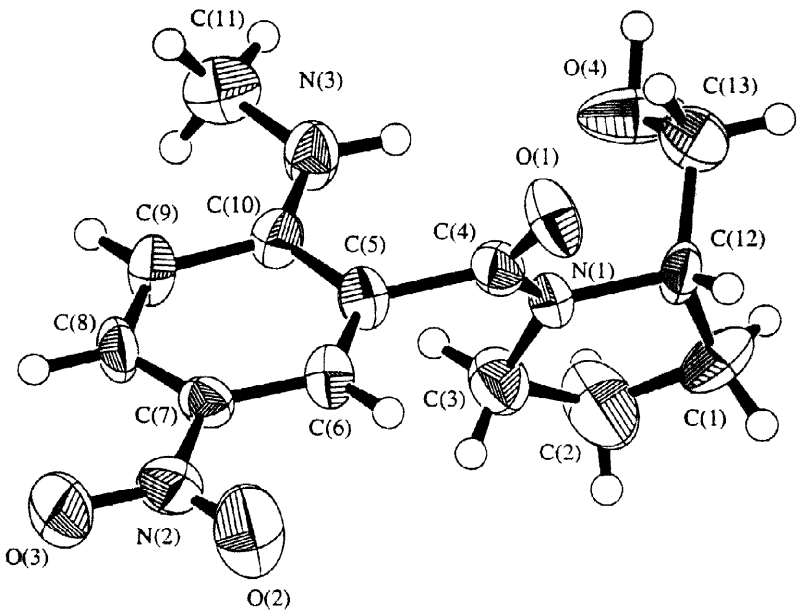
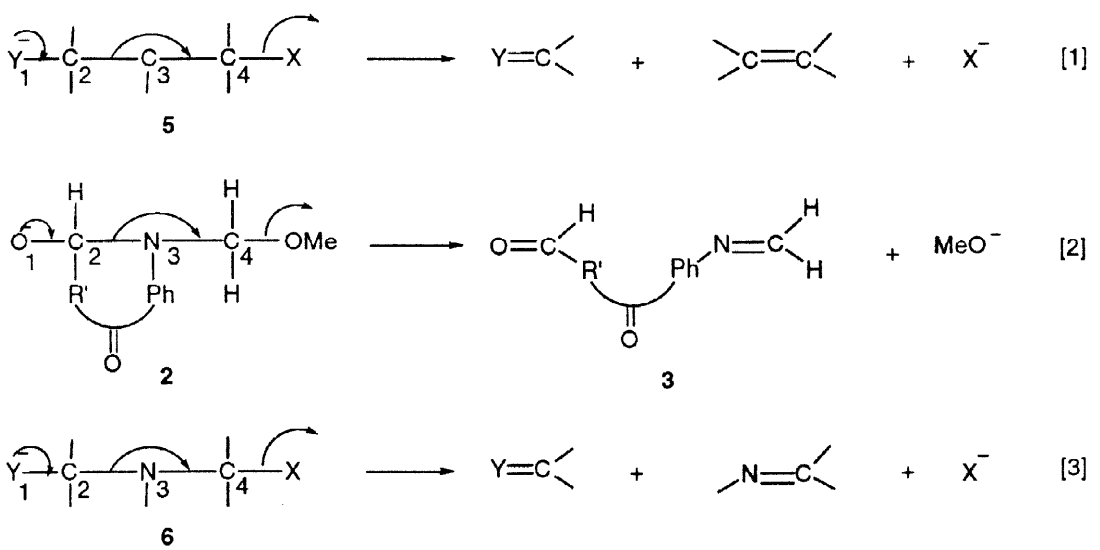


Figure 2. X-ray crystallographic structure of **4c**.

Based upon the products obtained, we propose the reaction mechanism shown in Scheme 1. $NaBH_4$ or LAH must serve as both a reducing agent and basic initiator. Once the secondary alcohol (**2**) is formed it must undergo fragmentation to give the imine aldehyde (**3**), although attempts to isolate this intermediate (**3**) have failed. However, under the reductive conditions, compound **3** would be converted rapidly to the saturated amino alcohol (**4**). This intriguing mechanism is similar to those of Grob[7] or Wharton fragmentations[8] as shown in Scheme 2. In Grob fragmentations (equation 1 of Scheme 2), systems such as compound **5** containing a nucleophilic atom with a negative charge or an unshared electron pair and a leaving group in a 1,4 relationship undergo a heterolytic fragment process. Reactions involving cyclic 1,3-diol derivatives are referred



Scheme 2. Grob and Wharton fragmentation (eq. 1) and aza type fragmentation (eq. 2 and 3).

to as a Wharton fragmentations. Nevertheless, to our knowledge, Grob or Wharton fragmentation systems bearing a nitrogen in the 3-position with the same electrofuge and nucleofuge have not yet been reported.[7,8] The Scheme 1, 2 (equations 2 and 3) and Table 1 illustrate specific examples of 3-aza-Grob fragmentation by hydride reduction of a MOM-protected dilactam.

In conclusion, the results reported here suggest that the novel 3-aza-Grob fragmentation may account for the observed reaction. We are continuing to investigate the generality of this type of reaction.

EXPERIMENTAL SECTION

Melting points were determined on a Yanaco MP apparatus and uncorrected. Infrared spectra were recorded on Perkin-Elmer Series 2000 spectrophotomer. ^{1}H NMR and ^{13}C NMR were recorded using Varian Unity Plus 400 (400 MHz) spectrometer. ^{1}H NMR chemical shifts are referenced to TMS or $CDCl_3$ (7.26 ppm). ^{13}C NMR was referenced to $CDCl_3$ (77.0 ppm) and the results of multiplicity are recorded as s, d, t, q. Low resolution mass spectra were recorded on a JOEL SX-102A spectrometer and high resolution mass spectroscopy (HRMS) were recorded on a JOEL JMX-HX 110 spectrometer. Elemental analysis were performed on a Hereus NCH rapid analyzer. Analytical TLC was carried out on precoated 0.25mm thick Merck 60 F_{254} silica plates. Flash chromatography was carried out using Merck Silica Gel 60 (230-400 mesh).

General procedure for hydride reduction of *N*-methoxymethylpyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones (1):

To a solution of compound **1** (0.2 mmol) in dry EtOH (3 mL) was added sodium borohydride (0.8 mmol) in one portion and the mixture was stirred at 0 °C until TLC (40:1 CH_2Cl_2-MeOH) revealed no more starting material. The solution was diluted with CH_2Cl_2 and washed twice with water. The combined aqueous phases were extracted three times with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and concentrated under vacuum. The crude product was subjected to flash chromatography (40:1 CH_2Cl_2-MeOH) to give compound **4**.

N-(2-methylamino-4-chlorobenzoyl)-2-hydroxymethylpyrrolidine (4a):

Yield 82%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.09 (d, J = 8 Hz, 1H), 6.61~6.57 (m, 2H), 5.71 (br s, NH), 4.78 (br s, 1H), 4.34 (br s, 1H), 3.78 (br s, 1H), 3.66 (br s, 1H), 3.50~3.40 (m, 2H), 2.80 (d, J = 4.0 Hz, 3H), 2.14~2.08 (m, 1H), 1.86~1.83 (m, 1H), 172 (br s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.7 (s), 148.7 (s), 137.0 (s), 128.9 (d), 117.8 (s), 114.8 (d), 110.4 (d), 65.3 (t), 60.2 (d), 50.6 (t), 29.7 (q), 27.9 (t), 24.6 (t). IR (neat) 3382, 2970,1622, 1576, 1521, 1400, 1092 cm^{-1}. LRMS (EI, *m/z*) 268 (M^+), 237, 170, 168, 70; HRMS (EI, *m/z*) for $C_{13}H_{17}N_2ClO_2$, calcd 268.0979, found 268.0979.

N-(2-methylamino-5-chlorobenzoyl)-2-hydroxymethylpyrrolidine (4b):

Yield 80%.^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.21 (dd, J = 8.8 and 2.4 Hz, 1H), 7.15 (d, J = 2.4 Hz, 1H), 6.58 (d, J = 8.8 Hz, 2H), 5.40 (br s, NH), 4.62 (br s, 1H), 4.36 (br s, 1H), 3.80 (br s, 1H), 3.69 (br s, 1H), 3.52~3.43 (m, 2H), 2.78 (s, 3H), 2.16~2.10 (m, 1H), 1.89~1.88 (m, 1H), 178~1.73 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.4 (s), 146.1 (s), 130.8 (d), 127.3 (d), 120.9 (s), 120.0 (s), 66.0 (t), 60.7 (d), 50.8 (t), 30.1 (q), 27.9 (t), 28.2 (t), 24.7 (t). IR (neat) 3400, 2970,1622, 1452, 1171 cm^{-1}. LRMS (EI, *m/z*) 268 (M^+), 237, 170, 168, 70; HRMS (EI, *m/z*) for $C_{13}H_{17}N_2ClO_2$, calcd 268.0979, found 268.0976.

***N*-(2-methylamino-5-nitrobenzoyl)-2-hydroxymethylpyrrolidine (4c):**
Yield 86%. Yellow crystals; mp 166~168°C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.20~8.16 (m, 2H), 6.79 (br s, NH), 6.64 (d, J = 9.2 Hz, 1H), 4.41 (br s, 1H), 4.15 (br s, 1H), 3.85~3.74 (m, 2H), 3.63~3.60 (m, 2H), 2.94 (d, J = 4.8 Hz, 3H), 2.23~2.16 (m, 1H), 1.97~1.92 (m, 1H), 181~1.64 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.9 (s), 153.0 (s), 135.9 (s), 127.9 (d), 125.3 (d), 117.1 (s), 109.7 (d), 66.4 (t), 61.4 (d), 51.4 (t), 29.9 (q), 27.9 (t), 28.3 (t), 25.0 (t). IR ($CHCl_3$) 3372, 3000, 1627, 1590, 1452 cm^{-1}. LRMS (FAB, *m/z*) 280 [(M + H)$^+$], 264, 248, 179, 136, 105; HRMS (FAB, *m/z*) for $C_{13}H_{18}N_3O_4$ [(M + H)$^+$], calcd 280.1297, found 280.1297. Anal. Calcd for $C_{13}H_{17}N_3O_4$: C, 55.91; H, 6.14; N, 15.05. Found: C, 55.92; H, 6.10; N, 14.97.

***N*-(2-methylamino-5-aminobenzoyl)-2-hydroxymethylpyrrolidine (4d):**
Yield 72%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.70 (dd, J = 8.8 and 2.8 Hz, 1H), 6.79 (br s, 1H), 6.60~6.55 (m, 2H), 4.35 (br s, 1H), 4.05~3.90 (m, 4H), 3.79 (br s, 1H), 3.67 (br s, 1H), 3.58~3.40 (m, 2H), 2.75 (s, 3H), 2.20~2.05 (m, 1H), 1.84 (br s, 1H), 180~1.60 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.8 (s), 140.4 (s), 136.2 (s), 121.9 (s), 118.8 (d), 115.1 (d), 112.5 (d), 66.5 (t), 60.7 (d), 50.7 (t), 30.8 (q), 28.4 (t), 24.7 (t). IR (neat) 3524, 3019, 1722, 1620, 1429, 1354, 1207 cm^{-1}. LRMS (FAB,*m/z*) 250 [(M + H)$^+$], 249, 189, 149, 109; HRMS (FAB,*m/z*) for $C_{13}H_{20}N_3O_2$ [(M + H)$^+$], calcd 250.1555, found 250.1555.

***N*-(2-methylamino-4-nitrobenzoyl)-2-hydroxymethylpyrrolidine (4e):**
Yield 85%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.49 (dd, J = 8.3 and 2.0 Hz, 1H), 7.46 (d, J = 2.0 Hz, 1H), 7.31 (d, J = 8.3 Hz, 1H), 5.69 (br s, NH), 4.43~4.23 (m, 2H), 3.86 (br s, 1H), 3.75~3.73 (m, 1H), 3.49~3.47 (m, 2H), 2.91 (d, J = 4.4 Hz, 3H), 2.23~2.15 (m, 1H), 2.00~1.90 (m, 1H), 189~1.63 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.6 (s), 150.0 (s), 148.5 (s), 128.4 (d), 110.0 (d), 105.2 (d), 66.6 (t), 61.2 (d), 50.9 (t), 20.9 (q), 28.4 (t), 24.9 (t). IR (neat) 3393, 2939, 1728, 1632, 1540, 1460, 1354, 1227 cm^{-1}. LRMS (FAB, *m/z*) 280 [(M + H)$^+$], 264, 248, 179, 136, 133; HRMS (FAB, *m/z*) for $C_{13}H_{18}N_3O_4$ [(M + H)$^+$], calcd 280.1297, found 280.1299.

***N*-(2-methylamino-4-aminobenzoyl)-2-hydroxymethylpyrrolidine (4f):**
Yield 80%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.04 (d, J = 8.0 Hz, 1H), 5.94 (dd, J = 8.0 and 2.0 Hz, 1H), 5.92 (d, J = 2.0 Hz, 1H),, 4.32 (d, J = 4.4 Hz, 1H), 4.05~3.90 (m, 4H), 3.79 (br s, 1H), 3.77~3.40 (m, 3H), 2.77 (s, 3H), 2.10~2.00 (m, 1H), 1.85~1.80 (m, 1H), 170~1.56 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.2 (s), 150.8 (s), 149.9 (s), 130.5 (s), 108.9 (s), 101.9 (d), 96.2 (d), 67.6 (t), 61.1 (d), 51.8 (t), 29.8 (q), 28.6 (t), 25.1 (t). IR (neat) 3453, 2929, 1687, 1611, 1530, 1460, 1374, 1278 cm^{-1}. LRMS (FAB, *m/z*) 250 [(M + H)$^+$], 249, 149, 105; HRMS (FAB, *m/z*) for $C_{13}H_{20}N_3O_2$ [(M + H)$^+$], calcd 250.1555, found 250.1556.

***N*-(2-methylamino-4-benzyloxy-5-methoxybenzoyl)-2-hydroxymethylpyrrolidine (4g):**
Yield 75%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43~7.27 (m, 5H), 6.80 (s, 1H), 6.23 (s, 1H), 5.15 (s, 2H), 4.33 (d, J = 5.0 Hz, 1H), 3.77~3.72 (m, 4H), 3.66~3.55 (m, 2H), 3.49~3.46 (m, 1H), 2.68 (s, 3H), 2.10~2.09 (m, 1H), 1.82~1.81 (m, 1H), 1.66~1.64 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.6 (s),

151.4 (s), 144.2 (s), 139.5 (s), 136.6 (s), 128.3 (d), 127.7 (d), 127.1 (d), 114.5 (d), 110.7 (s), 98.0 (d), 70.6 (t), 66.0 (t), 60.4 (d), 57.4 (q), 50.8 (t), 30.2 (q), 28.1 (t), 25.0 (t). **IR (neat)** 3383, 2929, 1732, 1617, 1585, 1520, 1399, 1223 cm^{-1}. LRMS (EI, *m/z*) 370 (M^+), 270, 251, 150, 91; **HRMS (EI,** *m/z*) for $C_{21}H_{26}N_2O_4$, calcd 370.1894, found 370.1896.

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(6) *Crystal data* for **4c**: $C_{13}H_{17}N_3O_4$, M = 279.29, orthorhombic, space group, $P2_12_12_1$, a = 9.792(2), b = 18.821(4), c = 7.432(2) Å, V = 1369.7(4)Å^3, Z = 4. Dc = 1.354 g/cm^3, T = 276 K. absorption coefficient: μ(Mo-Kα) = 1.0 cm^{-1}, diffractometer: Rigaku AFC6S, scan type: ω-2θ, $2\theta_{max}$ = 50.1°. 1446 reflections measured, 932 observed reflections (I>3.00σ(I)), residuals: R = 0.058, Rw = 0.031. The unit-cell parameters were determined by a least-aquares refinement on diffractometer angles for 24 (17.52-27.00°) automatically centred reflections. The crystal structure was solved by directed methods. Atomic parameters, bond lengths, bonds angles and torsion angles have been deposited at the Cambridge Crystallographic Data Center.

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