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A COMBINED ELECTROPHILIC DIAZO AND NUCLEOPHILIC AZIDE TRANSFER REACTION FOR THE EFFICIENT CONVERSION OF AN *N*-HYDROXY-β-LACTAM TO A CARBACEPHEM PRECURSOR

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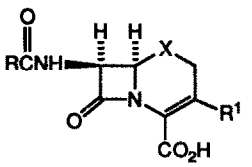
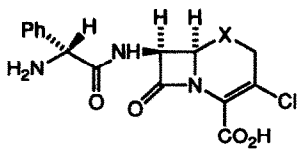
Abstract. A new method for the synthesis of carbacephems has been developed. A combined diazo transfer, *N-O* reduction and azide transfer reaction of *N*-hydroxy-β-lactam **10b** produced **11** in 78.8% yield by treatment with trisyl azide and $TMSN_3$ in the presence of *N,N*-diisopropylethylamine. Rhodium-mediated cyclization of diazo/azide **11** to carbacephem **12** proceeded without interference from the azide.

Cephalosporins (**1**) are the most widely used antibiotics. Replacement of the sulfur in the cephalosporins with a methylene group to give the carbacephalosporins (**2**) has required considerable research and development, but has produced useful new antibiotics. For example, although Ceclor® (**3**) is an excellent antibiotic, its carbon analog, Lorabid® (**4**), has a significantly enhanced physiological half life while retaining a similarly potent antimicrobial spectrum.[1] Unlike penicillins and cephalosporins which are ultimately derived from fermentation products, carbacephems have been made only by total syntheses. Most of the synthetic routes to carbacephems utilize a [2+2] reaction of a suitable imine and an *in situ* generated ketene to form the initial β-lactam.[2] Procedures for the formation of the second fused ring then differentiate each individual method. Our laboratory recently reported an alternative synthesis of the carbacephem nucleus from *anti* β-hydroxy-α-amino acids.[3] Here we describe an effective approach to the entire carbon framework of carbacephems with peripheral functionality appropriate for eventual elaboration to antibiotics (Scheme 1). The key to the process is an improved version of the recently discovered[4] novel azide transfer reaction (**10b**→**11**) and direct cyclization of diazo/azide **11** to carbacephem nucleus **12**.

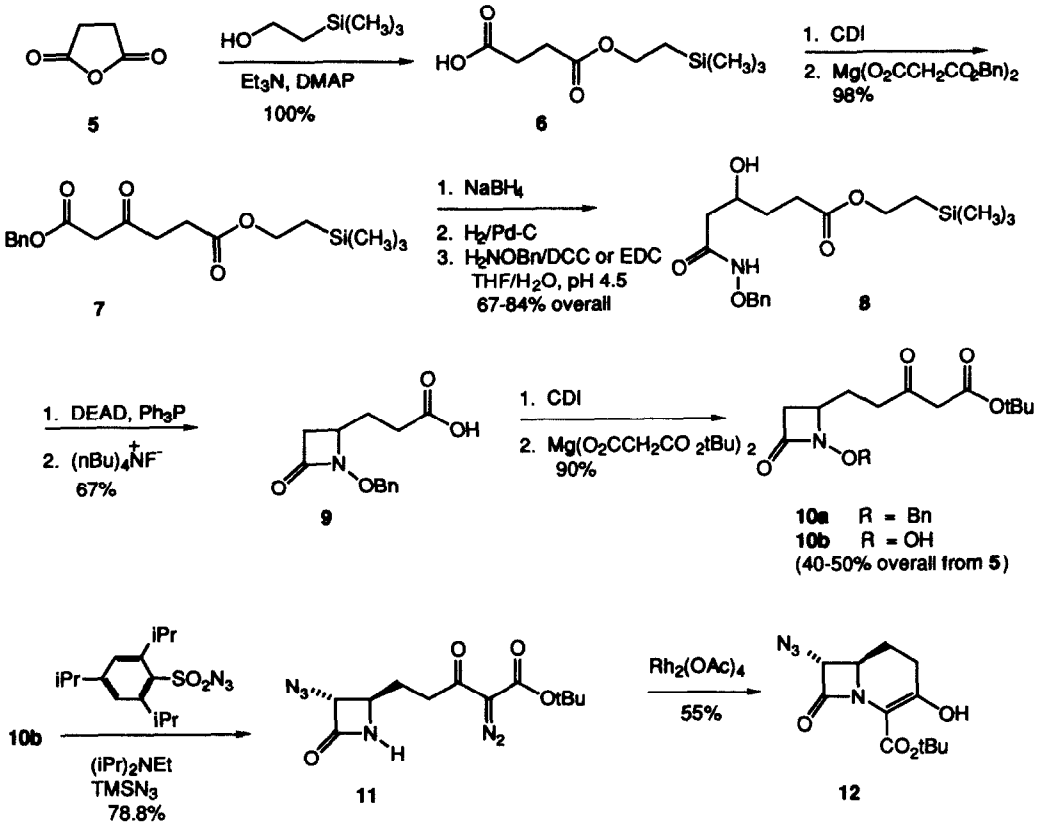


1 X = S, cephalosporins
2 X = CH_2, carbacephalosporins



3 X = S, Ceclor®
4 X = CH_2, Lorabid®

Scheme 1



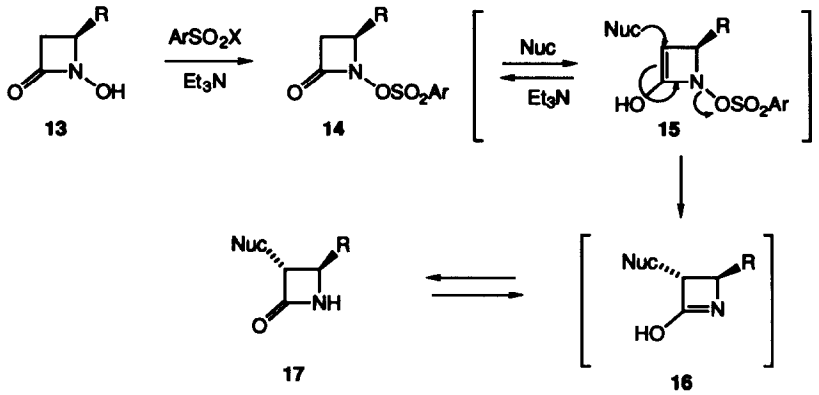
5 6 7 8 9 11 12

Results and Discussion

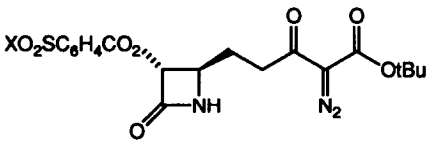
Methods describing the preparation of keto ester **10b** and related compounds in Scheme 1 have been reported earlier.[5] The focus here is on the novel transformation of **10b** to **11** and the subsequent cyclization to **12**. The conversion of **10b** to **11** involves three remarkably effective transformations in one reaction. The diazo transfer reaction to the β-keto ester was completely expected, but the simultaneous N-O reduction of **10b** with transfer of azide to the α-position of the β-lactam ring was unanticipated. Our initial discovery of the N-O reduction/azide transfer reaction involved treatment of **10b** with 4-(azidosulfonyl)benzoic acid in the presence of triethylamine to give **11** in only 27% yield.[4a] Further investigation of this interesting reaction indicated that the N-O bond reduction and azide transfer reaction were coupled. In fact, we subsequently demonstrated that conversion of *N*-hydroxy β-lactams to the corresponding tosylates followed by reaction with a variety of nucleophiles induces *nucleophilic* attack at the α-carbon to give the corresponding substitution products (Scheme 2).[4b] The resulting *trans* stereochemistry of final product **17** is a consequence of the presumed S_N2'-like mechanism in the β-lactam series, although related reactions with acyclic hydroxamates appear to be mechanistically different.[6] While these nucleophile transfer reactions may facilitate the synthesis of a number of novel β-lactams, the utility of the conversion of **10b** to **11** for the preparation of carbacephems

was diminished by the low (27%) yield of the transformation. Variation of the reagents and conditions of the reaction were anticipated to improve this potentially useful process.

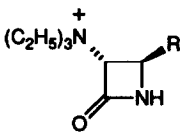
Scheme 2



The azide transfer reagent used in our earlier studies was 4-(azidosulfonyl)benzoic acid, because of the ease of extractive removal of the sulfonamide by-products after the reaction. However, our later studies of reactions of nucleophiles with *N*-tosyloxy-β-lactams indicated that carboxylates were very effective nucleophiles. Thus, the yield of **11** from **10b** could have been diminished by the competitive reaction of the *p*-carboxy benzene sulfonamide to produce **18a**, or the corresponding sulfonic acid **18b**, which would have been lost on extractive and chromatographic purification of **11**. Indeed, we found that use of tosyl azide improved the yields of the azide transfer reactions, but the resulting *p*-toluenesulfonamide and **11** had the same R_f values and were difficult to chromatographically separate. As a result, trisyl azide became our ultimate choice of reagent. During the general studies of the nucleophile transfer reaction (Scheme 2) we also discovered that even relatively hindered bases like triethylamine were competitive nucleophiles and formed quaternary salts **19**. Change to the even more hindered *N,N*-diisopropylethylamine was beneficial. Finally, since the required nucleophilic azide was generated only during the reaction of the arylsulfonylazide with the *N*-hydroxy β-lactam, trimethylsilylazide was added to facilitate the reaction. Thus, the combined use of trisyl azide, trimethylsilylazide and *N,N*-diisopropylethylamine resulted in the dramatic improvement of the conversion of **10b** to **11** to 78.8% isolated, purified yield.



18a X = NH_2
18b X = OH



19

Formation of bicyclic β-lactams by rhodium catalyzed reactions of α-diazo-β-keto esters has considerable precedent.[7] However, the reactivity of the azide substituent during generation of the carbenoid was of concern. We were pleased to find that treatment of **11** with a catalytic amount of rhodium acetate

produced **12**, with no interference from the azide. Preliminary analysis of the reaction mixture indicated that the reaction was very clean. However, chromatographic purification resulted in a 55% yield of the relatively unstable product as a 1:3 mixture of keto and enol forms. Conversion to the corresponding more stable enol tosylate or vinyl chloride is recommended. [2d,8]

In summary, we have described an improved synthetically useful method for the one-pot multifunctional transformation of *N*-hydroxy β-lactams to α-azido-*N*-unsubstituted β-lactams, and in the case of the conversion of **10b** to **11** the reaction proceeded with concurrent diazo transfer. Rhodium acetate-induced cyclization produced carbacephem **12**. Precedented epimerization of the *trans* azide to the *cis* isomer[9] and reduction of the azide to an amine,[10] will provide an effective synthesis of carbacephems related to Lorabid®. Extensions of this methodology to an asymmetric synthesis are in progress.

Experimental Procedures

***t*-Butyl 5-(*trans*-3-azido-2-oxo-4-azetidinyl)-2-diazo-3-oxopentanoate (11).** A solution of t-butyl 5-(1-benzyloxy-2-oxo-4-azetidinyl)-3-oxopentanoate (**10a**, 73 mg, 0.21 mmol) in methanol (2.0 mL) was hydrogenolyzed with H_2 (1 atm) and 10% Pd/C (5 weight %) for 2 h at room temperature. Removal of excess hydrogen gas with a stream of nitrogen, followed by filtration of the catalyst and evaporation of the solvent produced *N*-hydroxy β-lactam **10b** as an oily product. To avoid precedented rearrangement,[4b] this product was not further purified. Instead it was carried on to the next reaction immediately. To a solution of **10b** (54 mg, 0.21mmol) and trisyl azide (162.5 mg, 0.526 mmol) in CH_3CN (1.0 mL) under a nitrogen atmosphere was added *N,N*-diisopropylethylamine (0.09 mL, 0.526 mmol). After stirring for 10 min, $TMSN_3$ (0.014 mL, 0.1 mmol) was added. The resulting light-brown reaction mixture was left at room temperature for 4 days. The reaction was concentrated under reduced pressure and the residue was purified by column chromatography eluting with ethyl acetate/hexanes (1:2) to produce **11** as a white solid (51 mg, 78.8%). R_f = 0.38 (1:1 ethyl acetate/hexanes); mp 89.5-91°C; (from ether) ^{1}H NMR δ 1.53 (s, 9H), 1.92-2.15 (m, 2H), 2.86 (dt, J = 6.9, 16.8 Hz, 1H), 3.02 (dt, J = 7.2, 16.8 Hz, 1H), 3.56 (dt, J = 2.1, ~6.5 Hz, 1H), 4.29 (apparent t, J = 1.8 Hz, 1H), 6.3 (bs, NH); ^{13}C NMR δ 27.94, 28.27, 36.10, 56.33, 69.64, 83.68, 160.39, 163.92, 191.65 (diazo C was not observed); IR (neat oil before recrystallization) 3100-3400, 2140, 2110, 1780, 1715, 1650 cm^{-1}; MS (FAB) 309 (M+1).

t-Butyl 3-hydroxy-7-azido-8-oxo-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylate (12). Compound **11** (46 mg, 0.15 mmol) was dissolved in thiophene-free, degassed benzene (1.0 mL). A catalytic amount (≤5 weight %) of $Rh_2(OAc)_4$ was added and the reaction mixture was heated in an oil bath for 15 min (bath temperature 68 ~ 80°C). The bath was removed and the reaction mixture was cooled down to room temperature. The catalyst was removed by filtering the reaction mixture through a plug of silica gel (2.5 mL) and eluting wih ethyl acetate. After concentration, the clear yellow oil was washed with hexanes ten times (total of 15 mL) to further purify the desired product from the yellow contaminants. The combined washes yielded **12** (20 mg) as colorless thick oil. The remaining yellow gum was further subjected to silica gel chromatography (5.5 mL column volume) with ethyl acetate/hexanes (1:2) to afford more product (3.0 mg). Therefore, the total amount of pure **12** isolated from this reaction was 23 mg (55%). ^{1}H NMR indicated the product existed as a 1:3 mixture of keto and enol forms. ^{1}H NMR (enol product) δ 1.57 (s, 9H), 1.67-1.81 (m, 1H), 2.02-2.36 (m, 1H), 2.48-2.51 (m, 2H), 3.43-3.53 (ddd, J = 0.6, J = 2.9, J = 10.7, 1H), 4.16-4.17 (d, J = 0.9, 1H), 4.84 (b, 1H); IR

(neat oil) 3350, 2980, 2940, 2110, 1770-1730, 1660, 1370, 1250, 1155cm^{-1}; Ms m/e 280 (M^+), 265, 224, 207, 196, 179, 123, 112, 96; HRMS calcd for $C_{12}H_{16}N_4O_4$, 280.1171, found 280.1177.

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62.62, 67.48, 77.97, 128.32, 128.46, 128.99, 135.11, 169.55, 173.92; CIMS (isobutane) *m/e* 368 (MH^+); Anal. Calcd for $C_{18}H_{29}NO_5Si$: C, 58.83; H, 7.95; N, 3.81. Found: C, 59.14; H, 7.65; N, 3.94. **9**: mp 62-64 °C; (recrystallized from ether-hexanes) IR (thin film) 3700-2500 (br), 2940, 1750 cm^{-1}; IR (CCl_4) 1775, 1710 cm^{-1}; ^1H NMR (300 Mz, $CDCl_3$) δ 1.72-1.84 (m, 1H), 1.87-1.99 (m, 1H), 2.32 (dd, 1H, J = 2.4, 13.8), 2.75 (dd, 1H, J = 5.2, 13.8), 3.55 (m, 1H), 4.96 (dd, 2H, AB system), 7.39 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.37, 29.94, 37.55, 57.01, 78.27, 128.69, 129.12, 129.37, 135.03, 164.13, 177.53. **10a**: oil; IR (thin film) 3040, 2970, 2925, 1775, 1740, 1715 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.46 (s, 9H), 1.71-1.95 (m, 2H), 2.29 (dd, 1H, J = 2.4, 13.7), 2.52 (m, 2H), 2.72 (dd, 1H, J = 5.2, 13.7), 3.30 (dd, 2H, AB system), 3.57 (m, 1H), 4.93 (d, 1H, J = 11.2), 4.97 (d, 1H, J = 11.2), 7.40 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.66, 27.29, 37.33, 38.02, 50.13, 56.45, 77.83, 81.76, 128.37, 128.74, 129.03, 134.97, 163.64, 165.94, 201.48; CIMS (isobutae) *m/e* 348 (MH^+), 292 (MH-56); HRMS calcd for (M-56) $C_{15}H_{17}NO_5$ 291.1107, found 291.1110.

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