Tetrahedron Letters 54 (2013) 4934–4936

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Halogen–metal exchange reactions of bromoaryl-substituted β-lactams

Maryll Geherty, James Melnyk, Keith Chomsky, David A. Hunt *

Department of Chemistry, The College of New Jersey, 2000 Pennington Road, Ewing, NJ 08628, United States

ARTICLE INFO

Article history:
Received 7 June 2013
Revised 24 June 2013
Accepted 1 July 2013
Available online 6 July 2013

Keywords:
Aryl-substituted β-lactams
Bromine–lithium exchange
Halogen–metal exchange
Functionalized aryllithiums

ABSTRACT

β-Lactams are quite susceptible to ring opening when exposed to nucleophilic reagents. The robustness of a variety of bromo- and iodoarenes containing electrophilic functional groups toward alkyllithium reagents during the halogen–lithium exchange process was first described by Parham, Bradsher, and co-workers. These observations led us to consider the behavior of bromoaryl-substituted β-lactams when treated with *n*-butyllithium at −100 °C in tetrahydrofuran. The work discussed herein describes successful halogen–metal exchange reactions on haloarene-substituted β-lactams thereby permitting a method for aromatic ring elaborations in the presence of the highly electrophilic β-lactam ring.

Introduction

In the 1970s, Parham and Bradsher demonstrated that halogen–metal exchange reactions were possible on aryl bromides to form aryl compounds bearing electrophilic groups (Scheme 1).[1] These reactions were conducted at low temperatures (typically −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 with little to no formation of unwanted side products resulting from reaction of the electrophilic groups contained in the molecule with the alkylithium reagents. Typically, these side reactions are observed at higher temperatures.

To the best of our knowledge, such reactions in the presence of the β-lactam electrophilic moiety have yet to be investigated. As previously indicated, these systems are of interest due to their inherent biological activity with possible uses as anti-fungal agents or β-lactamase inhibitors.[2,3] While biological activity stems from the very reactive four-membered β-lactam ring due to 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[5] leading to ring opening and a concomitant 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, would be of possible value toward the design of new β-lactam derivatives, thereby serving as a tool in designing β-lactam compounds as novel pharmaceutical agents (Scheme 2).

Results and discussion

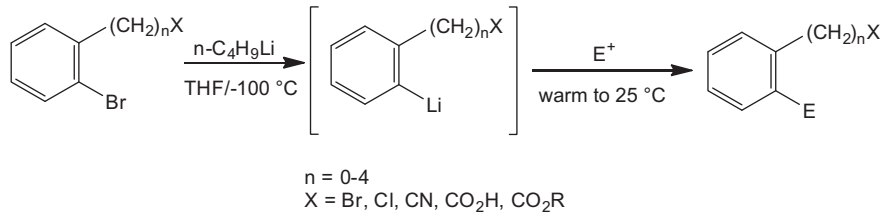
Compounds containing the basic structure illustrated below (**4**) are known to possess biological activity against some strains of bacteria as well as fungi and constitute a new generation of β-lactams.[6] In addition, closely related analogs have proven effective as cholesterol absorption inhibitors.[7] The preparation of bromoaryl β-lactams within this series serves as a starting point for the study described herein and involves a straightforward two-step process as shown in Scheme 3. [8,9]

While bromine substitution can occur at any position in either aromatic ring, for the purpose of this study we prepared derivatives containing bromine at the *ortho*- or *meta*-positions relative to the point of attachment to the β-lactam due to ready availability of the requisite starting materials (**1**, **2**).

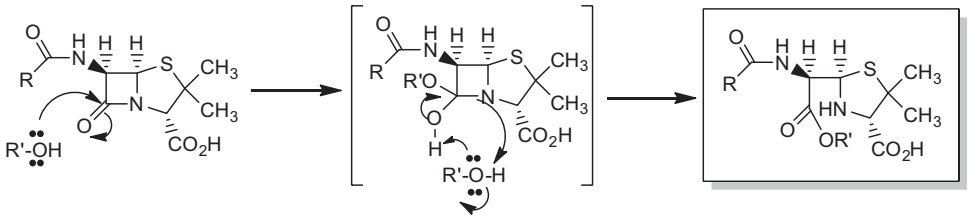
Halogen–lithium exchange was conducted at −100 °C in tetrahydrofuran using *n*-butyllithium as the organometallic exchange reagent (Scheme 4). In order to determine whether the exchange reaction occurred, the reaction mixture was quenched with various electrophiles at low temperatures (H_2O, CH_3I, benzaldehyde, and CO_2/H_3O^+). Analysis of the reaction mixtures confirmed that intermediates (**5**) did indeed form in the presence of the reactive β-lactam ring, thereby proving that the β-lactam is indeed robust enough to withstand the reaction conditions. The structures of the elaborated β-lactams were confirmed by ^1H NMR, ^{13}C NMR, IR, and GC/Mass spectra. (See Table 1)

* Corresponding author.
E-mail address: hunt@tcnj.edu (D.A. Hunt).

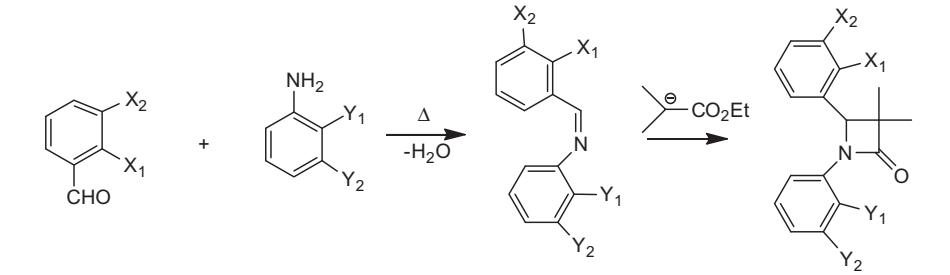
0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.07.007



Scheme 1.



Scheme 2.



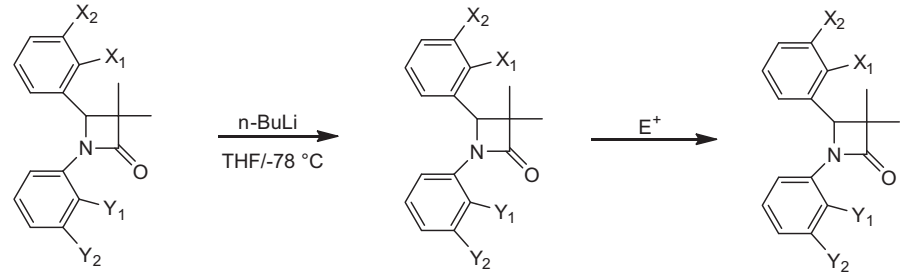
1a: X_1=Br; X_2=H
1b: X_2=Br; X_1=H
1c: X_1=H; X_2=H

2a: Y_1=H; Y_2=H
2b: Y_1=Br; Y_2=H
2c: Y_2=Br; Y_1=H

3a: X_1=Br; X_2=Y_1=Y_2=H
3b: X_2=Br; X_1=Y_1=Y_2=H
3c: Y_1=Br; X_1=X_2=Y_2=H
3d: Y_2=Br; X_1=X_2=Y_1=H

4a: X_1=Br; X_2=Y_1=Y_2=H
4b: X_2=Br; X_1=Y_1=Y_2=H
4c: Y_1=Br; X_1=X_2=Y_2=H
4d: Y_2=Br; X_1=X_2=Y_1=H

Scheme 3.



4a: X_1=Br; X_2=Y_1=Y_2=H
4b: X_2=Br; X_1=Y_1=Y_2=H
4c: Y_1=Br; X_1=X_2=Y_2=H
4d: Y_2=Br; X_1=X_2=Y_1=H

5a: X_1=Li; X_2=Y_1=Y_2=H
5b: X_2=Li; X_1=Y_1=Y_2=H
5c: Y_1=Li; X_1=X_2=Y_2=H
5d: Y_2=Li; X_1=X_2=Y_1=H

6a: X_1=E; X_2=Y_1=Y_2=H
6b: X_2=E; X_1=Y_1=Y_2=H
6c: Y_1=E; X_1=X_2=Y_2=H
6d: Y_2=E X_1=X_2=Y_1=H

Scheme 4.

The reaction of the bromoaryl β-lactams **4** in which a halogen–metal exchange occurred at low temperatures to generate the reactive intermediates **5** proved successful. The aryllithium which formed was quenched with various electrophiles (including H_2O, CH_3I, PhCHO, and CO_2/H_3O^+) to afford the elaborated intermediates in moderate to low yield with no products resulting from ring opening of the highly reactive β-lactam ring observed.[10]

While these results indicate that halogen–metal exchange can indeed occur at low temperatures without opening the β-lactam ring system, efforts directed toward better understanding the regioselectivity effects of ring position (i.e., **4a** vs **4b**) with regard to the efficiency of the exchange reaction remain to be studied. In addition, further optimization work is necessary in order to fully ascertain the potential of this method.

Table 1

Entry	Compound	E^+	X/Y	% Yield (isolated)
1	**6c**	H_2O	H	62
2	**6c**	CH_3I	CH_3	66
3	**6c**	PhCHO	CH(Ph)OH	9
4	**6a**	H_2O	H	46
5	**6c**	C_2H_5I	C_2H_5	62
6	**6b**	H_2O	H	69
7	**6a**	CH_3I	CH_3	50
8	**6d**	CH_3I	CH_3	47
9	**6a**	CO_2/HCl	CO_2H	67

Acknowledgments:

We wish to thank The College of New Jersey and Bristol Myers Squibb for their generous support of this work.

References and notes

1. Parham, W. E.; Bradsher, C. K. *Acc. Chem. Res.* **1982**, *10*, 300–305.
2. Lewis, R. *The Rise of Antibiotic-Resistant Infections*. http://dwb4.unl.edu/chem/chem869k/chem869klinks/www.fda.gov/fdac/features/795_antibio.html; [accessed May 21, 2013].
3. http://www.cdc.gov/drugresistance/; [accessed May 21, 2013].
4. Patrick, G. L. *Introduction to Medicinal Chemistry*, 3rd ed.; Oxford Press: Oxford, 2005. Chapter 16.
5. For heteronucleophiles see: (a) Mukerjee, A. K.; Singh, A. K. *Synthesis* **1975**, 547–589; (b) Mukerjee, A. K.; Singh, A. K. *Tetrahedron* **1978**, *34*, 1731–1767; (c) Manhas, M. S.; Wagle, D. R.; Chiang, J.; Bose, A. K. *Heterocycles* **1988**, *27*, 1755–1802; For carbon nucleophiles see (d) Spero, D. M.; Kapadia, S.; Vittorio, F. *Tetrahedron Lett.* **1995**, *36*, 4543–4546; (e) Palomo, C.; Aizpurua, J. M.; Garcia, J. M.; Iturburu, M.; Odriozola, J. M. *J. Org. Chem.* **1994**, *54*, 5184–5188; (f) Kano, S.; Ebata, T.; Shibuya, S. *Chem. Pharm. Bull.* **1979**, *27*, 2450–2455; (g) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F. *Tetrahedron: Asymmetry* **1999**, *10*, 4841–4849; (h) Panaiotova, B.; Pencheva, B. A.; Spasov, A. W. *Doklady Bolgarskoi Akademii Nauk* **1972**, *25*, 787–790.
6. For example, see Vildan, G.; Yildirir, S.; Ozcelik, B.; Abbasoglu, U. *Farmaco* **2000**, *55*, 147–150.
7. Vaccaro, W.; Sher, R.; Davis, H. R. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 319; (b) Repa, J. J.; Dretschy, S. D.; Turley, S. D. *J. Lipid Res.* **2002**, *43*, 1864–1874. and references cited therein.
8. *General procedure for preparation of Schiff bases* **3**: Preparation of *N*-benzylidine-*o*-bromoaniline (**3c**). *o*-Bromoaniline (25.00 g; 0.145 mol) and benzaldehyde (15.41 g; 0.145 mol) were dissolved in toluene (500 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 an oil which was purified by distillation in vacuo to afford the product as a viscous yellow oil (29.59 g, bp 116 °C/0.7 Torr) which solidified on standing, mp 43–44.5 °C (lit mp 45 °C. ^{1}H NMR ($CDCl_3$): δ 6.73–7.80 (m, 9, Ar*H*); 8.04 (s, 1, azomethine C*H*); IR (film) 1625 cm^{-1}. Anal. Calcd for $C_{13}H_{10}BrN$; C, 60.00; H, 3.85; Br, 30.77; N, 5.38. Found: C, 59.80; H, 3.68; Br, 30.42; N, 5.18.
9. *General procedure for the preparation of bromoaryl β-lactams* **4**: Preparation of 1-(2-bromophenyl)-3,3-dimethyl-4-phenylazetidin-2-one (**4c**): diisopropylamine (809 mg, 8 mmol) in dry THF (15 ml) was placed in an oven-dried 100 mL 3-neck round bottomed 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; 8 mmol) was added dropwise. After the resulting mixture was stirred at −78 °C under nitrogen for 20 min, ethyl isobutyrate (928 mg; 8 mmol) in THF (10 mL) was added dropwise. Stirring at −78 °C continued for an additional 20 min at which point the desired Schiff base (2.07 g; 8 mmol) was added dropwise at such a rate so as to maintain the temperature below −70 °C. The resulting solution was allowed to stir for 1 h at −78 °C, and 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 × 75 mL). The organics were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with a mixture of hexanes/ethyl acetate. 1-(2-Bromophenyl)-3,3-dimethyl-4-phenylazetidin-2-one (**4c**) was isolated as pale yellow needles (2.27 g, 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 ($CDCl_3$) δ 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}. Anal. Calcd for $C_{17}H_{16}BrNO$; C, 61.83; H, 4.88; Br, 24.20; N, 4.24. Found: C, 61.63; H, 4.56; Br, 24.31; N, 4.37.
10. *General procedure for halogen–metal exchange of bromoaryl β-lactams* **4**: Preparation of 3,3-dimethyl-1,4-diphenylazetidin-2-one (**6b**: X=Y=H): bromoaryl β-lactam (**4**; 200 mg; 0.61 mmol) in dry THF was cooled to −100 °C under nitrogen. *n*-Butyllithium (1.2 equiv of a 1.6 M solution in hexanes) 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 equiv of the electrophile. The low temperature was maintained for another hour and then the mixture was allowed to slowly warm to room temperature. The reaction mixture was poured into water (100 mL), and the resulting mixture was washed with EtOAc (2 × 75 mL). The organics were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was 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 (103 mg, 69%), mp 146–47.5 °C (lit[11] mp 147.5–48.5 °C); ^{1}H NMR ($CDCl_3$) δ 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 ($CDCl_3$) δ 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) 1733 cm^{-1}.
11. Gluchowski, C.; Cooper, L.; Bergbreuter, D. E.; Newcomb, M. *J. Org. Chem.* **1980**, *45*, 3413–3416.