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Reactions of *N*-Chloro β-Lactams

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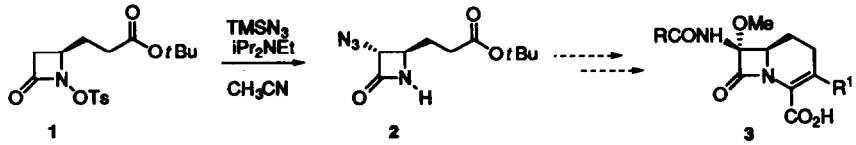
Abstract: *N*-Chloro β-lactam **4** was prepared to explore its potential for a methoxy transfer to the C3 position of the β-lactam. Methoxy addition to C3 of β-lactam **4** with concomitant loss of chloride to give α-methoxy β-lactam **5** occurred under mild alkaline conditions but was accompanied by methanolysis of the β-lactam ring as the major reaction pathway. Reaction of **4** with $AgNO_3$ promoted methoxy addition to C4 of the β-lactam followed by subsequent reactions.

INTRODUCTION

We previously described a catalytic, asymmetric synthesis of the carbacephem framework.[1] In this synthesis, the introduction of the amino substituent at the α-position of the β-lactam utilized the "nucleophile transfer reaction"[2] with *N*-tosyloxy β-lactam **1**. Tertiary amine promoted nucleophilic azide introduction to **1** was highly diastereoselective and provided azido β-lactam **2** with *trans* stereochemistry. However, for biological activity in the carbacephem series, *cis* stereochemistry about the β-lactam is required.[3]



1 **2** **3**

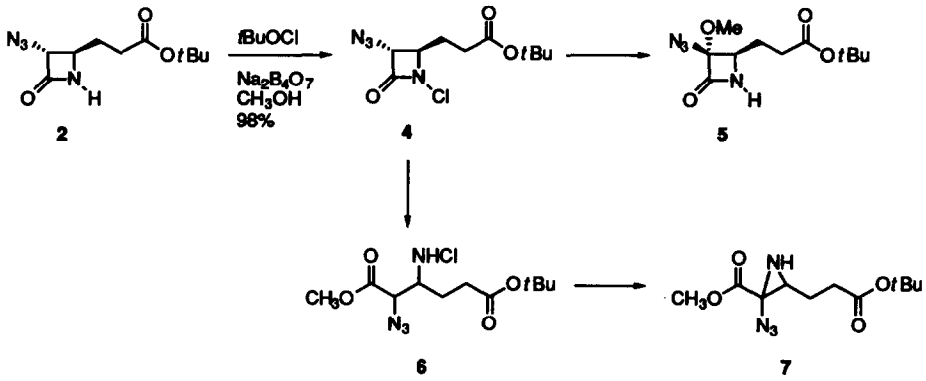
Our objective for this study was to explore extensions of the nucleophile transfer reaction. We were particularly intrigued by the possibility of α-methoxy addition to azido β-lactam **2** with a second nucleophile transfer reaction, thereby controlling absolute stereochemistry at the α-center, utilizing an *N*-chloro β-lactam intermediate. Methoxy addition to *N*-tosyloxy β-lactams has been explored in our group and an α-phthalimido group was found to expedite the reaction.[2b] Potentially, this new methodology could provide access to α-methoxycarbacephem framework **3**.[4]

N-Chloro and *N*-bromo β-lactams have been prepared but their chemistry is largely unexplored.[5] One set of studies found that *N*-chloro and *N*-bromo β-lactams rearranged in the presence of olefins or alkynes to afford β-chloro and β-bromoalkyl isocyanates, respectively.[5d-e] This radical rearrangement was promoted by irradiation, radical initiators, or thermal energy.

RESULTS AND DISCUSSION

Azido β-lactam **2** was converted to the less polar, UV active *N*-chloroamide **4** by treatment with *t*-butyl hypochlorite and $Na_2B_4O_7$ in methanol for 25 min at 0° C following a literature protocol.[5b] Surprisingly, substitution of triethylamine for sodium borate as base in this reaction proved incompatible and gave only starting β-lactam **2** after an exothermic reaction. Noteworthy was the shift of the β-lactam carbonyl stretching frequency from **2** (1770 cm^{-1}) to **4** (1795 cm^{-1}).

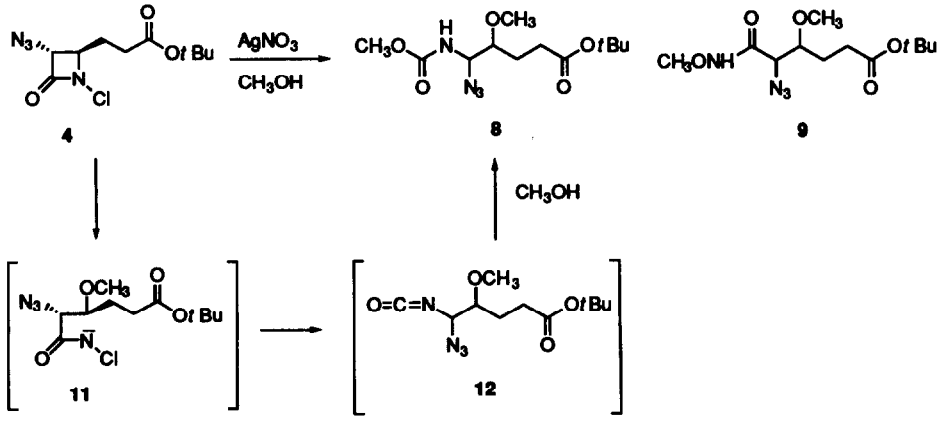
In an attempt to transfer a methoxy group, *N*-chloro β-lactam **4** was allowed to react with three equivalents of diisopropylethylamine (DIEA) in methanol. By analogy to our previous reactions with *N*-tosyloxy β-lactams,[2] the excess base was anticipated to facilitate the nucleophile transfer reaction by promoting enolization. α-Methoxy-β-lactam **5** was isolated as anticipated, but in only 12% yield from a complex mixture of products, which also contained small amounts of **2** from dechlorination and polar, non-chromatographically mobile products. Repetition of the reaction with a reduced amount (1.1 equiv) of DIEA in 2:1 acetonitrile:methanol at 0° C to room temperature over 5 h increased the amount of the competitive dechlorination giving azido β-lactam **2** in 75% yield. Thus, in contrast to the previously studied *N*-tosyloxy β-lactams, the *N*-chloro analogs are susceptible to an alternate mode of nucleophilic attack at chlorine. While it is not surprising that **4** would serve as a halogenating agent, these results prompted studies with less nucleophilic bases.

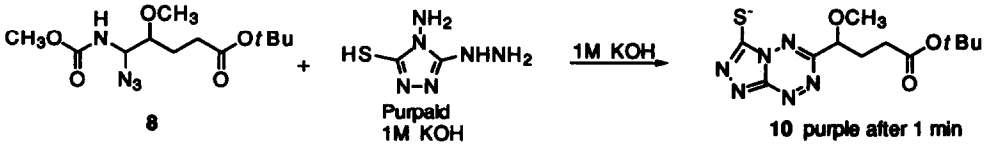


Reaction of *N*-chloro β-lactam **4** with a 3.2% methanolic potassium carbonate solution did not lead to any of the desired β-lactam **5**, but again provided a very complex mixture of polar non-characterizable products, presumably from ring opening reactions. Sodium borate was considered as a potential base since it is moderate and non-nucleophilic and might also activate the β-lactam carbonyl to enolization (and/or nucleophilic attack). Reaction of azido β-lactam **2** with *t*-butylhypochlorite in 4% methanolic sodium borate for 18 h at room temperature led to the isolation of 15% of α-methoxy β-lactam **5** after column chromatography. Careful analysis of all the chromatographed fractions revealed *N*-chloramine **6** (36%), aziridine **7** (18%), as well as starting material **2** (3%) to give a combined recovery of 72%.

Presumably, the desired α-methoxy β-lactam **5** was formed by the same type mechanism as the nucleophile transfer reaction with *N*-sulfonyloxy β-lactams.[2b] Boron-assisted enolization of β-lactam **4** in the methanol solution, followed by an S_N2' addition of methanol to displace the chloride and subsequent tautomerization would account for the product formation. The stereochemistry indicated for the product is based upon considerable precedent with the nucleophile transfer reaction.[2b] Possible boron-mediated activation of the β-lactam carbonyl was reflected by isolation of the methyl ester of chloramine **6**, which had not been observed in the previous reactions. Aziridine **7** was shown to be derived from chloramine **6**. Independent treatment of pure chloramine **6** with 4% methanolic sodium borate solution gave **7** as observed by ^{1}H NMR and TLC analysis. *N*-Chloramines are electrophilic nitrogen sources[6] and apparently deprotonation adjacent to the azide group of **6** followed by displacement of chloride provided aziridine **7**. The azido-aziridine sub-structure of **7** has been prepared previously by different synthetic approaches.[7] The synthesis of aziridines from chloramines, however, has not appeared in the literature to our knowledge.[8]

Potentially, Lewis acidic conditions also could be used to supply the proposed reactive enol intermediate of *N*-chloro β-lactam **4** for nucleophilic methoxy transfer reactions and obviate the major methanolysis pathway observed under basic conditions. Silver (I) has been used to promote a variety of rearrangements with *N*-chloramines.[9] We hypothesized that silver (I) would coordinate with the chlorine atom of the *N*-chloro β-lactam, potentially facilitating enolization, thus promoting methoxy transfer to the α-position of β-lactam **4**. Reaction of *N*-chloro β-lactam **4** with three equivalents of silver nitrate in methanol for three days formed a gray precipitate. Surprisingly, 60% of the starting material **4** and 20% of another product were obtained after chromatography. Two structural isomers **8** or **9** agreed with the ^{1}H NMR, mass spectroscopic, and IR data obtained for the product. Unambiguous determination of structure was proven by a Purpald® test, a general test for the aldehyde function.[10] A small aliquot of the product was dissolved in 1M KOH and Purpald® was added. After 1 minute, the solution turned purple and was compared with the appropriate control reaction as positive proof of a latent aldehyde function assigned to structure **8**. Compound **10** was responsible for the purple color.[10] In further support, close inspection of the ^{1}H NMR spectrum revealed a doublet for the NH proton which is in agreement with the proposed structure **8**.





Presumably, silver (I) coordinated to the chlorine of *N*-chloro β-lactam **4** and instead of promoting enolization it increased the leaving group ability of the *N*-chloroamide function. Nucleophilic S_N2 displacement by methanol at the C4 carbon of the β-lactam released the acyclic *N*-chloroamide **11** which underwent facile Hoffmann rearrangement[11] to give reactive isocyanate **12**. Subsequent reaction of isocyanate **12** with methanol provided methyl carbamate **8**. Treatment of *N*-chloro β-lactam **4** with ferric chloride in methanol led to a similar product distribution as observed with $AgNO_3$.

In conclusion, relative to *N*-tosyloxy β-lactams, nucleophilic addition to the α-carbon of *N*-chloro β-lactams is complicated by competitive side reactions. However, DIEA or borate-promoted methanol addition to *N*-chloro β-lactam **4** with concomitant loss of chloride to give α-methoxy β-lactam **5**, although low yielding, is the first example of a nucleophilic transfer reaction with this class of molecule. Nucleophile transfer reaction to *N*-chloro β-lactams with other more potent, less basic nucleophiles may prove more promising than the methoxy transfer reaction. In fact, methanol was found to be one of the poorer nucleophiles in reactions with *N*-tosyloxy β-lactams.[2b] Future research to explore the scope of *N*-chloro β-lactams as intermediates in the nucleophile transfer reaction is being considered.

EXPERIMENTAL SECTION

General Methods. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra were obtained on a General Electric GN-300 spectrometer and were performed in chloroform-*d*. ^1H NMR chemical shifts are reported in parts per million relative to tetramethylsilane. *J* values are given in hertz. For ^{13}C NMR, reference was the center peak of chloroform-*d* (77.0 ppm). IR spectra were recorded on a Perkin-Elmer 1420 spectrophotometer. TF refers to thin film, and KBr refers to potassium bromide disk. Electron impact (EI) mass spectra, Chemical ionization (CI) mass spectra, and fast atom bombardment (FAB) were recorded on an AEI Scientific Apparatus MS 902 and Finnigan MAT Model 8430 spectrometers. Analytical TLC was carried out using commercially available aluminum-backed 0.2-mm silica gel 60 F-254 plates. Flash silica gel column chromatography was conducted using Merck silica gel 60 (230-400 mesh).

All reactions were periodically monitored by TLC and worked up after the complete consumption of starting material unless specified otherwise. Solvents for flash column chromatography were distilled. Anhydrous CH_2Cl_2, CH_3CN, and Et_3N were freshly distilled from CaH_2 and stored under nitrogen. All purchased reagents were of reagent grade quality and were used without further purification.

2-Azetidinepropanoic acid, 1-chloro-3-azido-4-oxo-(1,1-dimethylethyl) ester, *trans* (4). Azido β-lactam **2** (70 mg, 0.292 mmol) was dissolved in 3 mL of 4% sodium borate in methanol and cooled to 0°C. *tert*-Butyl hypochlorite (58 μL, 0.408 mmol, 1.4 eq) was added by syringe and the solution was stirred for 25 min. at 0°C. TLC analysis with 1:1 ethyl acetate : hexanes showed only one

spot (R_f = 0.6 UV, PMA blue) and no starting material (R_f = 0.37 PMA blue). Ethyl acetate (10 mL) was added and the organic layer was washed with 5% sodium bicarbonate solution three times. The organic layer was dried over $MgSO_4$, filtered, and evaporated to give 75 mg (95%) of **8** as an oil. ^1H NMR δ 4.54 (d, 1H, J = 2.1 Hz) 3.65-3.71 (m, 1H), 2.3-2.5 (m, 2H), 2.1-2.2 (m, 1H), 1.85-2.0 (m, 1H), 1.47 (s, 9H); ^{13}C NMR δ 171.2, 163.0, 81.5, 69.0, 66.7, 30.7, 28.0, 25.4; IR (TF) 2105 s, 1795 s, 1720 s cm^{-1}; MS (isobutane CI) gave MH^+ = 275 + 277; MS (EI) gave 183, M - (Cl + C_4H_8).

Reaction of azido-β-lactam 4 with 4% methanolic sodium borate and isolation of compounds 5, 6, 7: Azido β-lactam **4** (50 mg, 0.208 mmol) was dissolved in 4 mL of 4% sodium borate in methanol, cooled in an ice bath and *t*-butylhypochlorite (32 μl, 0.228 mmol) was added by syringe. The reaction was allowed to warm to room temperature and stirred for 18h. TLC analysis with 1:1 ethyl acetate : hexanes showed four spots at R_f = 0.61 (UV, PMA blue), 0.50 (PMA blue), 0.45 (UV slight, PMA blue), 0.40 (PMA blue). Column chromatography was done with ethyl acetate:hexanes (1:4) mixture to give compound **6** (36%, R_f = 0.61), compound **7** (18%, R_f = 0.50), compound **5** (15%, R_f = 0.40) and starting β–lactam **1** (3%) to give a 71% total yield after chromatography.

Spectral Characteristics of isolated compounds:

2-Azetidinepropanoic acid, 3-azido-3-methoxy-4-oxo-(1,1-dimethylethyl) ester (2R, 3R) (5): ^1H NMR δ 6.21 br (s, 1H), 3.68-3.78 (C_4 of β-lactam with impurities), 3.59 (s, 3H), 2.2-2.5 (m, 2H), 1.8-1.9 (m, 2H), 1.450 (s, 9H); IR (TF) 3300 br, 2110 s, 1770 s, 1720 s cm^{-1}; MS (isobutane CI) gave MH^+ = 271, MH^+ -28 = 243, MH^+ (-28, -56) = 187; HRMS (ammonia CI) Calcd M^+NH_4 288.16718, Found: 288.1646.

Hexanedioic acid, 2-azido-3-chloramino-1-methyl-6-(1,1-dimethylethyl) ester (6): ^1H NMR δ 4.75 (d, 1H, J=3.9 Hz), 4.50 (d, 1H, J=9.6Hz), 3.86 (s, 3H), 3.3-3.4 (m, 1H), 2.3-2.4 (m, 2H), 1.65-1.75 (m, 2H), 1.44 (s, 9H); IR (TF) 3250 br, 2100 s, 1715-1740 s cm^{-1}; MS (FAB) gave MH^+ at 307, MH^+ - 56 = 251. Compound **6** slowly decomposed upon storage over a period of 1 week.

Hexanedioic acid, 2-azido-2,3-aziridino-1-methyl-6-(1,1-dimethylethyl) ester (7): ^1H NMR δ 3.87 (s, 3H), 2.61-2.7 (m, 1H), 2.40 (t, 2H, J = 7.2Hz), 2.15-2.2 br (s, 1H), 1.83 (m, 2H), 1.45 (s, 9H); IR (TF) 3300, 2105 s, 1720-1735 s cm^{-1}; MS (isobutane CI) MH^+ at 271, MH^+ - 28 = 243, MH^+ -28, -56 = 187; MS (FAB) gave MH^+ = 271, MH^+ - 28 = 243, MH^+ -56 = 215, MH^+ -28, -56 = 187 and also observed a cluster 2n + 1 = 541.

Pentanoic acid, 4-methoxy-5-azido-5-[(1-oxo-1-methoxy)methylamino]-(1,1-dimethylethyl) ester (8): Chloro β-lactam **4** (20 mg, 0.091 mmol) was dissolved in methanol (2 mL) and $AgNO_3$ (45 mg, 0.273 mmol, 3 eq.) was added. The solution was initially homogeneous but a gray precipitate was evident after 30 minutes. The reaction was stirred for 3 days, filtered, evaporated and chromatographed to give 12 mg (60%) of starting material **4** and 4 mg (20%) of **8** as an oil after concentration. R_f = 0.52 (1:1 ethyl acetate:hexanes, PMA blue visualization). ^1H NMR δ 4.9 br (1H), 4.42 (d, 1H), 3.85-3.95 (m, 1H), 3.68 (br s, 3H), 3.53 (s, 3H), 2.3 (t, 2H), 1.8-1.95 (m, 1H), 1.7-1.8 (m, 1H), 1.44 (s, 9H); IR (TF) 3335 br, 2105 s, 1725, 1700, 1530, 1450 cm^{-1}; MS (isobutane CI) MH^+ 303, 260, 247, 204.

Purpald® test: A small sample of product **8** was dissolved in 0.25 mL of 1M KOH and a small amount of Purpald was added. After 1 min, a deep purple color appeared which intensified with time. A control reaction was run side by side where Purpald was added to a solution of 1M KOH. Over the same period of time, only a faint hint of purple was apparent which did not intensify over time.

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