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The Development of a Manufacturable Synthesis of LY213829

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Abstract:

The development of a manufacturable synthesis of LY213829 (4-thiazolidinone-5-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl] methyl) is described. Rather than reduction to eliminate the thiocarbonyl from the rhodanine moiety, the new route utilizes a novel concurrent ring opening with ammonia and recyclization with formaldehyde. This change obviates a potentially problematic zinc solid waste stream.

Introduction

LY213829 (**1**) is a potent anti-oxidant and 5-lipoxygenase inhibitor.[1] Currently **1** is under clinical investigation for a variety of inflammatory bowel diseases. The short and efficient route used for manufacture of early clinical trial materials is shown below (Scheme 1).[2] Evaluation of this route for commercial manufacture identified only one potential liability. The condensation of 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde (**2**) and rhodanine (**3**) is straightforward and produced high quality adduct **4** in good yield. While the reduction of olefin **4** via Hantzch's ester **5** to form **6** is somewhat unusual, it presented no challenges to scale-up. The challenge for full-scale manufacture occurred in the last chemical transformation, in which the reduction of the thiocarbonyl moiety to form **1** required 5 equiv of zinc. This roughly translated to a kilo of solid Zn waste per kilo of **1**. At the time of this development a reclamation site could not be identified, and thus the waste would need to be landfilled. As the potential annual requirements of **1** are large, this translates to a major environmental challenge. This study examined an alternative method that avoids the use of Zn.[3]

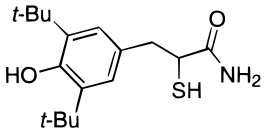
Results

Initially, considerable effort was dedicated to developing a catalytic hydrogenation version of the reduction of intermediates **6** or **4** to **1**. This approach was used in the initial synthesis of LY213829 by the discovery chemists.[4] These conditions are near optimal from the perspective of solid waste. Due to the high value of the noble metal catalysts, the spent catalyst can be sent back to the supplier for reclaiming. However, the catalyst loading (340 mass % of 5% Pd/C), and conditions (500 psi H_2, 120 °C) were unsuitable for manufacturing. We explored palladium, platinum, ruthenium, and rhodium catalysts on normal carbon and sulfided carbon supports at 100 mass % loadings of 5% metal catalysts. All catalysts were explored under acidic, neutral, and basic conditions at up to 100 °C and at a maximum pressure of 60 psig. In no case was greater than 1 area % (HPLC) of **1** observed. Interesting, if not particularly useful for avoiding solid wastes, results were obtained with a large excess of active nickel. While **6** was found to be unreactive with Ni, as much as a 38% yield of **1** could be obtained from the reduction of olefin **4** with most of the remaining mass present as **6**.

Table 1: **Results of Hydride Reduction of Rhodanine 6**

reagent	optimum result
$NaBH_4$/MeOH	<55% **7**
$NaBH_4/TiCl_4$	complex mixture
$LiAlH_4$	no reaction
$LiAlH_4/ZnBr_2$	~50% **7**
Dibal-H	no reaction
$LiBHEt_3$	no reaction
$Zn(BH_4)_2$	no reaction
$NaBH_4/NiCl_2$ or $CoCl_2$	20% **7**, 65% **1**

Hydride-reducing agents were also studied. The results of these experiments are listed in Table 1. Either no reaction or inefficient production of thiolamide **7** was observed.



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Only the recently reported desulfurization conditions utilizing $NaBH_4$ in the presence of Ni^{II} or Co^{II} provided a reasonable yield of **1**.[5] In exploratory experiments a greater than 50% in situ yield of **1** was obtained. Unfortunately, these reactions require stoichiometric metal. Attempts to make the reaction catalytic, or use a different catalyst, were unsuccessful. This is in agreement with the literature. This reaction was not optimized since stoichiometric Ni or Co, with the environmental concerns those metals carry, was not superior to the large excess of Zn.

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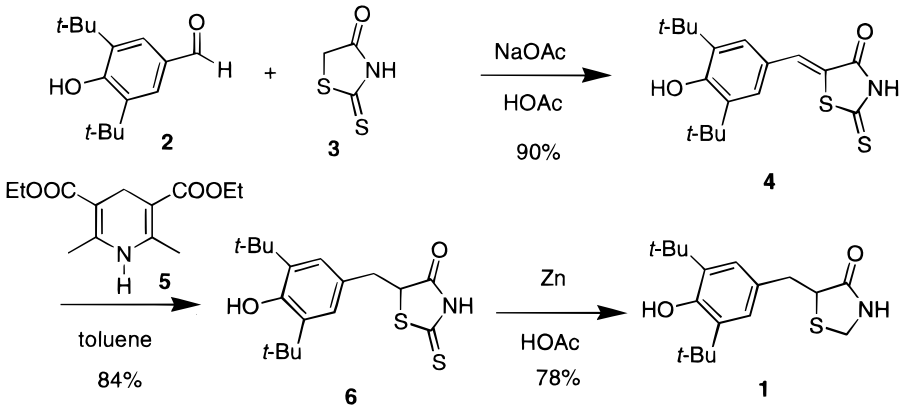
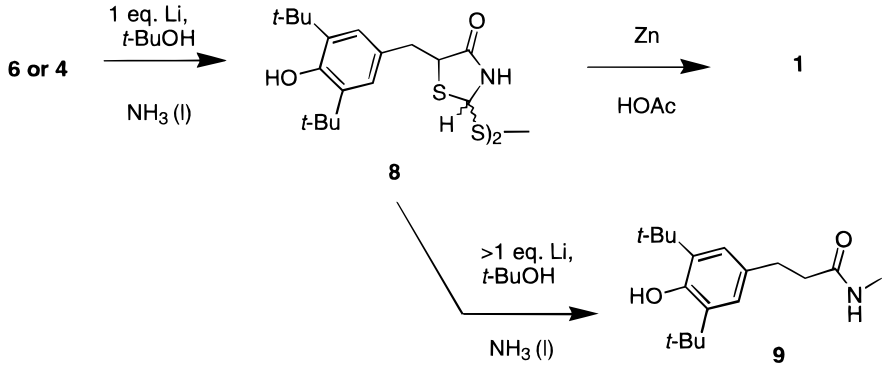
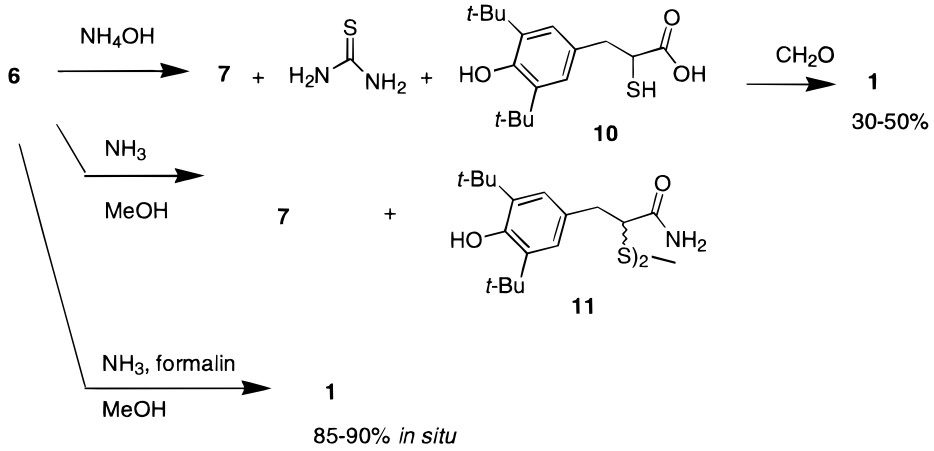
Scheme 1



Scheme 2



Scheme 3



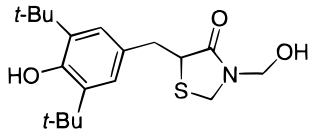
Reductions employing dissolving metal conditions were also explored. Interesting results were obtained with lithium and *tert*-butyl alcohol in liquid ammonia. An unknown (tentatively assigned as disulfide **8** based on ^{1}H NMR) was formed under these conditions (Scheme 2). By careful addition of stoichiometric lithium a 90% isolated yield of **8** could be obtained. Addition of additional lithium did not lead to further reduction to **1**; instead a new compound assigned as the methyl amide **9** by HPLC/MS was formed. The disulfide **8** could be further reduced to **1** by using Zn in acetic acid. While interesting, this result is of no commercial value. Attempts to increase the reducing power of the dissolving metal conditions via a change to sodium or to higher boiling amines lead to formation of the over-reduction product **9**.

Because an alternative reducing agent for zinc was not found, the two-step route shown in Scheme 3 was investigated.

Rhodanine **6** has been observed to react with ammonium hydroxide at reflux to generate **7**.[3] All that would be required was addition of formaldehyde to **7** to form **1**. In fact, when **7** isolated from the ammonium hydroxide reaction was exposed to formalin in a two-phase aqueous ammonia/toluene system, **1** was formed. Isolation of **7** could be avoided by direct addition of formalin and toluene to the reaction mixture. Yields of **1** from these conditions varied from 30 to 50%.

The major source of yield loss and variability under these aqueous conditions was via saponification to form the thiolacid **10**, which did not react appreciably with formal-

dehyde. We reasoned that nonaqueous conditions should be used to avoid this side reaction. Therefore, gaseous ammonia in methanol in a sealed system at 80 °C was explored. These conditions were found to produce **7** contaminated with large amounts of two very late eluting (by reverse phase HPLC)[6] impurities. These impurities were assigned by HPLC-MS as the diastereomers of the disulfide **11**. Disulfide formation is competitive well before consumption of the starting **6** is complete. At 50% consumption of rhodanine **6** the yields were 22% **7** and 17% **11**. The mercaptan would be expected to oxidize easily under these very basic and elevated temperature conditions. Therefore, we added formalin to the gaseous ammonia in a methanol solution of **6** prior to heating the mixture in an attempt to trap **7** prior to oxidation. This approach to the formation of the desired thiazolidinone **1** was successful. Under optimum conditions (10 equiv NH_3, 1.1 equiv formalin, 80−95 °C) an in situ yield of 90% thiazolidinone **1** was achieved. The remaining mass was primarily the starting material **6** (3.3%) and the disulfides **11** (6.4%). At lower formaldehyde stoichiometries, consumption of intermediate **7** is less complete. At higher stoichiometries, reaction of a second equivalent of formaldehyde to form **12** becomes competitive. These conditions are no longer nonaqueous as some water is reintroduced with the formalin, yet thiolacid **10** is not observed. We were unable to achieve any measurable yield of thiazolidinone **1** with any of the commercially available formaldehyde oligomers or acetals.



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Thiourea is formed stoichiometrically in the reaction. This is an area of concern since thiourea is a suspect carcinogen. Therefore, a tradeoff exists between these conditions and those of the zinc procedure. We have replaced a large solid zinc waste stream, but we have also introduced a carcinogen concern.

To ensure that the product was not contaminated by thiourea a separate assay was developed with a detection limit of 2 ppm. No thiourea contamination of the product resulting from the isolation procedure described below was detected. All the liquid waste streams could be incinerated to obviate environmental impact.

The pressure generated by these conditions is another added concern. At both the laboratory and manufacturing scale pressure reactions have inherent risk. The conditions chosen were designed to mitigate the risk. A pressure of 40 to 50 psia develops under the chosen conditions at 80 °C, which is well within the safe operating range of all of our lab and production equipment. Care must be taken to follow the manufacturer's recommendations for safe operation of any laboratory pressure equipment. We successfully, and safely, ran the process in pressure tubes, shaker bottles, and metal pressure reactors. Production could be executed in standard alloy tanks with isolated overheads due to the moderate pressure generated.

Isolation of pharmaceutical quality **1** from the reaction mixture proved problematic. Addition of solvents in which **1** is insoluble to the reaction mixture typically resulted in intractable, tarry solids. Addition of acetic acid and water led to the crystallization of **1**. Filtration and washing of the solids with water led to **1** without measurable thiourea. This isolation procedure marginally raised the quality from the in situ results (to 91% **1**), primarily by rejecting most of the starting material **6** (from 3.4 to 1.1%). The disulfide was not rejected. Further purification and a change in crystal form were still required. These goals were achieved via recrystallization from ethyl acetate. Overall, the process as developed showed yields of 67−72%, HPLC purities of greater than 99%, and total related substances (by HPLC) of <0.4%.

In conclusion, we have developed a modified synthesis of **1** which avoids the generation of a large quantity of solid Zn waste. The new route is competitive economically with the Zn-based reduction and provides an option if Zn reclamation is not viable.

Experimental Section

Compounds **4** and **6** were prepared as described.[2,4] Compound **1** had spectral data identical to that reported.[4] The purity of **1** was assessed by HPLC using a reference standard.

4-Thiazolidinone-5-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl] methyl (1). Compound **6** (3.22 g, 9.2 mmol), and methanol (13 mL) were combined in a 25 mL glass pressure tube equipped with a magnetic stir bar. Ammonia (1.6 g, 91 mmol), and formalin (0.76 mL, 0.8 g, 10 mmol) were added sequentially at 0 °C. The pressure tube was sealed and heated to 80 °C for 8 h with good stirring. The resulting reaction mixture was transferred to a three-neck 50-mL flask equipped with mechanical stirring. Deionized water (12 mL) was added in a dropwise manner followed by acetic acid (6 mL). After 15 min, the reaction mixture was cooled to 0 °C for 1 h. The resulting colorless crystals were recrystallized from ethyl acetate (3 mL), filtered, and washed with water (2 × 10 mL) and 1/4 ethyl acetate/hexane (2 × 10 mL). The product was then dried in an oven at 50 °C to give 2.04 g (69%) of white, crystalline **1**. Purity by HPLC was 99.9%.[6]

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(6) Suitable HPLC conditions are: Zorbax RX-C8 column (25 cm × 4.6 mm, 5 μm), detect at 280 nm, 1 mL/min flow, isocratic elution with 70% CH_3-CN, 30% of aqueous 60 mM phosphoric acid, and 10 mM octanesulfonic acid adjusted to pH 2 with NaOH.