EFFICIENT PREPARATION OF PENICILLANATE ESTER: A REDUCTIVE DEBROMINATION OF BROMOPENICILLANATE ESTER AND BROMOPENICILLANATE-S,S-DIOXIDE ESTER WITH TRI-N-BUTYLPHOSPHINE

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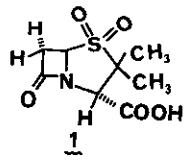
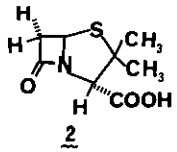
Dedicate to Professor Kang-Chien Liu on the occasion of his 60th birthday.

Abstract—Benzyl bromopenicillanate (5) and benzyl bromopenicillanate-S,S-dioxide (6) were subject to a reductive debromination in an effect of tri-n-butylphosphine furnishing benzyl penicillanate (7) and benzyl penicillanate-S,S-dioxide (8) in 50% and 81% yield respectively.

Penicillanic acid S,S-dioxide (sulbactam) (1)[1] is a semisynthetic β-lactam antibiotic. It lacks antibacterial activity but shows potent β-lactamase inhibitory activity. Therefore, several sulbactam derivatives were synthesized and found to inactivate β-lactamase as well[2]. Derivatives of penicillanic acid (2) are essential intermediates towards the synthesis of novel β-lactamase inhibitors such as sulbactam and their analogs. Key to synthesize these penicillanate ester intermediates involves an effective reductive debromination of 6-bromopenicillanate ester.



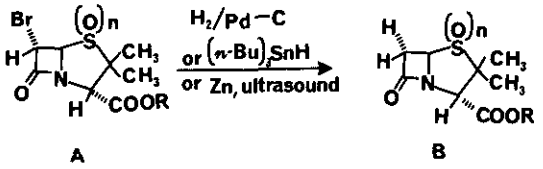
1



2

A literature survey indicated that there are several methods available to conduct a cleavage of the carbon-bromine bond of compound A such as tributyltin hydride[3], zinc in a sonic bath[4] and palladium catalysed hydrogenolysis[5] (Scheme 1). Reagents such as tributyltin hydride and zinc give rise to a large amount of organometallic intermediates which are difficult to remove cleanly from the reaction mixture, while the latter approach suffers from the drawbacks of the penam or cephem having the ester groups which are unstable to hydrogenolysis conditions (e.g. benzyl or allyl). However, an ester group on the penam or cephem nucleus is essential to have a human leukocyte elastase inhibitory activity[6].

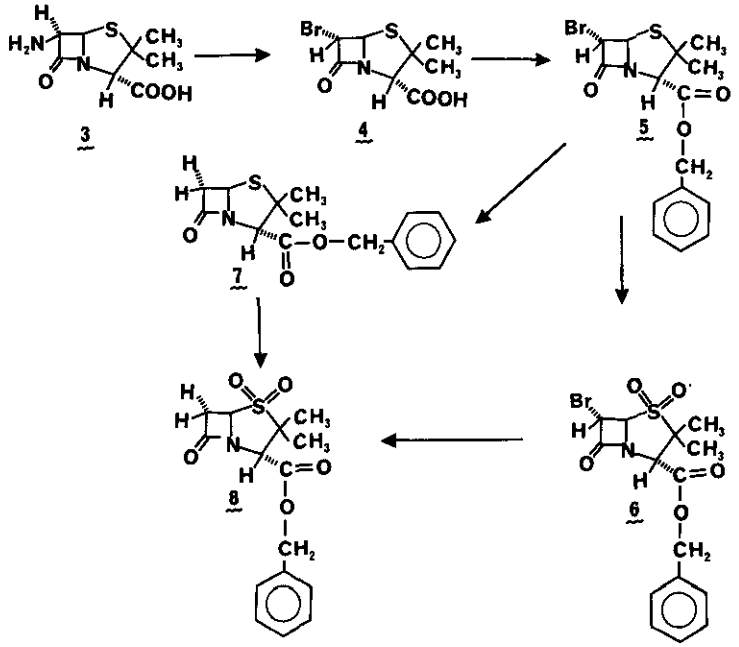
During a course of search for cephem or penam as potent human leukocyte elastase inhibitors and β-lactamase inhibitors respectively in our laboratory, we needed to develop a more convenient and practical approach for the synthesis of penicillanate ester. tri-n-Butylphosphine has been used as a reductive debromination agent towards various organic synthetic compounds.[7-8] However, to our best knowledge, this reagent has not been reported as a reductive debromination agent for the synthesis of penicillanate ester from 6-bromopenicillanate ester.



A B

Scheme 1

We chose benzyl 6-bromopenicillanate (5) to initiate this model study. Compound 5[9] was prepared in 53% yield by a literature approach from 6-aminopenicillanic acid (3) via diazotization, halogenation and subsequent esterification with benzyl bromide. Subsequently, compound 5 was treated with tri-n-butylphosphine in methanol at room temperature. The reaction was complete in 30 min. Benzyl penicillanate (7)[10] was isolated in 50% yield after liquid chromatography. Benzyl bromopenicillanate-S,S-dioxide (6)[11] prepared by



Scheme 2

literature was similarly treated with tri-n-butylphosphine affording benzyl penicillanate-S,S-dioxide (8)[12] in 81% yield. Compound 8 was also synthesized in 75% yield from compound 7 by oxidation with potassium permaganate.

This mild and efficient method by means of tri-n-butylphosphine-mediated reductive debromination is therefore suitable for the formation of penicillanate ester and penicillanate-S,S-dioxide ester. The scope of this method is still under active investigation in our laboratory.

ACKNOWLEDGEMENTS

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9. Compound 5[4] was isolated as an oil. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.36(s,3H), 1.56(s,3H), 4.55(s,1H), 4.78(s,1H), 5.17(d,2H), 5.38(s,1H), 7.24(s,1H), 7.35(s,4H); ^{13}C-NMR (75 MHz, DMSO-d_6):δ 25.20, 32.48, 49.14, 64.48, 66.85, 69.09, 69.76, 128.39, 128.46, 128.51, 135.10, 166.67, 167.76.

10. Commpound 7[4] was isolated as an oil. ^{1}H-NMR (300 NHz, DMSO-d_6):δ 1.33(s,3H), 1.56(s,3H), 3.31(s,2H), 4.45(s,1H), 5.16(s,2H), 5.26(s,1H), 7.36(s,1H), 7.39(s,2H), 7.40(s,2H): ^{13}C-NMR (75 MHz, DMSO-d_6):δ26.16 30.74, 45.73, 60.17, 65.17, 66.66, 69.61, 128.37, 128.48, 128.58, 135.24, 167.47, 172.61. Anal. Calcd. for $C_{15}H_{17}NOS$: C 61.83; H, 5.88; N, 4.81. Found: C, 61.79; H, 5.99; N, 4.50.

11. Compound 6[4] was isolated as an oil. ^{1}H-NMR (100 MHz, DMSO-d_6):δ1.26(s,3H), 1.55(s,3H), 4.44(s,1H), 4.67(s,1H), 5.22(m,3H), 7.25(s,1H), 7.38(s,4H): ^{13}C-NMR (25 MHz, DMSO-d_6): δ18.53, 19.79, 39.98, 63.03, 68.23, 68.62, 128.00, 128.53, 128.78, 133.89, 165.55, 166.27. Anal. Calcd for $C_{15}H_{16}NBrOS$: C, 44.78; H, 4.01; N, 3.48. Found: C, 44.83; H, 4.03; N, 3.44.

12. Compound 8[4] was isolated as an oil. ^{1}H-NMR (300 MHz, DMSO-d_6):δ1.28(s,3H), 1.45(s,3H), 3.23(d,2H), 4.49(s,1H), 5.19(s,2H), 5.26(d,1H), 7.35(s,4H), 7.42(s,1H); ^{13}C-NMR (75 MHz, DMSO-d_6):δ 17.50, 19.21, 37.04, 39.52, 60.24, 62.02, 67.14, 128.05, 128.32, 134.79, 166.48, 171.80.

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