HALOGEN-METAL EXCHANGE REACTIONS OF BROMOARYL-SUBSTITUTED β-LACTAMS

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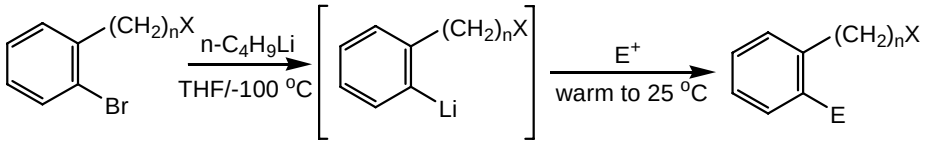
ABSTRACT

Compounds possessing the β-lactam ring system have long been of intense interest because of their antibiotic properties.[1,2] Among the more well-known examples of compounds belonging to this class are penicillins and cephalosporins. This project focused on determining the feasibility of elaborating bromoaryl-substituted β-lactam systems via a halogen-metal exchange reaction in order to make novel derivatives which would be difficult to synthesize otherwise because of to the highly electrophilic nature of the β-lactam ring system.

INTRODUCTION/STATEMENT OF THE PROBLEM

In the 1970s, W. E. Parham and his research group demonstrated that halogen-metal exchange reactions were possible on aryl bromides to form aryl compounds bearing electrophilic groups (Scheme 1).[3] These reactions were conducted at low temperatures of -100 ° C using either *n*-butyllithium or *t*-butyllithium as the exchange reagent. These studies established a new reaction paradigm: halogen-lithium exchange reactions can occur at low temperatures chemoselectively without the formation of unwanted side products resulting from reaction of the electrophilic groups contained in the molecule with the alkylithium reagents. These side reactions would be the primary reaction pathway at higher temperatures.

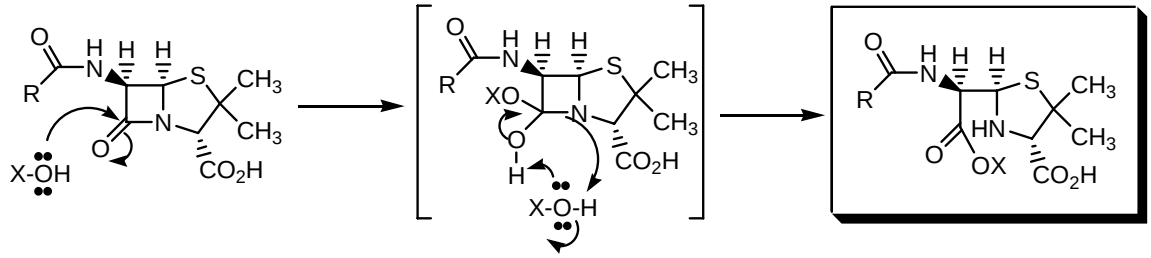
Scheme 1



n = 0-4
X = Br, Cl, CN, CO_2H, CO_2R

This research project focused on determining the feasibility of conducting halogen-metal exchange reactions on bromoaryl β-lactams. As previously indicated, these systems are of interest because of their inherent biological activity with possible uses as anti-fungal agents or β-lactamase inhibitors. While biological activity stems from the very reactive four-membered β-lactam ring as a result of strain, the same strain is also responsible for the reactivity of the system as an electrophilic moiety (Scheme 2 – penicillin reactivity).[4] Nucleophiles, particularly oxygen nucleophiles, can attack the carbonyl carbon leading to ring opening and a loss of biological activity. The ability to perform chemical transformations on an assembled β-lactam system, especially through the use of organometallic reagents which function as potent nucleophiles under normal conditions,

Scheme 2



would be of possible value toward the design of new β-lactam derivatives, thereby serving as a tool for designing a new generation of β-lactams compounds for combating antibiotic resistance.

EXPERIMENTAL

General

All reactions involving organolithium reagents were conducted under an atmosphere of nitrogen. Tetrahydrofuran was purchased as "dry" (OmniSolv) and was stored under a nitrogen blanket. Reaction temperatures of -100 °C were achieved with a liquid nitrogen-toluene bath; reaction temperatures of -78 °C were achieved with an acetone-dry ice bath. All organic residues were dried over anhydrous magnesium sulfate.

^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) data were obtained from a Varian Gemini 300 300MHz nuclear magnetic resonance spectrometer referencing tetramethylsilane. ^{13}C NMR data utilized $CDCl_3$ lock; IR data ere obtained from a Perkin-Elmer Model Spectrum 2000 FT-IR spectrometer; mass spectra were obtained from a Varian Model CP-3800 gas chromatograph interfaced to a Varian Saturn 2000 GC/MS/MS.

Microanalyses were performed by Quantitative Technologies, Inc., Whitehouse, N. J. All melting points were obtained from a Mel-Temp heating block apparatus and are uncorrected.

General Procedure for Preparation of Schiff Bases 3a, 3b[6]

o-Bromoaniline and benzaldehyde (or o-bromobenzaldehyde and aniline) (38mmol each) were dissolved in toluene (20 mL) and placed in a round-bottomed flask equipped with a Dean-Stark trap and reflux condenser and allowed to reflux until all of the water was removed through azeotrope formation. The resulting solution was then permitted to cool and was concentrated *in vacuo* to afford the imine (**3a** or **3b**). The products were characterized by ^{1}H NMR spectroscopy and were deemed pure enough for use without additional purification.

Preparation of Bromoaryl β-Lactams 4, 5[7]

Diisopropylamine (809 mg, 8mmol) in dry THF (15ml) was placed in an oven-dried 100 mL 3-neck round bottom flask equipped with a low temperature thermocouple, pressure-equalizing addition funnel, and nitrogen inlet. Under nitrogen, the flask and its contents were cooled to -78 ° C at which point *n*-butyllithium (5 mL of 1.6 M in hexanes; 8mmol) was added as drops. After the resulting mixture was stirred at -78 ° C under nitrogen for 20 minutes, ethyl isobutyrate (928 mg; 8 mmol) in THF (10 mL) was added as drops. Stirring at -78 ° C continued for an additional 20 minutes at which point the desired Schiff base (2.07 g; 8 mmol) was added as drops at such a rate in order to maintain the temperature below -70 °C. The resulting solution was allowed to stir for 1 h at -78 ° C, then allowed to warm to room temperature and stir overnight under nitrogen. The reaction mixture was poured into water (100 mL), and the mixture was washed with EtOAc (2 x 75 mL). The organics were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue purified by column chromatography on silica gel eluting with a mixture of hexanes/ethyl acetate.

4-(2-Bromophenyl)-3,3-dimethyl-1-phenylazetidin-2-one (4) was isolated as clear needles (1.77g; 71%), mp 115-117 °C; ^{1}H NMR ($CDCl_3$) □1.43 (s,3H,CH_3), 1.56 (s, 3H,CH_3), 5.06 (s,1H,azetidinone ring CH), 6.95-7.18 (m,8H,ArH), 7.52 (d,1H,ArH).

1-(2-Bromophenyl)-3,3-dimethyl-4-phenylazetidin-2-one (5) was isolated as pale yellow needles (2.27g, 91%), mp 58-62 °C; ^{1}H NMR ($CDCl_3$) 1.42 (s,6H,CH_3), 5.30 (s,1H, azetidinone ring CH); 6.92 (t,1H,ArH), 7.05-7.26 (m,6H,ArH), 7.40 (d,1H,ArH), 7.55 (d,1H,ArH); ^{13}C NMR ($CDCl_3$) 18.39, 23.04, 55.90, 69.78, 116.54, 126.38, 126.89, 127.62, 128.11, 128.21, 128.69, 134.25, 134.86, 136.42, 172.45; IR (nujol) 1756 cm^{-1}.

General Procedure for Halogen-Metal Exchange of Bromoaryl β-Lactams

The bromoaryl β-lactam (**4** or **5**; 200 mg; mmol) in dry THF was cooled to -100 ° C under nitrogen at which point *n*-butyllithium was added at such a rate so as to maintain the temperature below -90 °C. The resulting mixture was allowed to stir for 1 h at ca. -100 °C and was then quenched with 1.5 equivalents of the electrophile. The low temperature was maintained for another hour and then the mixture was allowed slowly to warm to room temperature. The reaction mixture was poured into water (100 mL), and the resulting mixture was washed with EtOAc (2 x 75 mL). The organics were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue purified by column chromatography on silica gel eluting with a mixture of hexanes/ethyl acetate.

3,3-Dimethyl-1,4-diphenylazetidin-2-one (7b: X=Y=H) was isolated as a white amorphous solid (63 mg, 42%), mp 146-47.5 °C (lit[7] mp 147.5-48.5 °C); ^{1}H NMR ($CDCl_3$) 1.43 (s,3H,CH_3), 1.46 (s,3H,CH_3), 5.30 (s,1H,azetidinone ring CH), 6.93-7.58 (m,10H,ArH); ^{13}C NMR ($CDCl_3$) 18.08, 22.95, 55.54, 66.59, 117.39, 123.80, 126.69, 128.15, 128.81, 129.15, 135.65, 137.99, 170.05; IR (nujol) 1733cm^{-1}.

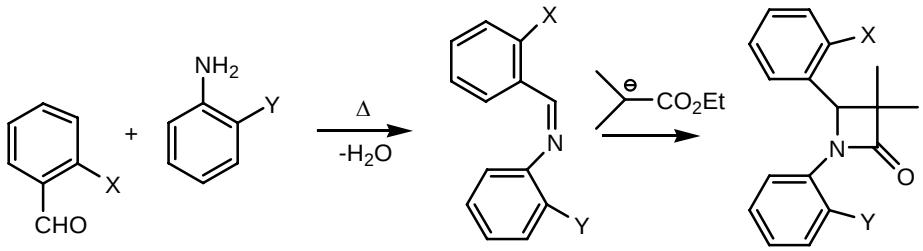
3,3-Dimethyl-4-phenyl-1-o-tolylazetidin-2-one (7b: X= H; Y= CH_3) was isolated as a white amorphous solid (74 mg, 46%), mp 149-50 °C; ^{1}H NMR ($CDCl_3$) 1.14 (s,3H,ArCH_3), 1.41 (s,3H,CH_3), 1.43 (s,3H,CH_3), 4.69 (s,1,azetidinone ring CH), 6.93-7.24 (m,9,ArH); ^{13}C NMR ($CDCl_3$) 18.09, 22.95, 29.78, 55.54, 66.59, 117.39, 123.80, 126.69, 128.15, 128.81, 129.15, 135.65, 138.00, 171.60; IR (nujol) 1732cm^{-1}.

1-[2-(Hydroxy(phenyl)methyl)phenyl]-3,3-dimethyl-4-phenylazetidin-2-one (7b: X=H; Y=CH(Ph)OH) was isolated as an amber oil (6 mg, 3%); ^{1}H NMR ($CDCl_3$) 1.41 (br s,6H,CH_3), 1.43 (s,3H,CH_3), 4.59 (s,1,azetidinone ring CH), 5.02 (s,1H,benzylic CH), 6.88-7.42 (m,13,ArH), 7.80 (d,0.5H,ArH – diastereomer A), 8.30 (d,0.5H,ArH – diastereomer B), 9.18 (br s, 0.5H, OH - diastereomer B), 10.21 (s, 0.5H, OH - diastereomer A); ^{13}C NMR ($CDCl_3$) 18.68, 22.42, 28.08, 65.54, 67.05, 119.88, 121.36, 125.28, 125.51, 126.66, 127.11, 127.80, 128.42, 128.47, 128.70, 128.95, 129.91, 132.43, 134.70, 189.53; mass spectrum (70 eV), m/z 265 (M^+ - 77).

RESULTS AND DISCUSSION

Compounds containing the basic structure illustrated below (**4**, **5**) are known to possess biological activity against some strains of bacteria as well as fungi and constitute a new generation of -lactams.[5] The preparation of these bromoaryl -lactams, which serve as a starting point for the study described herein, involves a straightforward two-step process and is shown in Scheme 3.[6]

Scheme 3



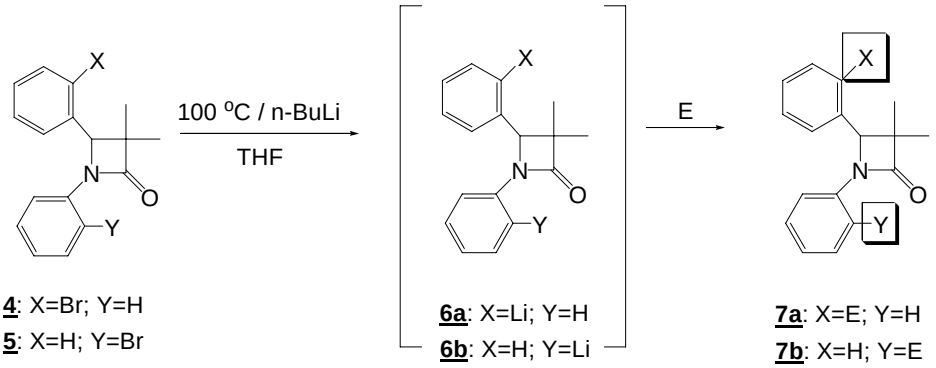
1 **2** **3a**: X=Br, Y=H **3b**: X=H, Y=Br **4**: X=Br, Y=H **5**: X=H, Y=Br

While bromine substitution can occur at any position in either aromatic ring, for the purpose of this study the derivatives containing bromine at the positions adjacent to the point of

attachment to the □-lactam were chosen because of the ready availability of the requisite starting materials (**1**, **2**).

The first reactions studied utilized **4** and **5** as the substrates. Halogen–metal exchange was attempted at -100 °C in tetrahydrofuran using *n*-butyllithium as the organometallic exchange reagent. In order to determine whether the exchange reaction did occur, the reaction mixture was quenched with various electrophiles at low temperature, including H_2O, CH_3I, and benzaldehyde. Analysis of the reaction mixtures confirmed that intermediates (**6a**, **6b**) did indeed form in the presence of the reactive β-lactam ring, thereby proving that the □-lactam is indeed robust enough to withstand the reaction conditions. The identities of the products were confirmed by ^{1}H NMR, ^{13}C NMR, IR and GC/mass spectrum.

Scheme 4



4: X=Br; Y=H
5: X=H; Y=Br

6a: X=Li; Y=H
6b: X=H; Y=Li

7a: X=E; Y=H
7b: X=H; Y=E

Table 1

Entry	*Compound*	*E*	*Y*	*X*	*% Yield*	*Melting Point (°C)*
1	**7b**	H_2O	H	H	42%	146.0-147.5
2	**7b**	CH_3I	CH_3	H	46%	149-150
3	**7b**	PhCHO	CH(Ph)OH	H	3%	N/A
4	**7a**	H_2O	H	H	26%	146.0-147.5

CONCLUSION

The reaction of the bromoaryl β-lactam **5** in which a halogen-metal exchange occurred at low temperature to generate the reactive intermediate **6b** proved successful. The aryllithium which formed was quenched with various electrophiles (including H_2O, CH_3I, and benzaldehyde) to afford the elaborated intermediates in moderate to low yield without opening the highly reactive β-lactam ring.

Generation of the intermediate **6a** from bromoaryl β-lactam **4** proved to be somewhat problematic. The GC/mass spectrum showed that the exchange occurred affording the des-bromo product (Table 1, Entry 4) and a side product which has not yet been identified. While this result indicated that halogen-metal exchange is indeed occurring to provide **6a**, when an electrophile of any substantial size is added it appears that addition does not occur. When the solvent for the reaction was changed to the diethyl ether (a solvent known to form weaker complexes with aryllithium reagents), the desired product was detected by GC/mass spectral analysis but could not be isolated because of poor conversion.

While these results indicate that halogen-metal exchange can indeed occur at low temperatures without attacking the □-lactam ring system, efforts directed toward better understanding the regioselectivity effects of ring position (i.e., **4** vs. **5**) with regards to the efficiency of the exchange reaction remain to be studied. In addition, a good deal of optimization work is necessary in order to realize the potential of this method.

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