Novel Examples of 3-Aza-Grob Fragmentation

Wan-Ping Hu, Jeh-Jeng Wang,* and Pei-Ching Tsai

School of Chemistry, Kaohsiung Medical University, Kaohsiung City 807, Taiwan, ROC

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Heterolytic fragmentation is widespread and serves as a useful reaction in organic synthesis.[1] We have previously reported[2] that an unusual heterocyclic fragmentation reaction occurs in the hydride reduction of *N*-methoxymethylpyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones, synthetic intermediates to a family of anticancer DNA alkylating agents known as pyrrolo[2,1-*c*]benzodiazepines. We postulated that this reaction proceeds via 3-aza-Grob fragmentation[3−9] as shown in Scheme 1.

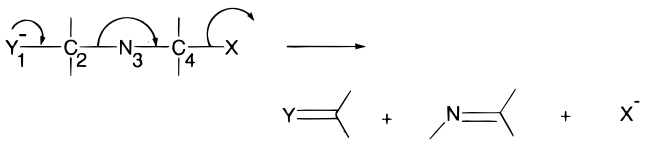
We recently extended our studies to ether-protected aromatic lactams with five- and six-membered rings. The results showed that hydride reduction of MOM-, MEM-, SEM-, and BOM-protected oxindole analogues gave ring-opening products via the same path as seven-membered ring lactams, *N*-methoxymethylpyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones, in excellent yields.[10]

Intrigued by the reductive fragmentation, we decided to further investigate the scope and limitations of this reaction. We designed and synthesized novel substrates for fragmentation studies. THF (tetrahydrofuranyl)[11] and THT (tetrahydrothienyl)[12] protected 3,4-dihydro-2(1*H*)-quinolinones were prepared in excellent yields as shown in Scheme 2. Table 1 summarizes the results for the optimization study of 3-aza-Grob fragmentation using various hydride reagents.

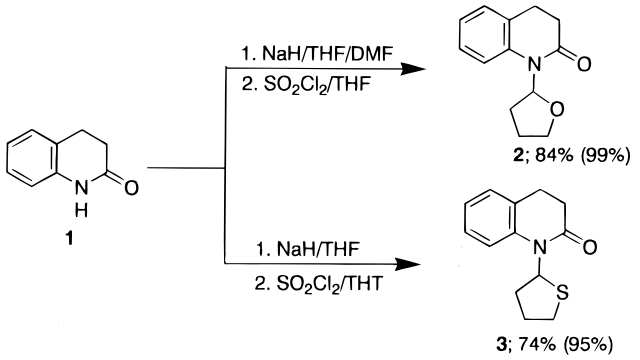
Treatment of substrates **2** and **3** with $NaBH_4$ gave fragmentation products **8** and **9** in excellent yields based upon the recovered starting material (Table 1, entries 1 and 2). Similar results were observed with other hydride agents such as $LiBH_4$, $LiAlH_4$, and L-selectride ($LiB[CH(CH_3)CH_2CH_3]_3$) (Table 1, entries 3−7). A proposed mechanism is presented in Scheme 3. The carbonyl group of THF- and THT-protected 3,4-dihydro-2(1*H*)-quinolinones (**2** and **3**) were reduced with hydride agents to form intermediates **4** and **5**, followed by 3-aza-Grob fragmentation, which involved two ring openings of one six-membered ring and the other five-membered ring, to give imine aldehyde (**6** and **7**). An excess of hydride converts the active intermediates **6** and **7** to the saturated amine alcohols **8** and **9**. These are the first examples to directly support 3-aza-Grob fragmentation, since the nucleofuges stay with the parent molecules after fragmentation.

The 3-aza-Grob fragmentation process is further supported by isotope studies. *N*-Tetrahydrofuranyl-3,4-dihydro-2(1*H*)-quinolinone (**2**) was reduced with $NaBD_4$ (98%) in THF to afford 1,1-dideutero-3-[2-(1-deutero-4-hydroxy-butylamino)-phenyl]-propanol **12** (Scheme 3). Mass spectra agreed with an empirical formula of $C_{13}H_{18}D_3NO_2$, i.e., trideuterated alcohol **12**. The comparison of ^1H NMR spectra between trideuterated alcohol **12** and nondeuterated alcohol **8** shows that compound **8** has four signals at 3.67, 3.63, 3.15, and 2.60 ppm, each integrating for two protons, that are, respectively, assigned to H13, H9, H10, and H7 (see Supplemental Information). Deuterated compound **12** shows three resonances at 3.67, 3.12, and 2.58 ppm, but the integration of H10 (3.12 ppm) is one proton.

Scheme 1



Scheme 2. Preparation of *N*-Tetrahydrofuranyl-3,4-dihydro-2-(1*H*)-quinolinone (2) and *N*-Tetrahydrothienyl-3,4-dihydro-2-(1*H*)-quinolinone (3)[a]



[a] Yields in paratheses are based upon the recovered starting material.

Table 1. Products (8 and 9) of Hydride Reduction of *N*-Tetrahydrofuranyl-3,4-dihydro-2-(1*H*)-quinolinone (2) and *N*-Tetrahydrothienyl-3,4-dihydro-2-(*1H*)-quinolinone (3)

entry	sub.	hydride	equiv	solvent	*T* (°C)	*t* (h)	prod.	yield (%)
1	**2**	$NaBH_4$	15	EtOH	60	30	**8**	54 (99)[a]
2	**3**	$NaBH_4$	15	THF	70	31	**9**	53 (96)[a]
3	**2**	$LiBH_4$	15	THF	25	8	**8**	79 (99)[a]
4	**3**	$LiBH_4$	15	THF	25	26	**9**	63
5	**2**	$LiAlH_4$	10	Et_2O	25	5	**8**	55 (99)[a]
6	**2**	L-selectride[b]	15	THF	25	21	**8**	65
7	**3**	L-selectride[b]	15	THF	25	17	**9**	44

[a] All yields are pure, isolated compound. The yields in parentheses are based upon the recovered starting material. [b] L-selectride: $LiB[CH(CH_3)CH_2CH_3]_3$.

* Tel: (886)-7-312-1101 ext 2275. Fax: (886)-7-312-5339. Email: jjwang@cc.kmu.edu.tw.

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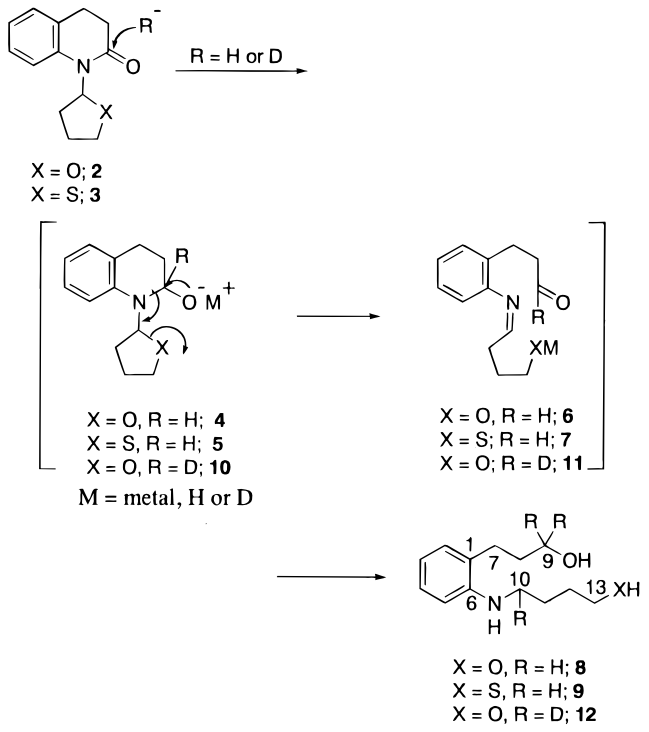
Scheme 3. Plausible Reaction Pathways for the 3-Aza-Grob Fragmentation



In conclusion, we examined 3-aza-Grob fragmentation of the hydride reduction of THF-protected 3,4-dihydro-2(1*H*)-quinolinone analogues. The results demonstrate that various hydride reagents can reduce aromatic lactams via 3-aza-Grob fragmentation. Further examination by stable isotope studies supports our observations. Efforts are now underway on synthetic applications of this reaction.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Series 2000 spectrophotometer. ^{1}H and ^{13}C NMR were recorded using a 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, and q. Low resolution mass spectra were recorded on a JEOL SX-102A spectrometer, and high-resolution mass spectra (HRMS) were recorded on a JEOL JMX-HX 110 spectrometer. Analytical TLC was carried out on precoated 0.25 mm thick Merck 60 F_{254} silica plates. Flash chromatography was carried out using Merck silica gel 60 (230−400 mesh).

***N*-Tetrahydrofuranyl-3,4-dihydro-2-(1*H*)-quinolinone (2).** To a stirred solution of 3,4-dihydro-2-(1*H*)-quinolinone **1** (148.6 mg, 1 mmol) in THF (8 mL) was added NaH (10 mmol) in one portion under nitrogen at 0 °C. 2-Chlorotetrahydrofuran, generated freshly by sulfuryl chloride (0.164 mL, 2 mmol) and THF (2 mL), was added to the solution dropwise. The resulting solution was stirred at room temperature for 4 h. The reaction mixture was poured into ice water (100 mL) and extracted four times with methylene chloride. The combined organic phases were washed with saturated $NaHCO_3$, H_2O, and brine, dried over $MgSO_4$, and concentrated under vacuum. The crude product was subjected to flash chromatography (hexane/AcOEt = 4:1) to give **2** (182.3 mg, 84%) (99% yield based upon the recovered starting material) as a light yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32 (d, J = 8 Hz, 1H), 7.22−7.15 (m, 2H), 7.03 (t, J = 7.6 Hz, 1H), 6.41 (t, 6.8 Hz, 1H), 4.27−4.22 (m, 1H), 3.91−3.86 (m, 1H), 3.00−2.76 (m, 2H), 2.68−2.53 (m, 2H), 2.36−2.01 (m, 2H), 2.09−1.99 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.0 (s), 138.9 (s), 128.5 (s), 127.4 (d), 126.9 (d), 123.5 (d), 117.6 (d), 85.9 (d), 67.9 (t), 33.4 (t), 27.3 (t), 25.4 (t), 25.4 (t); IR (neat) 2957, 1681, 1053 cm^{-1}; LRMS (EI, *m*/*z*) 217 (M^+); HRMS (EI, *m*/*z*) for $C_{13}H_{15}NO_2$ calcd 217.1104, found 217.1095.

***N*-Tetrahydrothienyl-3,4-dihydro-2-(1*H*)-quinolinone (3).** To a stirred solution of 3,4-dihydro-2-(1*H*)-quinolinone (**1**) (520.1 mg, 3.5 mmol) in THF (43 mL) was added NaH (35 mmol) in one portion under nitrogen at 0 °C. 2-Chlorotetrahydrothiophene, generated freshly by sulfuryl chloride (0.63 mL, 7.7 mmol) and tetrahydrothiophene (4.4 mL), was added to the solution dropwise. The resulting solution was stirred at room temperature for 24 h. The reaction mixture was poured into ice water (300 mL) and extracted four times with ethyl acetate. The combined organic phases were washed with saturated $NaHCO_3$, H_2O, and brine, dried over $MgSO_4$, and concentrated under vacuum. The crude product was subjected to flash chromatography (hexane/AcOEt = 4:1) to give **3** (611.6 mg, 74%) (95% yield based upon the recovered starting material) as a yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.49 (d, J = 8 Hz, 1H), 7.25 (td, J = 8 and 1.6 Hz, 1H), 7.18 (dd, J = 8 and 1.2 Hz, 1H), 7.04 (dd, J = 7.6 and 0.8 Hz, 1H), 6.46 (t, 8 Hz, 1H), 3.36 (td, J = 10.8 and 5.2 Hz, 1H), 3.05−3.01 (m, 1H), 2.87−2.78 (m, 2H), 2.70−2.43 (m, 4H), 2.22−2.15 (m, 1H), 2.05−1.96 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.6 (s), 139.1 (s), 128.7 (s), 127.6 (d), 126.8 (d), 123.3 (d), 117.6 (d), 63.1 (d), 34.0 (t), 33.4 (t), 32.1 (t), 31.2 (t), 25.4 (t); IR (neat) 2935, 1681, 1189 cm^{-1}; LRMS (EI, *m*/*z*) 233 (M^+); HRMS (EI, *m*/*z*) for $C_{13}H_{15}NSO$ calcd 233.0876, found 233.0877.

3-[2-(4-Hydroxy-butylamino)-phenyl]-propanol (8). The hydride reductions of *N*-tetrahydrofuranyl-3,4-dihydro-2-(1*H*)-quinolinone (**2**) were prepared according to the method of Wang et al. (*Tetrahedron* **1998**, *54*, 13149) and Table 1. Pure **8** was obtained as a yellow oil by flash chromatography (CH_2Cl_2/MeOH = 20:1): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.12 (td, 8.0 and 1.6 Hz, 1H), 7.04 (dd, 7.6 and 1.6 Hz, 1H), 6.69 (td, 7.6 and 0.8 Hz, 1H), 6.65 (dd, 8.0 and 0.8 Hz, 1H), 3.67 (t, 6.0 Hz, 2H), 3.63 (t, 6.0 Hz, 2H), 3.22 (br s, 2 × OH), 3.15 (t, 6.0 Hz, 2H), 2.60 (t, 7.6 Hz, 2H), 1.86−1.65 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 146.0 (s), 129.4(d), 127.3 (d), 126.2 (s), 117.4 (d), 110.8 (d), 62.5 (t), 61.7 (t), 44.0 (t), 32.1 (t), 30.1 (t), 27.0 (t), 26.0 (t); IR (neat) 3358, 2936, 1603, 1514, 1056 cm^{-1}; LRMS (EI, *m*/*z*) 223 (M^+); HRMS (EI, *m*/*z*) for $C_{13}H_{21}NO_2$ calcd 223.1573, found 223.1571.

3-[2-(4-Mercapto-butylamino)-phenyl]-propanol (9). The hydride reductions of *N*-tetrahydrothienyl-3,4-dihydro-2-(1*H*)-quinolinone (**3**) were prepared according to the method of Wang et al. (*Tetrahedron* **1998**, *54*, 13149) and Table 1. Pure **9** was obtained as a yellow oil by flash chromatography (hexane/AcOEt = 1:1): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.12 (td, 7.6 and 1.6 Hz, 1H), 7.04 (dd, 7.2 and 1.6 Hz, 1H), 6.69 (td, 7.6 and 1.2 Hz, 1H), 6.63 (d, 7.6 Hz, 1H), 3.64 (t, 6 Hz, 2H), 3.16 (t, 6.4 Hz, 2H), 2.73 (t, 6 Hz, 2H), 2.60 (t, 7.6 Hz, 2H), 1.89−1.71 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.9 (s), 129.3(d), 127.3 (d), 125.9 (s), 117.3 (d), 110.6 (d), 61.7 (t), 43.6 (t), 38.6 (t), 31.4 (t), 28.2 (t), 26.9 (t), 26.8 (t); IR (neat) 3389, 2927, 1603, 1513, 1056 cm^{-1}; LRMS (EI, *m*/*z*) 239 (M^+); HRMS (EI, *m*/*z*) for $C_{13}H_{21}NOS$ calcd 239.1344, found 239.1345.

1,1-Dideutero-3-[2-(1-deutero-4-hydroxy-butylamino)-phenyl]-propanol (12): yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.10 (td, 8.0 and 1.6 Hz, 1H), 7.02 (dd, 7.6 and 1.6 Hz, 1H), 6.69 (td, 7.6 and 0.8 Hz, 1H), 6.62 (d, 8.0 Hz, 1H), 3.67 (t, 6.0 Hz, 2H), 3.12 (dd, 13.2 and 6.8 Hz, 1H), 2.72 (br s, 2 x −OH), 2.58 (t, 7.6 Hz, 2H), 1.82−1.66 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 146.0 (s), 129.4(d), 127.3 (d), 126.1 (s), 117.4 (d), 110.8 (d), 62.5 (t), 43.6 (d), 31.8 (t), 30.4 (t), 26.9 (t), 26.0 (t); LRMS (EI, *m*/*z*) relative intensity: 226 (M^+, 34), 167 (73), 149 (80), 119 (83), 91 (100); HRMS (EI, *m*/*z*) for $C_{13}H_{21}NO_2$ calcd 226.1761, found 226.1762.

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Supporting Information Available: Proton and carbon spectra for compounds **2**, **3**, **8**, **9**, and **12** (10 pages). This material is available free of charge via the Internet at http://pubs.acs.org.

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