



**THE REACTION OF ISATOIC ANHYDRIDE WITH DIMETHYLSULFOXIDE.
ISOLATION OF PRODUCTS FORMED THROUGH A PUTATIVE PUMMERER
REARRANGEMENT**

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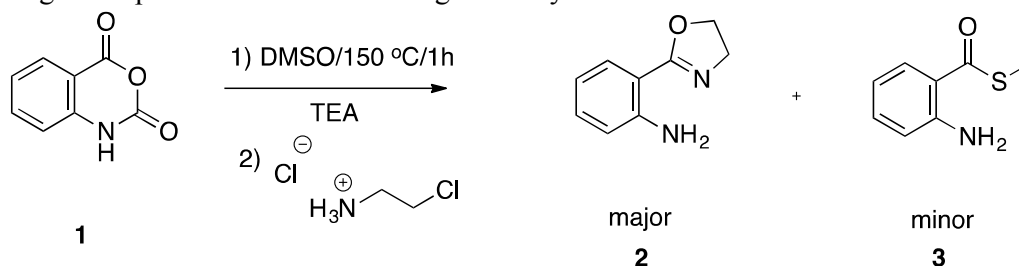
ABSTRACT

Reaction of isatoic anhydride with dimethyl sulfoxide at 150 °C results in the formation of S-methyl-2-aminobenzothioate as the result of a Pummerer rearrangement. While the reaction can be conducted in the absence of a base, yields of isolated product are higher in the presence of a base. The reaction appears to be optimal using dimethyl sulfoxide as the substrate.

KEYWORDS: Isatoic anhydrides, Pummerer rearrangement, S-methyl 2-aminobenzothioates

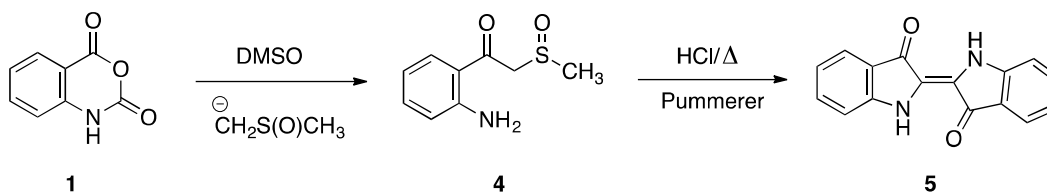
1. INTRODUCTION

Previous work in our laboratories has resulted in the development of an alternate synthesis for aminoaryl oxazolines.¹ This method required basic conditions, the addition of 2-chloroethyl ammonium chloride, utilized DMF as the solvent, and provided product yields ranging from 54- 81%. During the course of the study to determine optimal conditions, solvent effects were investigated. When DMSO was used in lieu of DMF, an unexpected thioester (**3**) was isolated, presumably as the result of a Pummerer rearrangement. In some cases, this rearrangement product was formed in significant yield.



Scheme 1 – Reaction of isatoic anhydride with 2-chloroethylammonium chloride in DMSO

The only other known description of a Pummerer rearrangement in the literature involved with isatoic anhydrides has been reported in association with a novel indigo synthesis (Scheme 2).^{II}



Scheme 2 – Preparation of indigo *via* Pummerer Rearrangement

2. EXPERIMENTAL

Method A: Reaction of Isatoic Anhydride with DMSO – Pummerer Conditions

To a 50 mL round bottom flask equipped with a reflux condenser and CaCl₂ drying tube were added isatoic anhydride (1.63 g; 10 mmol), pyridine (1 mL; 0.982 mg; 12.4 mmol), and DMSO (30 mL). The mixture was then heated in an oil bath at 150 °C for 2h. The mixture was allowed to cool and was poured into 60 mL of water. The mixture was extracted with 3 x 50 mL of CH₂Cl₂. The combined organics were then washed with 5 x 75 mL of water, dried over MgSO₄, filtered and concentrated to provide a brown oil which was purified by column chromatography on silica gel eluting with CH₂Cl₂ to afford the pure product as a pale yellow oil which solidified on standing, 533 mg; 32% yield; mp = 26-28 °C (lit mp = 27-28 °C).^{III} ¹H NMR (300 MHz CDCl₃): □□7.86 (d, J = 8.0 Hz, 1 H), 7.27-6.60 (m, 3H), 6.02 (br s, 2 H), 2.38 (s, 3H). ¹³C NMR (75 MHz, CDCl₃): □ 193.4, 147.9, 134.1, 129.9, 118.4, 117.1, 116.3, 11.6. IR: 3480, 3367, 1642, 1615, 1582, 1206, 1161, 913 cm⁻¹.^{IV}

Method B: Reaction of Isatoic Anhydrides with Sodium Methanethiolate

To a 50 mL round bottom flask equipped with a reflux condenser and CaCl₂ drying tube were added mixture of sodium methanethiolate (0.717g; 10.2 mmol) and isatoic anhydride (1.88g; 11.5 mmol) in DMF (25 mL), and the mixture was heated at 70-85 °C for 2h. Processing as previously described afforded the pure thioester product (1.17 g; 63%) that was characterized *via* IR and GC-MS and proved identical to that prepared by Method A.

DMSO-150 °C for 2h	Isatoic Anhydride (% yield)
Triethylamine	0%
Pyridine	32%
Diisopropyl-ethylamine	19%

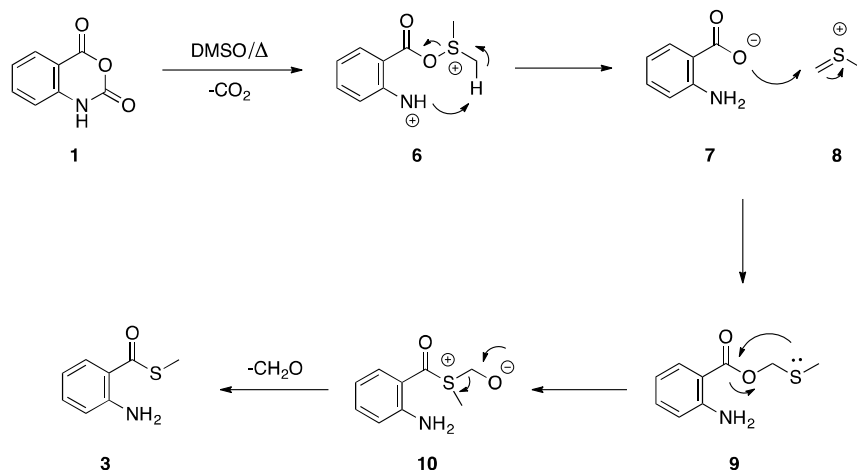
Table 1- Reaction of Isatoic Anhydrides with DMSO and Various Bases

3. RESULTS AND DISCUSSION

The proposed mechanism involves a nucleophilic attack by the DMSO oxygen on the carbonyl carbon followed by the elimination of CO₂ to form **6**. The resulting nitrogen anion

could then function as a base resulting in a fragmentation to afford the anthranilate **7** and the methyl- (methylene)sulfonium species **8**. Nucleophilic addition of **7** to **8** results in the formation of the (methylthio)methyl 2-aminobenzoate **9**. The more nucleophilic sulfur then displaces oxygen by attacking the carbonyl carbon to afford the intermediate **10**. Loss of formaldehyde results in the observed thioester **3**.

There is little doubt that the thioester is forming since GC/MS data and the ^1H and ^{13}C spectra from the rearrangement product correspond to that obtained for the thioester prepared by the alternate route. Although a base appears non-essential for rearrangement to occur, it appears to enhance the yield. It seems that aromatic bases are superior to sterically hindered amines that, in turn, are superior to less hindered amines. Less hindered amines, like TEA, result in the formation of side products that were not identified. These rearrangements work best with the parent (-NH) isatoic anhydride.



Scheme 3 – Proposed Mechanism for Rearrangement

4. CONCLUSION

The formation of anthranilate thioesters from isatoic anhydride by reaction with DMSO followed by subsequent a heretofore unreported Pummerer-type rearrangement has been observed. While unoptimized, the rearrangement product has been observed in substantial yield and this side product is of concern whenever conducting chemistry with isatoic anhydrides using DMSO as a solvent system. Studies to determine the scope and limitations of this reaction will be the subject of future studies.

ACKNOWLEDGEMENTS

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