Conversion of a Cyclic Anhydride to an Imide

CHEM HELP *ASAP*

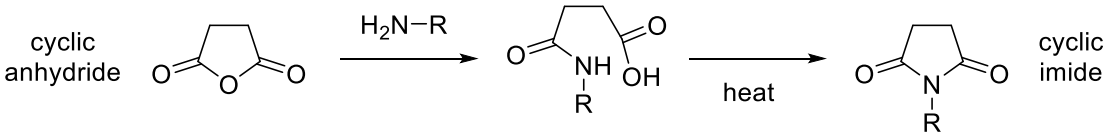
experiment video: https://youtu.be/_64JRPGsW4Y

Purpose

The purpose of this experiment is to convert a molecule that contains a cyclic anhydride to an imide through reaction with a primary NH_2 group. The specific imide isolated from this reaction is called tecovirimat and is the active pharmaceutical ingredient in TPOXX, a drug that is approved for the treatment of smallpox infections.

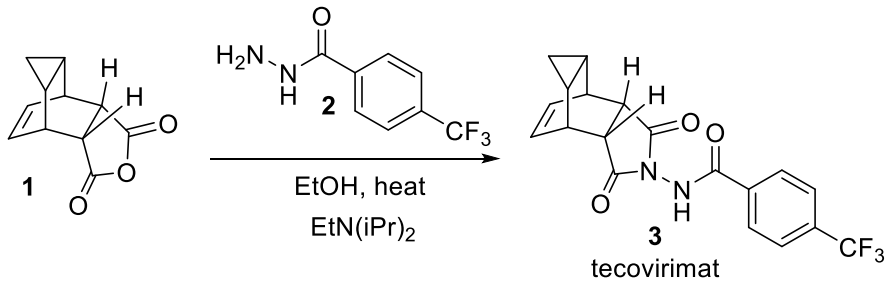
Background

The interconversion of different acid derivative functional groups is a common reaction in organic chemistry. Procedures to make esters and amides are often encountered, but imides are much less prevalent. Imides, especially cyclic imides, are frequently made through the reaction of a cyclic anhydride with an amine (Scheme 1). The reaction first involves attack of the nitrogen on one carbonyl. Once the ring has opened, the nitrogen, now part of an amide, can attack the other carbonyl to close the ring. The ring closure generally requires heat.



Scheme 1. Conversion of a cyclic anhydride to an imide

In this laboratory experiment, a polycyclic anhydride (**1**) is heated with hydrazide **2** to form imide **3**. The product, tecovirimat, is the active pharmaceutical ingredient in an approved antiviral, TPOXX, which is used to treat smallpox infections.



Scheme 2. Today's reaction – synthesis of tecovirimat (**3**), a cyclic imide

Procedure – *N*-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1*H*)-yl)-4-(trifluoromethyl)benzamide (3)

(adapted from supplementary information for Bailey, T. R. *et al. J. Med. Chem.* **2007,** *50,* 1440-1442.)

In a 20 mL vial equipped with a stir bar, mix hydrazide **2** (0.95 mmol), *N*-ethyldiisopropylamine (1 drop), and ethanol (3 mL). Allow the hydrazide to dissolve and add anhydride **1** (1.00 mmol). Heat the solution close to the boiling point of ethanol (85-90 °C) for 4 hours. Cool the mixture to room temperature and then in an ice bath. Add water (3 mL) with stirring to precipitate the product. Filter the solid with a small Buchner funnel and a side-arm Erlenmeyer flask. Use cold 1:1 ethanol:water for rinsing glassware. Allow the product to dry. Record the mass of the product, determine the percent yield, record a TLC of the product (mobile phase: 50% EtOAc:50% hexane), determine the melting range, and analyze the ^{1}H NMR spectrum.