Development of the Hofmann Rearrangement of *N*α-Tosylasparagine through Calorimetric and NMR Analysis

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Introduction

Recently, we had need to prepare kilogram quantities of 2-(*S*)-(tosylamino)-*β*-alanine (**6**), an important intermediate in the synthesis of potent fibrinogen receptor antagonist **1**[1] (Figure 1). This non-peptide molecule is an active fibrinogen receptor antagonist that offers a promising approach to the treatment of vascular diseases through a mechanism of control of platelet aggregation.[2]

*N*α-Tosylaminoalanine (**6**) was prepared via the Hofmann rearrangement of *N*α-tosylasparagine. Although this reaction is described in the literature,[3] in our hands the reaction was inconsistent, with yields oscillating between 10 and 70%. Herein, we report a delineation of the sequence of intermediates involved in the reaction of sodium hypobromite with *N*α-tosylasparagine in aqueous sodium hydroxide. This study has resulted in an understanding of the sequence of reaction intermediates which has allowed greater control of the reaction parameters to achieve reproducibly high isolated yields (70%) of *N*α-tosylaminoalanine (**6**) on scales ranging from 1 g to 3 kg.

Results and Discussion

The Hofmann rearrangement of *N*α-tosylasparagine (**2**) has been described as a reaction that requires utmost care to achieve the reported yield, and efforts to improve the yield of the rearrangement were unsuccessful.[4,5] We observed similar problems with the reproducibility of this venerable reaction with *N*α-tosylasparagine (**2**) when the rearrangement was run on a kilogram scale, with significant variability in yield (10−70%) and no discernible differences noted in the procedure that was followed.

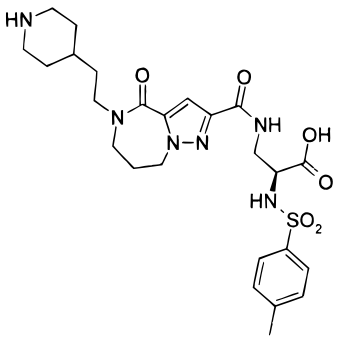

Figure 1. Fibrinogen receptor antagonist **1**.

Looking to unravel the critical reaction parameters led us to an examination of the calorimetry during the reaction. Reactions were studied in a Mettler RC1 unit[6] in which the heat flows were measured, samples were withdrawn after each thermal event, and ^{1}H and ^{13}C NMR measurements were performed. A cold solution of sodium hypobromite (prepared by the addition of 1 equiv of bromine to 1 equiv of aqueous sodium hydroxide) was added to a cold solution of asparagine in aqueous sodium hydroxide in the RC1 unit during which a −23.5 kcal/mol heat flow was measured. A sample was withdrawn to record the NMR. This sample gave spectra consistent with expected *N*-bromo intermediate **3** but also consistent with initial bromination of the tosylamide nitrogen (which could transfer to the primary amide). After the reaction was stirred at 0 °C for 15 min, external heat was supplied from the jacket of the reactor, and the calories of heat were measured during the heating. At 28 °C an exothermic event was observed in which a −64.7 kcal/mol heat flow was measured. The reaction temperature rose to 35 °C while heat was removed from the jacket of the reactor. After this thermal event a sample was withdrawn. Examination by ^{1}H and ^{13}C NMR found complete conversion of *N*-bromo intermediate **3** to the imidazolidine derivative **4** via rapid intramolecular trapping of the expected isocyanate intermediate. Imidazolidine **4** can be isolated as a crystalline solid at this point by cooling and acidifying with aqueous HCl.[7]

Heat was again supplied to the reaction from the jacket of the reactor, and at 50 °C another thermal event was observed, in which −13.5 kcal/mol heat flow was measured. NMR analysis of the reaction after this thermal event was consistent with carbamic acid **5**. Further heating of the reaction to 70 °C produced a final thermal event, in which −17.8 kcal/mol heat flow was measured. NMR and HPLC analysis, with comparison with known

(1) Askew, B. C.; McIntyre, C. J.; Hunt, C. A.; Claremon, D. A.; Gould, R.; Lynch, R. J.; Armstrong, D. J. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 475.

(2) (a) Ojima, I.; Charkravarty, S.; Dong, Q. *Bioorg. Med. Chem.* **1995**, *3*, 337. (b) Schror, K. *Drugs* **1995**, *50*, 7. (c) Cook, N. S.; Kottirsh, G.; Zerwes, H.-G. *Drugs Future* **1994**, *19*, 135. (d) Nichols, A. J.; Vasko, J. A.; Koster, P. F.; Valocik, R. E.; Samenen, J. M. In *Cellular Adhesion: Molecular Definition to Therapeutic Potential*; Metcalf, B. W., Dalton, B. J., Poste, G., Eds.; Plenum Press: New York, 1994; pp 213−237.

(3) (a) Rudinger, J.; Poduska, K.; Zaoral, M. *Collect. Czechoslov. Chem. Commun.* **1960**, *25*, 2022. (b) Hayashi, K.; Nunami, K.; Kato, J.; Yoneda, N.; Kubo, M.; Ochiai, T.; Ishida, R. *J. Med. Chem.* **1989**, *32*, 289.

(4) Aders, K.; Vesterager, E. *Acta Chem. Scand.* **1960**, *14*, 961.

(5) Shiba, T.; Koda A.; Kusamato, S.; Kanefko, T. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2748.

(6) Mettler Instrument Co.

(7) Imidazolidine **4** was isolated from reaction mixtures after warming to 40 °C: ^{1}H NMR (500.13 MHz, DMSO-d_6) δ 13.4 (br s, 1H), 7.86 (m, 2H), 7.66 (s, 1H), 7.41 (m, 2H), 4.86 (dd, J = 10.3, 4.8, 1H), 3.71 (t, J = 10.3, 1H), 3.26 (dd, J = 10.3, 4.8, 1H), 2.40 (s, 3H); ^{13}C NMR (125.76 MHz, DMSO-d_6) δ 171.3, 154.0, 144.2, 135.9, 129.2, 127.9, 56.3, 40.8, 20.9. In-situ data (referenced to external dioxane): ^{1}H NMR (399.87 MHz, NaOD) δ 7.36 (d, J = 8.0, 2H), 6.93 (d, J = 8.0, 2H), 3.98 (dd, J = 10.4, 6.8, 1H), 3.14 (dd, J = 12.1, 10.4, 1H), 2.77 (dd, J = 12.1, 6.8, 1H), 1.92 (s, 3H); ^{13}C NMR (100.55 MHz, NaOD) δ 180.6, 160.9, 145.9, 134.6, 130.5, 127.7, 62.5, 49.9, 21.5. Anal. Calcd for $C_{11}H_{12}N_2SO_5$: C, 46.47; H, 4.25; S, 11.28; N, 9.85. Found: C, 46.16; H, 4.11; S, 11.30; N, 9.68. This intermediate was shown to proceed to product in NMR experiments consistent with the original NMR experiments.

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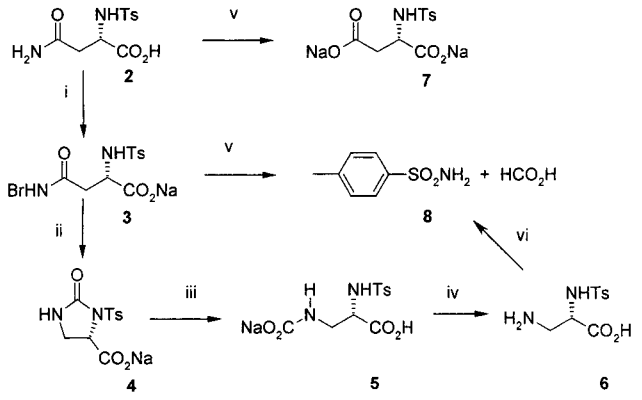
Scheme 1. Intermediates and Products of the Hofmann Rearrangement of (*l*)-Asparagine



i: NaOH, Br_2, 5-10 °C; ii: 28-35 °C; iii: 50 °C; iv: 70 °C; v: NaOH; vi: NaOBr or **3**.

samples, allowed identification of sodium *N*α-tosylaminoalanine (**6**) as the major product, and tosylamide (**8**) as a minor component.

The overall experimental heat of reaction was −116.3 kcal/mol, which was consistent with a calculated value from the heats of formations of the products and reactants from a model reaction.[8]

With the identification of critical reaction intermediates, our attention turned to a study of the stability of reaction intermediates, reagents, and product at each stage of the reaction. Heating of *N*α-tosylasparagine (**2**) with sodium hydroxide produced aspartic acid sodium salt (**7**). *N*α-tosylaminoalanine (**6**) was rapidly decomposed by either sodium hypobromite or *N*γ-bromoasparagine **3** to produce tosylamide (**8**) along with formic acid. Adding *N*-bromo-intermediate **3** dropwise to hot sodium hydroxide led to product mixtures that were similar to the reaction seen when the product was exposed to *N*γ-bromo-*N*α-tosylasparagine **3**. It became evident from these observations that the key to obtaining a high yield in the rearrangement was to ensure that all of intermediate **3** was consumed prior to formation of any product and that excess hypobromite be avoided.

The calorimetric and NMR data indicated that the sequence of reactions could be separated by control of temperature and heating time cycles and that this control was essential to achieve good reproducible yield in this Hofmann reaction. On the basis of these data, a procedure was developed with discrete heating stages. Sodium hypobromite was added to sodium asparaginate at <10 °C to give rapid *N*-bromination as determined by HPLC and NMR assays. Upon complete addition of sodium hypobromite, the reaction is heated to 40 °C, heating is suspended at 40 °C, but the heat generated during this exothermic reaction brings the temperature of the mixture to 50−55 °C. When this exothermic event is over complete consumption of *N*-bromo intermediate **3** has occurred to form imidazolidine **4**. When the internal temperature begins to fall, the reaction is heated to 70 °C in order to hydrolyze imidazolidine **4** and decarboxylate carbamate **5**, thus completing the sequence of reactions to produce 2-(*S*)-(tosylamino)-*β*-alanine (**6**) as the sodium salt.

The understanding of the discrete intermediates, exothermic events, and sensitivity of intermediates and product to reagents and to each other in the Hofmann rearrangement of *N*α-tosyl-(*l*)-asparagine led to a process that gave 2-(*S*)-(tosylamino)-*β*-alanine (**6**) on multikilogram scale in consistent 90% in-process yield and 70% isolated yield (Scheme 1).

Experimental Section

2-(*S*)-(Tosylamino)-*β*-alanine[3] (6). Sodium hydroxide (3.48 kg, 87.0 mol) was dissolved in water (22 L), and the solution was cooled to 0 °C. Bromine (0.63 L, 11.8 mol) was added over 30 min while the temperature was maintained at 0−10 °C. In a second vessel, *N*α-tosylasparagine (2.86 kg, 9.48 mol) was added in portions to a solution of NaOH (0.8 kg, 20.0 mol) in water (7.2 L) kept cold at 0−10 °C. The solution was cooled to 0 °C, and the sodium hypobromite solution was added over 10 min while maintaining a temperature <10 °C. After the addition, the resulting yellow solution was aged for 15 min at 10−15 °C, and then heated to 40 °C within 30 min. Heating was suspended and the reaction temperature was allowed to increase to 50 °C over 20 min due to the exothermic reaction. When the internal temperature dropped to 45 °C, the reaction solution was heated to 70 °C over 20 min and kept at 70 °C for 10 min. HPLC analysis measured a 90% solution yield of 2-(*S*)-(tosylamino)-*β*-alanine (**6**). The reaction was cooled to 10−15 °C, and with vigorous stirring the pH of the mixture was adjusted to 7 by the addition of concentrated hydrochloric acid (4 L), whereupon the product precipitated. The mixture was stirred for 20 min at 15 °C, and the product was filtered. The cake was slurry washed with water (2 × 8 L) and then displacement washed with water (8 L). The product was dried with a nitrogen stream at 20 °C affording 1.67 kg of 2-(*S*)-(tosylamino)-*β*-alanine (**6**) in 70% isolated yield.

Supporting Information Available: ^1H and ^{13}C NMR spectra for compound **4** (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of this journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(8) The value of the heat of formation of **6** was estimated on the basis of the heat of formation of 3-aminopropionic acid (−138 kcal/mol) plus the heat of formation of a secondary amine from hydrocarbon (−3.8 kcal/mol).