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A REEVALUATION OF THE HOFMANN REARRANGEMENT IN ELECTRON DEFICIENT SYSTEMS: PREPARATION OF 2-(^{15}N)-AMINO-4,6-DINITROTOLUENE AND 4-(^{15}N)-AMINO-2,6-DINITROTOLUENE

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Summary

The Hofmann rearrangement is an excellent synthetic method to introduce amino functions into aromatic molecules; however, it becomes less efficient in electron-deficient systems because of competitive hydrolytic reactions. This report describes the preparation of the aminodinitrotoluenes (ADNTs) 2-(^{15}N)-amino-4,6-dinitrotoluene and 4-(^{15}N)-amino-2,6-dinitrotoluene by developing conditions using HPLC as a reaction monitoring technique. Both ADNTs were prepared in >70% yield and >95% isotopic purity by using organic solvents and controlling pH during the formation of N-chlorobenzamides and then performing the rearrangement.

Key words: 2-(^{15}N)-amino-4,6-dinitrotoluene, 4-(^{15}N)-amino-2,6-dinitrotoluene, Hofmann rearrangement, electron-deficient systems.

Introduction

Two important microbial metabolites of 2,4,6-trinitrotoluene (TNT) are 2-amino-4,6-dinitrotoluene (2-ADNT) and 4-amino-2,6-dinitrotoluene (4-ADNT). Both of these metabolites may be conveniently prepared by the Curtius rearrangement from the corresponding dinitrobenzoic acids and sodium azide as reported by Zbarskii et al (1). However, for the preparation of ^{15}N amino-labeled ADNTs, the use of the Curtius rearrangement becomes less desirable because of the higher cost of ^{15}N reagents currently available (sodium azide-^{15}N: $5,000/g; ammonium chloride-^{15}N: $80/g). This economic factor prompted us to

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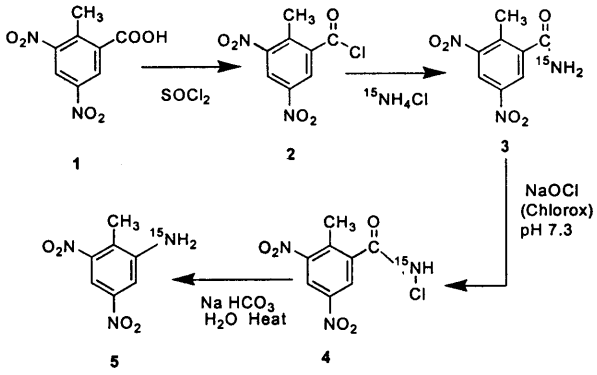
reevaluate the Hofmann rearrangement as a possible alternative synthetic route for the preparation of the ADNTs even though this rearrangement has been reported to be less successful in electron-deficient systems (2). The preparation of 2-ADNT by the Hofmann rearrangement has been reported by McGookin (3) in 1940 and modified by Sitzmann (4) in 1974. In attempting to reproduce the work of McGookin and Sitzmann , we found this reaction proceeded in very poor yield which prompted us to examine the reaction more closely using high-performance liquid chromatography (HPLC) as a reaction monitoring technique.

Results and Discussion

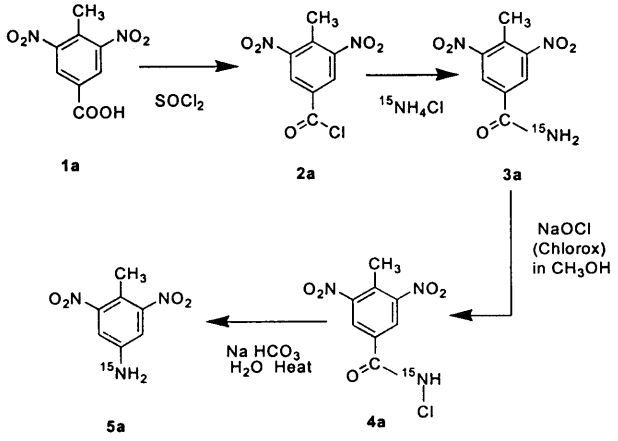
The reaction pathway for the formation of the ^{15}N analogs of ADNTs is shown in **Scheme 1,** where the pathway for 2-ADNT is used as an example. A HPLC procedure was developed to separate the major components key to the Hofmann rearrangement; these include the acid (**1**), amide (**3**), chlorobenzamide (**4**), and amine (**5**), (Figure 1). While the preparation of the benzamide (**3**) is straightforward, the conversion of the benzamide to the N-chlorobenzamide (**4**) is less successful because of competitive hydrolytic reactions at the carbonyl group. Using the procedure of Sitzmann, we found by HPLC analysis of the reaction mixture that the major product was the starting acid (**1**) with only a small amount of the chlorobenzamide (**4**) being formed. This reaction is biphasic, with reactants and products continually in the solid and liquid phases. In Sitzmann's procedure, sodium hypochlorite (Chlorox), which is sold commercially with sodium hydroxide as a stabilizer (pH 12.5), was used as the halogenating agent. When the pH of the hypochlorite solution was reduced to 7.3 and acetonitrile used as an amide-solubilizing agent, the chlorobenzamide (**4**) was formed in quantitative yield. Heating of compound (**4**) in water initially formed the amine, but the production of HCl promoted hydrolysis leading to the acid (**1**). When the pH was controlled with sodium bicarbonate, the amine was formed in 80% yield. A chemical purity of 97.2% was determined by chromatographic analysis and an isotopic purity of 97.4% was determined by mass spectrometry.

The preparation of 4-ADNT by the Hofmann rearrangement has not been reported in the literature to our knowledge. When the same procedure as described above was attempted on the 4-position amide (**3a**, **Scheme 2**), hydrolysis occurred under acid, neutral, and alkaline pH conditions, yielding only the acid (**1a**). When the chlorination was tried in methanol under alkaline conditions, the 4-chlorobenzamide (**4a**) was formed in excellent yield even in the

SCHEME 1



SCHEME 2



presence of excess hydroxide. Neutralization of the sodium hypochlorite solution increased hydrolysis as a competitive pathway. When the chlorobenzamide was heated in water to induce the Hofmann rearrangement, hydrolysis to the acid was the major route of transformation, because of the generation of hydrochloric acid, as observed by HPLC analysis. However, when the rearrangement was performed in bicarbonate solution, the 4-amine (**5a**) was formed in 90% yield. A chemical purity of 99.4% was determined by chromatographic analysis and isotopic purity of 99.0% was determined by mass spectrometry.

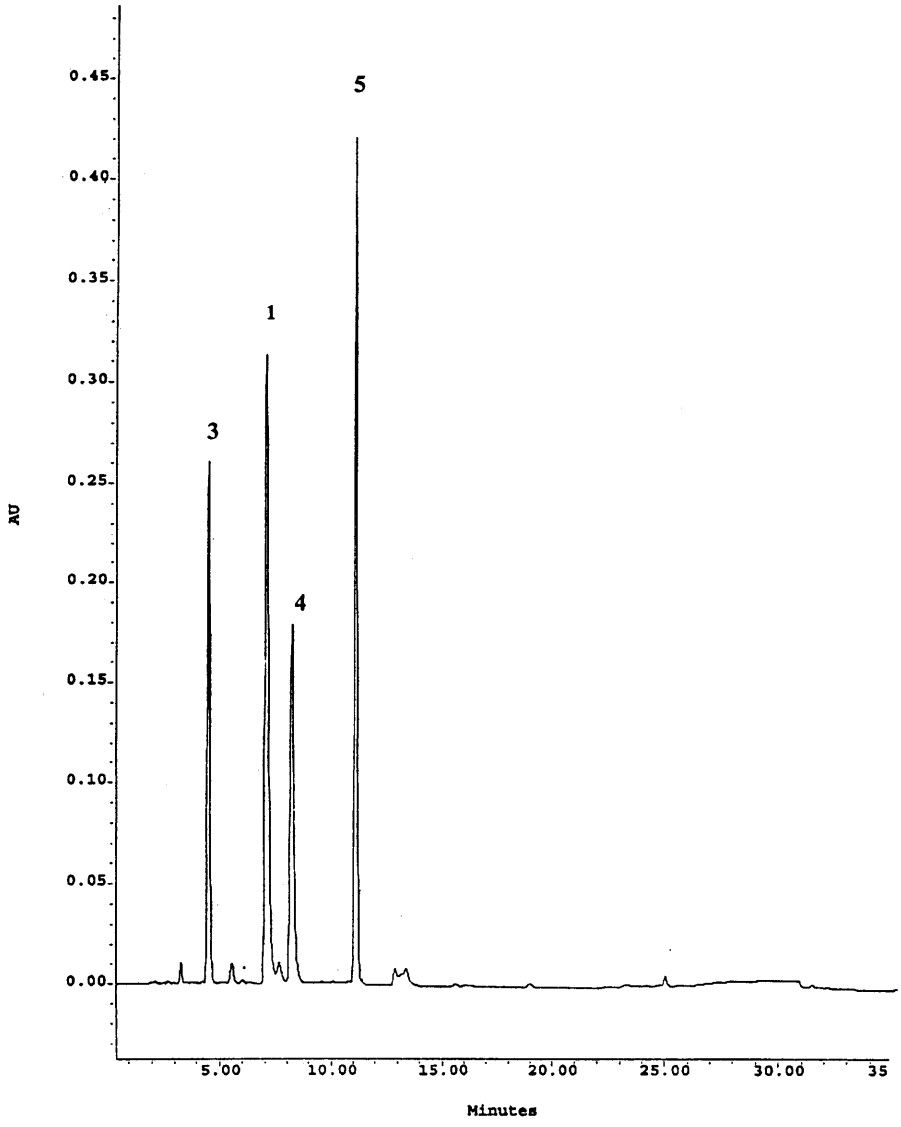


Figure 1. HPLC Profile of Hofmann Rearrangement Intermediates and Products. **1** = 2-Methyl-3,5-dinitrobenzoic Acid; **3** = 2-Methyl-3,5-dinitrobenzamide; **4** = N-Chloro-2-methyl-3,5-dinitrobenzamide; **5** = 2-Amino-4,6-dinitrotoluene.

The structural differences between the two ADNT isomers have a pronounced effect on the Hofmann rearrangement, with the 4-isomer amide (**3a**) and chlorobenzamide (**4a**) being more susceptible to hydrolysis than compounds **3** and **4**. The steric effect of the methyl group appears to inhibit the hydrolysis of compounds (**3**) and (**4**) in the absence of acid or base. The use of organic

solvents, such as acetonitrile or methanol in the presence of small amounts of water, apparently helps to limit hydrolysis during the formation of the chlorobenzamide as well as helping solubilize both reactants and products. There was no evidence of the formation of methyl esters. In addition, the pK_a's of the amines, reported to be 0.59 for 2-ADNT and 1.23 for 4-ADNT (5), suggest that very little of the acid generated in the initial stages of the rearrangement can be taken up by the amines. By controlling the pH of the rearrangement in water, the amines can be prepared in good yield.

With HPLC used to monitor reaction conditions, the Hofmann rearrangement becomes more feasible as an economical procedure to prepare amines in electron-deficient systems. This is especially true for the introduction of ^{15}N labels, when reagent costs can become a factor.

Experimental

Reactions were performed in all-glass round-bottomed flasks. Proton NMR was measured in the indicated solvents at 300 MHz and calibrated against a TMS standard. HPLC was performed using an Alltech Altima C-18, 5 μ, 4.6 x 250 mm column and a gradient mobile phase using the following solvents: A = 10% acetonitrile in Milli-Q water brought to pH 2.6 with H_2SO_4 and B = acetonitrile. The gradient was 64% A and 36% B at time 0, 64% A and 36% B at time 2 min, 45% A and 55% B at time 6 min, and: 45% A and 55% B at time 14 min.

3,5-Dinitro-2-methylbenz-^{15}N-amide (3). To a solution of 22.9 g (93.6 mmol) of 3,5-dinitro-2-methylbenzoyl chloride [prepared from the corresponding acid (Aldrich) and thionyl chloride, 98%] in 250 mL of chloroform and cooled in an ice bath were added 5.0 g (91.8 mmol) of ^{15}N-ammonium chloride (98% isotope purity) and 7.6 g sodium hydroxide in 70 mL water. The reaction mixture was stirred with a magnetic stir-bar in the cold for 15 min and then at room temperature for 1 hr. The resulting solid was isolated by filtration, washed with 100 mL of chloroform and then 100 mL of water, and air-dried to yield an off white solid. The solid was dried under house vacuum over P_2O_5 for 1.5 hr to yield 16.5 g of product (79%). 1-H NMR (DMSO) δ 8.78 (s, 1H), 8.41 (s, 1H), 8.23 (d, 1H, J = 81 Hz), 7.94 (d, 1H, J = 81 Hz), 2.52 (s, 3H).

2-(^{15}N)-Amino-4,6-dinitrotoluene (5). A HOCl solution was prepared by dissolving 6.3 mL (4.44 mmol) of 5.25% NaOCl (Chlorox) in 50 mL water and ajusting the pH to 7.47 with conc HCl. This solution was added slowly to a solution of 1.0 g (4.44 mmol) of amide (**3**) in 40 mL of acetonitrile that had been diluted with 60 mL of Milli-Q water. The combined solution was stirred with a magnetic stir-bar for 30 min. After this time period, HPLC analysis of a sample aliquot indicated a quantitative conversion to the chlorobenzamide (**4**). The solution was extracted with 100 mL of chloroform, the chloroform extract was dried over anhydrous sodium sulfate and decanted, and the dried extract was rotary evaporated to a solid residue. To the residue was added 100 mL of a 2% $NaHCO_3$ solution, and the suspension was heated on a steam bath for 40 min. The suspension dissolved and a precipitate formed during the heating period. The yellow suspension was cooled, filtered, and recrystallized from 95% ethanol to yield 0.71 g (3.58 mmol, 81%) of product, mp 173°C (lit.[6] 173-174°C). 1-H NMR ($CDCl_3$) δ 7.99 (d, 1H, J = 2.2 Hz), 7.68 (dd, 1H, J = 2.2 Hz, J = 2.1 Hz), 4.30 (d, 2H, J = 85 Hz), 2.33 (s, 3H).

3,5-Dinitro-4-methylbenz-^{15}N-amide (3a). To a solution of 6.5 g (26.5 mmol) of 3,5-dinitro-4-methylbenzoyl chloride [prepared from the corresponding acid (Aldrich) and thionyl chloride, 99%] in 100 mL of chloroform contained in an ice-water bath was added a solution containing 2.00 g (25.0 mmol) of ^{15}N-ammonium chloride (98% isotope purity) and 3.5 g sodium hydroxide in 35 mL water. The reaction mixture was stirred with a magnetic stir-bar in the cold for 15 min and then at room temperature for 1 hr. The resulting solid was isolated by filtration, washed with 100 mL of water, and air-dried to yield an off-white solid. The solid was dried under house vacuum over P_2O_5 for 1.5 hr yielding 5.4 g of product (96%). 1-H NMR (DMSO) δ 8.67 (s, 2H), 8.42 (d, 1H, J = 89 Hz), 7.90 (d, 1H, J = 88 Hz), 2.52 (s, 3H).

4-(^{15}N)-Amino-2,6-dinitrotoluene (5a). To 5.2 g (20.7 mmol)of **3a** in 250 mL of methanol was added 34 mL of 5.25% NaOCl (Chlorox) drop-wise over a period of 10 min while stirring with a magnetic stir-bar. During the addition, the reaction mixture became homogeneous. After the addition, the solution was concentrated to dryness using a vacuum pump at <30°C. The resulting solid was dissolved in 350 mL of water containing 2.5 g of sodium bicarbonate and heated on a steam bath. After 10 min, solid began to precipitate from solution. Heating

was continued for 1 hr. The flask was cooled in an ice-water bath and the solid was filtered, washed with water, and dried under vacuum to yield 4.1 g of a brown solid. The solid was dissolved in 30 mL of dioxane and dry HCl was bubbled into the solution. A white precipitate formed and was filtered, washed with dioxane, and air-dried. The solid was gently heated in dilute base and a yellow solid precipitated. The solid was filtered, air dried, and crystallized from 25 mL of 95% ethanol to yield 3.50 g (85%) of an orange crystalline solid, mp 170.5-171.5 [lit.(6) 171°C]. 1-H NMR ($CDCl_3$) δ 7.28 (d, 2H, J = 1.7 Hz), 4.77 (d, 2H, J = 85.3 Hz), 2.37 (s, 3H)

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