A Facile Reductive Removal of Bromine Atom(s) of 6,6-Dibromo- and 6-Bromopenicillanate Derivatives in a Pb/Al Bimetal System

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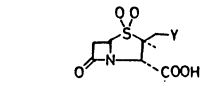
(Received September 1, 1988)

Synopsis. Reductive removal of the bromine atom(s) of 6,6-dibromo- and 6-bromopenicillanate 1-oxides has been performed successfully on treatment with aluminum metal in the presence of a catalytic amount of lead(II) bromide in methanol containing 1% aqueous hydrobromic acid. In a similar manner, 6,6-dibromopenicillanates and their 1,1-dioxides can be converted to the corresponding debromination products, respectively.

Since the discovery of the β-lactamase inhibitory properties of penicillanic acid 1,1-dioxide (sulbactam) **1a**,[1] its homologues, bearing the proper substituents at the β-C(2)-methyl group, have received much attention as potential β-lactamase inhibitors. Namely, the chloro, triazolyl, and tetrazolylthio substituted derivatives **1b** (BRL-2013),[2] **1c** (YTR-830),[3] and **1d**[4] have been proven to exhibit potent β-lactamase inhibitory activities. The syntheses of the penicillanic acid 1,1-dioxides **1** have been performed by the transformation of commercially accessible 6-aminopenicillanic acid (**2**). An inevitable task in the transformation (**2**→**1**) is the removal of the C(6)-amino moiety of **2**. The procedures available for this purpose have generally relied on the catalytic hydrogenation of 6-bromo- or 6,6-dibromopenicillanic acid derivatives **3**—**6**,[1c,5,6] derived from 6-aminopenicillanic acid **2**. Reductive debromination reactions with tributyltin hydride[7] or zinc[8] have also been utilized. However, most of these procedures suffer from one or more drawbacks: unsatisfactory yields of the hydrogenation products **7**—**10**, instability of protecting groups of C(3)-carboxylic acid (e.g., benzhydryl and allyl) under hydrogenolysis conditions and difficulty in removing the metal complexes generated in the zinc and tributyltin hydride reductions. Consequently, continuing efforts have been made to look for a new method for the reductive removal of the C(6)-bromine atom(s).

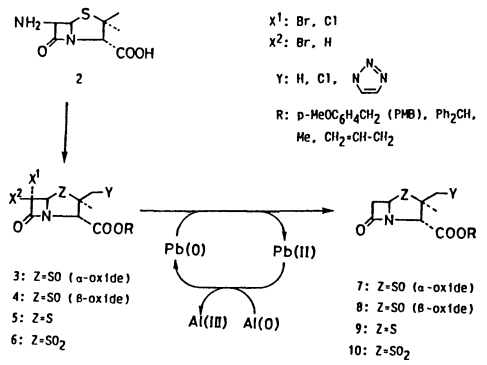
We have recently developed a new Pb/Al bimetal system, involving aluminum and a catalytic amount of lead salts, which acts as a powerful reductant for various synthetic purposes.[9] A new application of the Pb/Al bimetal system for the reductive debromination of the 6-bromo- and 6,6-dibromopenicillanates **3**—**6**, providing a simple and efficient route to the corresponding hydrogenation products **7**—**10**, respectively (Scheme 1), is described herein.

Reduction of 6,6-dibromopenicillanate 1-oxide **3a** (X^1=X^2=Br, Y=H, R=PMB) with aluminum and a catalytic amount of lead(II) bromide (0.1 equiv) was carried out at 30 °C in various media. Some of the examples are shown in Table 1. In aqueous media (Entries 3 and 4), the reduction of **3a** was completed in 1—2 h to afford 60—86% yields of the hydrogenation product **7a**, while in nonaqueous media, e.g., methanol and acetone, (Entries 1 and 2), only less than 24% yield of **7a** was obtained. Notably, addition of a small amount of 1% hydrobromic acid facilitates the hydrogenation of **3a**, affording up to 92% yield of **7a** (Entries 5—7). The reduction (**3a**—**7a**) can similarly be performed in a mixed solvent, e.g., MeOH/THF/aq HBr and MeOH/CH_2Cl_2/aq HBr (Entries 8 and 9).



1

	Y		Reference
a	H	Sulbactam	1
b	Cl	BL-P 2013	2
c		YTR 830	3
d			4



Scheme 1.

Table 1. Reduction of 6,6-Dibromopenicillanate 1α-Oxide **3a** with $PbBr_2$/Al[a]

Entry	Condition	Time / h	Yield of **7a**[b] / %
1	MeOH	3	23
2	Acetone	8	—(98)[c]
3	Acetone/H_2O(9/1)	1	60
4	MeOH/H_2O(9/1)	2	86
5	MeOH/aq 1% HBr(9/1)	2	92
6	MeOH/aq 1M NH_4Cl(9/1)	3	82
7	MeOH/aq 1M AcOH(9/1)	2	85
8	MeOH/CH_2Cl_2/aq 1% HBr (4/5/1)	3	95
9	MeOH/THF/aq 1% HBr(9/5/1)	3	87

a) Carried out with $PbBr_2$ (0.1 equiv) and Al(2.2 equiv) at 30°C. b) Isolated Yield. c) Recovered **3a**.

The presence of lead(II) bromide is essential for this purpose, since, in the absence of lead(II) bromide, most of the starting material **3a** is recovered intact (Table 2, Entry 2). This fact can be well understood by assuming that lead(0) generated by two-electron reduction of lead(II) on the aluminum surface[9] acts as a reductant in the reductive removal of the bromine atoms and thus generated lead(II) is again submitted to reduction with aluminum (Scheme 1). Satisfactory results were also obtained by use of lead(II) chloride or lead powder in combination with aluminum (Entries 3 and 4), while bismuth(III) chloride is less effective (Entry 5) and tin(II) bromide, titanium(IV) chloride, manganese(III) chloride, and chromium(III) chloride are not effective at all (Entries 6—9).

The Pb/Al bimetal system was successfully applied to the reduction of various halopenicillanate derivatives **3—6**. The conditions and results are summarized in Table 3. The reductive removal of bromine atoms of 6,6-dibromopenicillanate 1α-oxides **3** was performed in a methanolic mixed-solvent containing aqueous 1% hydrobromic acid to afford the penicillanate 1α-oxides **7** in 77—93% yields (Entries 1—3). Similarly, 6α-bromopenicillanate 1β-oxides **4**, 6,6-dibromopenicillanate **5**, and 6,6-dibromopenicillanate 1,1-dioxides **6** underwent the reductive debromination affording the hydrogenation products **8**, **9**, and **10**, respectively (Entries 4, 5, 7—12), in which, the substituents on the 2β-methyl group, e.g., chlorine and 1,2,3-triazolyl moiety, were retained intact. However, 6α-chloropenicillanate 1-oxide (**4c**) gave no appreciable amount of hydrogenation product **8c** (Entry 6).

Table 2. Reduction of 6,6-Dibromopenicillanate 1α-Oxide **3a** with MX_n/Al[a]

Entry	MX_n	Time	Yield/%[b]	
		h	**7a**	**3a**[c]
1	$PbBr_2$	3	92	—
2	None	4	—	98
3	$PbCl_2$[d]	6	82	—
4	Pb	4	79	—
5	$BiCl_3$	2	65	—
6	$SnBr_2$	5	—	92
7	$TiCl_4$	5	—	80
8	$MnCl_3$	5	—	93
9	$CrCl_3$	5	—	92

a) Carried out with MX_n (0.1 equiv) and Al(2.2 equiv) in MeOH/aq 1% HBr (9/1) at 30 °C. b) Isolated Yield. c) Recovered **3a**. d) aq 1% HCl was used in place of 1% HBr.

The proper choice of the solvent for each compound **4—6** is significant. For example, when 6,6-dibromopenicillanate (**5a**) was treated with the aluminum and lead(II) bromide combination in methanol and aqueous 1% hydrobromic acid (9/1), the reaction was quite slow and, even after 15 h, afforded only 52% yield of penicillanate **9a** along with monobromo derivatives **5** (X^1=H; X^2=Br; and X^1=Br; X^2=H, 24%) (Entry 8). In contrast, when a small amount of acetone was added to this medium, the reaction was significantly accelerated and completed in 5 h to give **9** in 72% (Entry 7).

Another interesting observation is that the *p*-methoxybenzyl (PMB), benzhydryl, methyl, and allyl esters of 6-bromo- and 6,6-dibromopenicillanates **3—6** are successfully reduced to the corresponding penicillanates **7—10** without affecting the ester moieties, while the *p*-nitrobenzyl ester **6e** is completely resistant to the reductive debromination (Entry 13). The latter failure is probably ascribable to the fact that the nitrobenzyl moiety is susceptible to reduction to form a stable anion radical.[8b,c]

Experimental

Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. IR spectra were recorded on a JASCO IRA-1 grating spectrophotometer. ^1H NMR spectra were taken on a Hitachi R-24 (60 MHz) and a JEOL MX-100 spectrometers (100 MHz) using tetramethyl-

Table 3. Reductive Removal of Bromine Atom(s) of 6-Halo- or 6,6-Dihalopenicillanates[a]

Entry		Halopenicillanates				Solvent[c]	Time	Product	
		X^1	X^2	Y	R[b]		h	Yield/%[d]	
1	**3a**	Br	Br	H	PMB	A	3	**7a**	95
2	**3b**	Br	Br	H	$CHPh_2$	B	2	**7b**	93
3	**3c**	Br	Br	H	CH_3	A	4	**7c**	77
4	**4a**	Br	H	H	PMB	A	3	**8a**	80
5	**4b**	Br	H	H	$CHPh_2$	B	5	**8b**	82
6	**4c**	Cl	H	H	PMB	B	22	**8c**	—(92)[e]
7	**5a**	Br	Br	H	PMB	C	5	**9a**	72
8	**5a**	Br	Br	H	PMB	D	15	**9a**	52
9	**6a**	Br	Br	H	PMB	B	3	**10a**	91
10	**6b**	Br	Br	H	$CH_2CH{=}CH_2$	A	3	**10b**	94
11	**6c**	Br	Br	Cl	$CHPh_2$	A	5	**10c**	85
12	**6d**	Br	H		PMB	D	5	**10d**	86
13	**6e**	Br	Br	H	PNB	A	7	**10e**	—

a) Carried out with $PbBr_2$ (0.1 equiv) and Al (2.2 equiv) at 30 °C. b) PMB: *p*-methoxybenzyl; PNB: *p*-nitrobenzyl. c) A: MeOH/aq 1% HBr/CH_2Cl_2 (4/1/5); B: MeOH/aq 1% HBr/THF (9/1/5); C: MeOH/aq 1% HBr/acetone (8/1/1); D: MeOH/aq 1% HBr (9/1). d) Isolated yield. e) Recovered **4c**.

silane as an internal standard. Mass spectra were obtained on a JEOL JMS-DX303 spectrometer. Microanalyses were performed in our laboratory. 6-Bromo- and 6,6-dibromopenicillanates **3—6** were prepared from 6-aminopenicillanic acid **2** according to the procedures reported in the literatures.[1c,2,5,9]

Reductive Removal of Bromine Atom(s) of 6,6-Dibromo- and 6-Bromopenicillanates with $PbBr_2$-Al: To a stirred mixture of *p*-methoxybenzyl 6,6-dibromopenicillanate 1α-oxide **3a** (2 mmol), $PbBr_2$ (0.2 mmol) and finely cut aluminum foil (4.4 mmol) in methanol (4 ml) and dichloromethane (5 ml) was added aqueous 1% hydrobromic acid (1 ml). The stirring was continued at 30 °C until most of **3a** was consumed (3 h). The reaction mixture was diluted with EtOAc, washed with aqueous 5% hydrochloric acid followed by brine, dried, and concentrated to give penicillanate 1α-oxide **7a** (95%) as a light yellow foam. The analytical sample was obtained by a short silica-gel column with benzene-EtOAc (5 : 1) as an eluant: mp 103—103.5 °C; IR ($CHCl_3$) 1780 and 1745 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.25 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 3.10—3.70 (m, 2H, 6-H), 3.82 (s, 3H, OCH_3), 4.38 (s, 1H, 3-H), 4.50—4.65 (m, 1H, 5-H), 5.17 (s, 2H, OCH_2), 6.88 (d, J=9 Hz, 2H, aromatic H), and 7.33 (d, J=9 Hz, 2H, aromatic H); Found: C, 56.83; H, 5.70; N, 4.11%. Calcd for $C_{16}H_{19}NO_5S$: C, 56.96; H, 5.68; N, 4.15%.

In a similar manner, the following compounds were obtained.

Benzhydryl Penicillanate 1α-Oxide (7b): IR ($CHCl_3$) 1785 and 1745 cm^{-1}; ^1H NMR δ=1.09 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 3.27, 3.51 (AB-X, J_{AB}=14, J_{AX}= 2, J_{BX}=4 Hz, 2H, 6-H), 4.40 (s, 1H, 3-H), 4.48 (dd, J=2, 4 Hz, 1H, 5-H), 6.82 (s, 1H, $CHPh_2$), and 7.22 (s, 10H, aromatic H); HRMS, Found: m/z 406.1107. Calcd for $C_{21}H_{21}NO_4SNa$: M+Na, 406.1089.

Methyl Penicillanate 1α-Oxide (7c):[8b] IR (neat) 1770 and 1745 cm^{-1}; ^1H NMR δ=1.34 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 3.34, 3.58 (AB-X, J_{AB}=14, J_{AX}=2, J_{BX}=4 Hz, 2H, 6-H), 3.77 (s, 3H, CH_3), 4.36 (s, 1H, 3-H), and 5.07 (dd, J=2, 4 Hz, 5-H).

***p*-Methoxybenzyl Penicillanate 1β-Oxide (8a):** Mp 144—145 °C; IR ($CHCl_3$) 1780, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.07 (s, 3H, CH_3), 1.62 (s, 3H, CH_3), 3.30 (d, J=4 Hz, 2H, 6-H), 3.80 (s, 3H, OCH_3), 4.49 (s, 1H, 3-H), 4.89 (t, J=4 Hz, 1H, 5-H), 5.06, 5.21 (AB-q, J=11 Hz, 2H, OCH_2), 6.84 (d, J=8 Hz, 2H, aromatic H), and 7.27 (d, J=8 Hz, aromatic H); Found: C, 56.71; H, 5.76; N, 4.15%. Calcd for $C_{16}H_{19}NO_5S$: C, 56.96; H, 5.68; N, 4.04%.

Benzhydryl Penicillanate 1β-Oxide (8b): Mp 150—151.5 °C (lit,[8a] mp 145—148 °C); IR ($CHCl_3$) 1780 and 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.94 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 3.30 (d, J=3 Hz, 2H, 6-H), 4.59 (s, 1H, 3-H), 4.86 (t, J=3 Hz, 1H, 5-H), 6.92 (s, 1H, $CHPh_2$), and 7.29 (s, 10H, aromatic H).

***p*-Methoxybenzyl Penicillanate (9a):** IR ($CHCl_3$) 1765 and 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.36 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 3.04, 3.54 (AB-X, J_{AB}=14, J_{AX}=2, J_{BX}=4 Hz, 2H, 6-H), 3.80 (s, 3H, OCH_3), 4.46 (s, 1H, 3-H), 5.12 (s, 2H, OCH_2), 5.27 (dd, J=2, 4 Hz, 1H, 5-H), 6.94 (d, J=8 Hz, 2H, aromatic H), and 7.30 (d, 2H, J=8 Hz, aromatic H); HRMS, Found: m/z 344.0851. Calcd for $C_{16}H_{19}NO_4SNa$: M+Na, 344.0932.

***p*-Methoxybenzyl Penicillanate 1,1-Dioxide (10a):** IR ($CHCl_3$) 1785 and 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.24 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 3.38 (d, J=4 Hz, 2H, 6-H) 3.77 (s, 3H, OCH_3), 4.33 (s, 1H, 3-H), 4.52 (t, J=4 Hz, 1H, 5-H), 5.03, 5.17 (AB-q, J=11 Hz, 2H, OCH_2), 6.80 (d, J=8 Hz, 2H, aromatic H), and 7.23 (d, J=8 Hz, 2H, aromatic H); HRMS, Found: m/z 376.0851. Calcd for $C_{16}H_{19}NO_6SNa$: M+Na, 376.0831.

Allyl Penicillanate 1,1-Dioxide (10b): Mp 82—84 °C; IR ($CHCl_3$) 1790 and 1745 cm^{-1}: ^1H NMR ($CDCl_3$) δ=1.41 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 3.47 (d, J=3 Hz, 2H, 6-H), 4.40 (s, 1H, 3-H), 4.61 (t, J=3 Hz, 1H, 5-H), 4.69 (d, J=6 Hz, 2H, OCH_2), and 5.15—6.30 (m, 3H, $CH{=}CH_2$); HRMS, Found: m/z 296.0562. Calcd for $C_{11}H_{15}NO_5SNa$: M+Na 296.0569.

Benzhydryl 2β-Chloromethyl-2α-methylpenam-3α-carboxylate 1,1-Dioxide (10c): IR ($CHCl_3$) 1795 and 1745 cm^{-1}; ^1H NMR δ=1.29 (s, 3H, CH_3), 3.48 (d, J=3 Hz, 2H, 6-H), 3.83, 4.01 (AB-q, J=12 Hz, 2H, CH_2Cl), 4.60 (t, J=3 Hz, 1H, 5-H), 4.67 (s, 1H, 3-H), 6.93 (s, 1H, $CHPh_2$), and 7.30 (s, 10H, aromatic H); HRMS, Found: m/z 456.0711. Calcd for $C_{21}H_{20}NO_5SClNa$: M+Na, 456.0648.

***p*-Methoxybenzyl 2α-Methyl-2β-[(triazol-1-yl)methyl]-penam-3α-carboxylate 1,1-Dioxide (10d):** IR($CHCl_3$) 1795 and 1745 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.20 (s, 3H, CH_3), 3.51 (d, J=3 Hz, 2H, 6-H), 3.81 (s, 3H, OCH_3) 4.57 (s, 1H, 3-H), 4.63 (t, J = 3 Hz, 1H, 5-H), 5.02 (s, 2H, CH_2N), 5.20 (s, 2H, OCH_2), 6.90 (d, J=9 Hz, 2H, aromatic H), 7.35 (d, J=9 Hz, 2H, aromatic H), 7.60 (s, 1H, aromatic H), and 7.74 (s, 1H, aromatic H); HRMS, Found: m/z 443.1001. Calcd for $C_{18}H_{20}N_4O_6SNa$: M+Na, 443.1001.

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