STEREOSELECTIVE SYNTHESIS OF 6α-HALOPENICILLANATES BY SAMARIUM(II) IODIDE-PROMOTED REDUCTION OF 6,6-DIHALOPENICILLANATES

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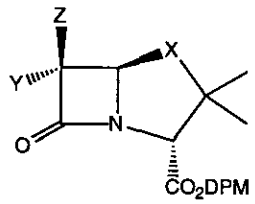
Abstract - A mild and efficient samarium(II) iodide promoted-reduction of 6,6-dibromopenicillanates for stereoselective synthesis of 6α-bromopenicillanates has been developed.

Preparation of 6–halosubstituted penicllanates has attracted considerable interest due to the potential of these compounds as β-lactamase inhibitors.[1] There have been many reported synthetic methods for 6β-bromopenicillanates[2-9] including several efficient reduction methods to prepare 6α– or β-bromopenicillanates from the corresponding 6,6-dibromopenicillanates.[4-8]

We have been interested in samarium(II) iodide-promoted organic reactions. Due to its powerful electron transferring ability, many synthetically useful transformations with this reagent have been developed.[10] Here we wish to report the preparation of 6α-bromopenicillanates *via* selective and mild reduction promoted by samarium(II) iodide. Since epimerization of 6α-bromopenicillanates to 6β-bromopenicillanates has already been reported, the efficient synthetic method for 6α-bromopenicillanates would also be a useful route to 6β-bromopenicillanates.[9]

Preparation of 6β-bromopenicillanates *via* a radical intermediate was reported in the literature.[4] Dibromopenicillanate (**1a**) was reduced by tributyltin hydride to a mixture of compounds including the 6β-bromopenicillanate (**2a**) as the major product. This reduction proved to be not so selective, and

formation of a small amount of α-bromopenicillanates (**3a**) and a completely reduced product (**4a**) was also observed. The corresponding sulfone (**1c**) was also subjected to the same conditions. In this case, similar results were obtained, that is, the corresponding 6β-bromopenicillanate (**2c**) was formed as the major product.



DPM = -$CHPh_2$

1a (X=S, Y=Z=Br)
1b (X=SO, Y=Z=Br)
1c (X=SO_2, Y=Z=Br)
1d (X=S, Y=Z=I)

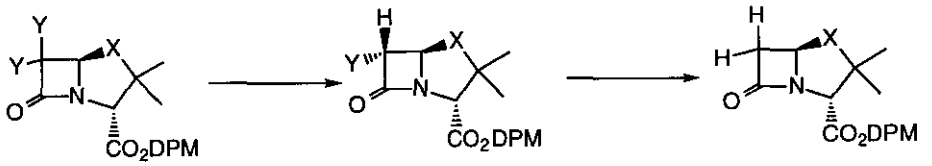
2a (X=S, Y=H, Z=Br)
2c (X=SO_2, Y=H, Z=Br)
3a (X=S, Y=Br, Z=H)
3b (X=SO, Y=Br, Z=H)
3c (X=SO_2, Y=Br, Z=H)
3d (X=S, Y=I, Z=H)

4a (X=S, Y=Z=H)
4b (X=SO, Y=Z=H)
4c (X=SO_2, Y=Z=H)

To develop a selective and efficient synthetic route for preparation of 6-bromopenicillanic acid derivatives, we performed the reduction promoted by samarium(II) iodide. The results are summarized in Table 1. The entire reduction proceeded easily at - 78 °C. Variable amounts of samarium(II) iodide are required to drive the reaction to completion. Reduction of 6,6-dibromopenicillanate (**1a**) with samarium(II) iodide in the presence of HMPA produced a single isomer which was identified as the corresponding 6α-bromopenicillanate (**3a**) in quantitative yield (Entry 1).[11] This result is quite interesting since the tin hydride reduction and the reduction with $AgNO_3$ in i-PrOH of **1a** generated 6β-bromopenicillanate (**2a**) as the major[4] or the only product,[7] respectively. In the case of the sulfone (**1c**), reduction with samarium(II) iodide-HMPA also afforded **3c** as a single isomer in quantitative yield (- 78 °C for 30 min)(Entry 5). When the corresponding sulfoxide derivative of 6,6-dibromopenicillanate (**1b**) was reacted under the same conditions, a mixture of the α-bromo product (**3b**) and fully debrominated product (**4b**) was formed in 7:1 ratio (88 % in total yield)(Entry 3).[12] Reduction of 6,6-diiodopenicillanate (**1d**) produced the desired 6α-iodopenicillanate (**3d**) in quantitative yield (Entry 7). Dehalogenation of monobromopenicillanates (**3**) was also promoted smoothly by samarium(II) iodide in HMPA-THF to afford the corresponding fully debrominated products (**4**) (Entries 1, 3, and 5). The effect of HMPA was also tested. Reduction in the absence of HMPA under the same conditions also produced the corresponding debrominated penicillanates. While reduction of dibromo derivatives produced monobromo products in similar yield to that of reduction in the presence of HMPA, the yields for reduction of 6-monobromopenicillantes (**3**) to fully debrominated products (**4**) were usually lower than the corresponding

reduction in the presence of HMPA (Entries 2, 4, and 6). The selectivity for the reduction of **1b** in the absence of HMPA was decreased and produced **3b** and **4b** in the ratio of 3:1 (Entry 4).

Table 1. Samarium(II) Iodide Reduction of 6-Halopenicillanates



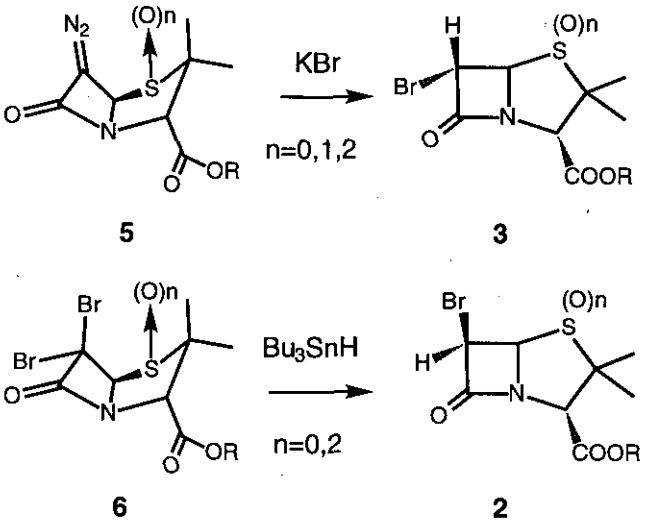
1 (X=S, SO, SO_2) (Y=Br, I) **3** **4**

Entry	Dihalopenicillanate	Reduction conditions (- 78 °C, 30 min)#	α-Halopenicillanate (yield)	Reduction conditions (- 78 °C, 30 min)#	Penicillanate (yield)
1	**1a**	A	**3a** (quantitative)	C	**4a** (60 %)
2	**1a**	B	**3a** (quantitative)	E	**4a** (40 %)
3	**1b**	A	**3b and 4b** (88 % yield **3b:4b**=7:1)	C	**4b** (60 %)
4	**1b**	B	**3b and 4b** (88 % yield **3b:4b**=3:1)	E	**4b** (40 %)
5	**1c**	C	**3c** (quantitative)	C	**4c** (60 %)
6	**1c**	D	**3c** (quantitative)	B	**4c** (50 %)
7	**1d**	C	**3d** (quantitative)	—	—

Reaction Conditions: (A) SmI_2 (3.0~3.5 equiv), HMPA, THF. (B) SmI_2 (3.0 ~ 3.5 equiv), THF. (C) SmI_2 (2.5 equiv), HMPA, THF. (D) SmI_2 (2.5 equiv), THF. (E) SmI_2 (4.0 ~4.5 equiv), THF.

The origin of stereoselectivity deserves discussion. The 6α-bromopenicillanates (**3**) as major products are known to form when the corresponding diazo derivatives (**5**), formed *in situ* from the 6β-

aminopenicillanates, were treated with potassium bromide in an acidic medium.[2,14] The predominant formation of α-bromo product (**3**) could be explained by the attack of a nucleophile from the α (bottom) face to the azetidinone ring due to steric reason. The steric factor also seems to play a major role in the tin hydride reduction of **6** to afford β-bromo product (**2**). Although the selectivity is reported to be not high, it can be explained by the delivery of hydrogen from the bottom (α) face to the radical intermediate.



The selectivity for β-bromo derivatives could be greatly enhanced when **6** is treated with $AgNO_3$-iPrOH.[7] In this case also, hydrogen is transferred from the α-face presumably due to the steric hindrance. Other reductions such as catalytic hydrogenation of 6,6-dibromopenicillantes[8] have been reported to give α-bromo derivatives predominantly.

The origin of selectivity for the present samarium(II) iodide reduction is, however, not clear at this moment. It could be explained by chelation by the samarium(III) species with the resulting enolate which is presumed to be formed after reduction with samarium(II) iodide. The samarium(III) species could also form a chelate with the carboxyl oxygen at the 3-position. As a consequence, the α-face could be well blocked and the proton would have to be delivered from the top (β) face of the azetidinone ring to furnish the α-bromo product selectively.

In conclusion, we have discovered an efficient synthetic method to prepare 6α-halopenicillanate derivatives. High conversion, selectivity, and mildness of the reaction proved that this samarium(II) iodide-promoted

reduction of 6,6-dihalopenicillanates is an efficient synthetic method to prepare 6α-bromopenicillantes.

ACKNOWLEDGMENTS

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11. Typical procedure: To a stirred solution of diphenylmethyl 6,6-dibromopenicillanate (**1a**, 200 mg, 0.38 mmol) in THF (5 ml) was added dropwise a solution of SmI_2 [in THF (7.5 ml), 1.22 mmol] containing HMPA (8.6 v/v %) at - 78 °C. After being stirred for an additional 30 min, aqueous ammonium chloride was added to the reaction mixture. The mixture was extracted with ethyl acetate, and the extract was washed with water, brine and dried with $MgSO_4$. The removal of the solvent under reduced pressure followed by drying under vacuum gave diphenylmethyl 6α-bromopenicillanate (**3a**)(170 mg, quantitative yield). ^{1}H Nmr (300 MHz, $CDCl_3$, δ): 1.31 (3 H, s, CH_3), 1.64 (3 H, s, CH_3), 4.68 (1 H, s, C3-H), 4.85 (1 H, d, J = 1.5 Hz, C6-H); 5.48 (1 H, d, J = 1.5 Hz, C5-H), 6.98 (1 H, s, $CHPh_2$), 7.39 (10 H, br s, Ph_2); ir (KBr) 1745, 1790 cm^{-1}.

12. The sulfoxide(**1b**)[(S)-isomer (α-sulfoxide)][13]: ^{1}H Nmr (300 MHz, $CDCl_3$) δ 1.21 (3 H, s, CH_3), 1.60 (3 H, s, CH_3), 4.67 (1 H, s, C3-H), 5.30 (1 H, s, C5-H), 6.95 (1 H, s, $CHPh_2$), 7.30 ~ 7.37 (10 H, m, Ph_2); ir (KBr) 1751, 1805 cm^{-1}. **3b**: ^{1}H Nmr (300 MHz, $CDCl_3$) δ 1.19 (3 H, s, CH_3), 1.52 (3H, s, CH_3), 4.58 (1H, s, C3-H), 4.84 (1H, d, J = 1.5 Hz, C6-H), 5.12 (1H, d, J = 1.5 Hz, C5-H), 6.95 (1 H, s, $CHPh_2$), 7.30 ~ 7.37 (10 H, m, Ph_2); IR (KBr) 1749, 1801 cm^{-1}. **4b**: ^{1}H Nmr (300 MHz, $CDCl_3$) δ 1.12 (3 H, s, CH_3), 1.58 (3 H, s, CH_3), 3.35 (1H, dd, J = 1.5, 17 Hz, C6-H), 3.60 (1H, dd, J = 4.8, 17 Hz, C6-H), 4.49 (1H, s, C3-H), 4.60 (1H, dd, J = 1.5, 4.8 Hz, C5-H), 6.97 (1 H, s, $CHPh_2$), 7.30 ~ 7.37 (10 H, m, Ph_2); ir (KBr) 1749, 1801 cm^{-1}.

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