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A safe and scalable synthesis of 2-hydroxy-3-alkoxypropionates by epoxide ring opening

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ABSTRACT

Epoxides are useful precursors for the synthesis of hydroxyl-bearing building blocks via Lewis acid catalyzed, nucleophilic ring opening. However, the reaction of glycidate esters with alcohol nucleophiles can be quite challenging with many of the classical paradigms for epoxide opening failing to give efficient reaction. In our hands, the most efficient catalyst described in the literature for effecting this transformation was magnesium perchlorate. However, ring opening of methyl glycidate with this catalyst revealed the potential for rapid and uncontrollable decomposition with onset at a relatively low temperature. Herein, the development of an alternative process, which is safe and scalable, is described. This allowed the synthesis of a series of novel 2-hydroxy-3-alkoxypropionates.

Introduction

The nucleophilic ring opening of epoxides under Lewis acid catalysis is a reliable, widely used method for the generation of chiral alcohol systems.[1] As part of ongoing efforts to discover glucokinase activators,[2,3] significant quantities of homochiral 2-hydroxy-3-alkoxypropionates were required. It was believed that epoxide opening of methyl glycidate with a suitable alcohol derivative would be an efficient means of furnishing such compounds (Scheme 1).[2] Perhaps surprisingly, there were few Letters of such a transformation in the literature with examples of successful reactions consisting mostly of acid catalyzed processes with substrates bearing β-dimethyl[4] or aryl[5] substituents (presumably occurring by S_N1 epoxide opening) or electron withdrawing substituents[6] which would render the epoxide significantly more reactive. Reported base mediated reactions of glycidate derivatives were mainly restricted to phenolic nucleophiles.[7] The few examples of direct reaction of an aliphatic alcohol nucleophile with an unactivated epoxide that were known highlighted problematic side reactions. For example transesterification and subsequent scrambling of the nucleophilic alcohol[8] or reaction of the glycidate with the catalyst had been reported.[9] These observations suggested that the desired transformation was not an efficient process. Subsequent to this work, the desired transformation mediated by $BF_3{\cdot}OEt_2$[10] and a cobalt-salen based catalyst[11] have been reported.

Accordingly, initial attempts to effect this transformation using classical conditions for epoxide opening were met with limited success and led to complex mixtures of products.[12] The most reliable method identified during these investigations used perchlorate salts as catalysts.[13] These reactions were typically carried out without solvent at a relatively low temperature (45–60 °C) over a period of 2–3 days using a slight excess of the alcohol and 0.25–0.5 equiv of magnesium or lithium perchlorate. While this chemistry allowed the synthesis of the desired products, rapid exotherms and pressure increases were observed when operating these reactions in microwave reactors. In addition, the use of perchlorate salts on scale was a significant safety concern in its own right.[14]

Results and discussion

In order to address these safety concerns, the reaction between (*S*)-methyl glycidate and isopropanol in the presence of magnesium perchlorate (Scheme 2) was investigated in detail. This reaction gave clean conversion to the desired product but with a significant exotherm which took the internal reaction temperature beyond the set heating point (60 °C). A Carius tube test of the reaction mixture (Fig. 1) showed an exotherm initiating at 138 °C which led directly to a second exotherm at 180 °C. A sudden

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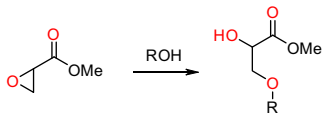


Scheme 1. Ring opening of methyl glycidate with alcohol nucleophiles.

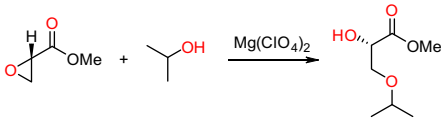
increase in pressure accompanied the exotherms and remained at the end of the test with the reaction mixture being reduced to a dark, solid mass.

At this stage it was believed that the decomposition was initiated by the perchlorate salt. Previous investigations of different catalysts suggested the highly ionic nature of magnesium perchlorate was critical for efficient catalysis and led to the hypothesis that magnesium trifluoromethanesulfonate might perform similarly without the liabilities of the perchlorate counter ion. However, the subsequent tube test with magnesium trifluoromethanesulfonate as catalyst showed the same exotherm and gas evolution noted with the corresponding perchlorate salt. A further tube test indicated that the isolated hydroxyester products were unstable in the presence of Lewis acid catalysts at elevated temperatures (Fig. 2).

Control of this exotherm presented a significant problem. The prolonged reaction times and instability of the product meant that slow addition of glycidate would be ineffective and a different reaction system was needed. Due to the inherent problems of perchlorate salts as catalysts, further investigations focused on the equally efficient magnesium trifluoromethanesulfonate. Dilution of the reaction mixture with an excess of the alcohol at 60 °C gave no reaction, while prolonged heating of these mixtures at elevated temperatures resulted in degradation of the glycidate with minimal product formation.

To help identify the most important factors governing the reaction efficiency, a basic Factorial Experimental Design (FED) approach was used (Table 1), exploring the effect of temperature (30 °C to reflux), concentration (2.0–10 mL g^{-1} of glycidate), and catalyst loading (0.1–1.0 equiv) across a range of six solvents (DCM, toluene, *iso*hexane, MTBE, acetonitrile, and ethyl acetate). Catalyst loading had little effect, possibly due to limited solubility in organic solvents. Of the solvents screened only ethyl acetate showed any potential for development with others either showing low conversion or resulting in degradation of the glycidate at higher temperatures. Concentration proved to be the most important factor with the rate of reaction decreasing markedly as dilution increased. However, even at relatively high concentrations the reaction still required approximately 3 days for the glycidate to be wholly consumed.

A Carius tube test[15] with (*S*)-methyl glycidate, isopropanol (1 equiv), and magnesium trifluoromethane sulfonate (0.1 equiv) in ethyl acetate (3 mL g^{-1}) showed no significant exotherm or gas evolution up to a temperature of 180 °C. This was felt to be an appropriate upper limit of concentration which would allow for small losses of solvent vapor during the prolonged heating period and allowed subsequent reactions to be run at a dilution of up to 15 mL g^{-1}.[16] Further tests confirmed that ethyl acetate solutions of glycidate, alcohol, and product did not pose any significant hazard in the absence of catalyst when heated to temperatures in excess of 200 °C indicating that standard work up procedures could be used for isolation of the crude product once the catalyst had been removed.



Scheme 2. Magnesium perchlorate catalyzed reaction.

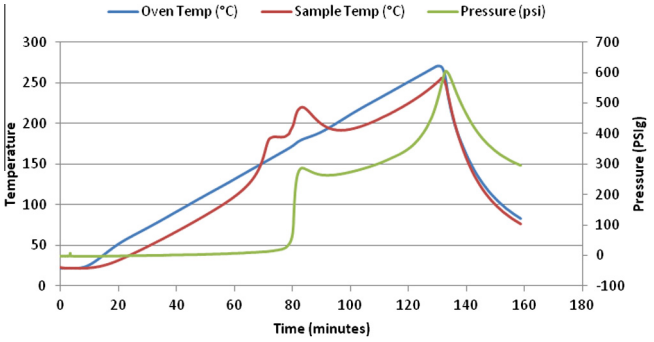


Figure 1. Carius tube test calorimetry and pressure measurement of the reaction between (*S*)-methyl glycidate and *iso*propanol in the presence of magnesium perchlorate.

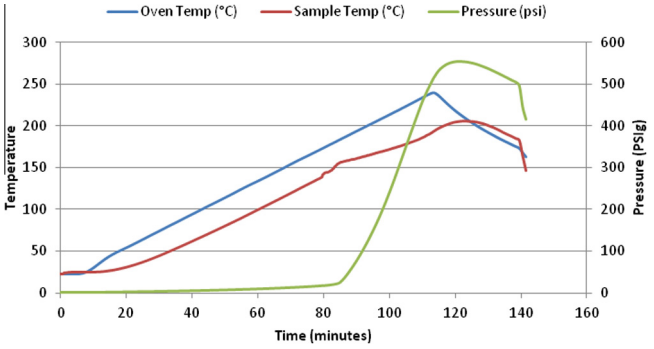


Figure 2. Carius tube test of methyl (2*S*)-2-hydroxy-3-*iso*propoxy-propanoate with magnesium trifluoromethane sulfonate.

Table 1
Optimisation of solvent, concentration, temperature, and catalyst loading by FED

Solvent	Concn[a]	Temp (°C)	Catalyst equiv	Observations
DCM	High	40	1.0	No reaction
Toluene	Medium	50	0.25	<5% conversion
Toluene	Medium	110	0.25	Decomposition products
Hexane	Medium	70	0.25	<5% conversion
MeCN	Medium	80	0.25	<5% conversion
MTBE	Medium	70	0.25	<5% conversion
EtOAc	Medium	50	0.25	~10% conversion
EtOAc	High	76	0.25	Slow clean conversion[b]
EtOAc	High	76	1.0	Slow clean conversion[b]
EtOAc	Low	76	0.25	<5% conversion

[a] Solvent to (*S*)-methyl glycidate ratios; High 5:1, Medium 10:1, Low 25:1.
[b] Reactions were stirred at the stated temperature until consumption of (*S*)-methyl glycidate was complete.

To demonstrate its broad applicability, this improved method was applied to a range of different alcohol nucleophiles (Scheme 3). This demonstrated that the method could be applied to primary (entries 1 and 2) and tertiary (entry 4) alcohols. Cyclic alcohols (entries 5 and 6) also reacted successfully and the reaction was also tolerant of inactivating β-oxygen substituted alcohols (entries 7–9). Standard silicon protecting groups (TBDMS, TIPS and TBDPS) were stable to the reaction conditions and chiral alcohols (entries 8 and 9) could be employed without loss of chiral integrity. The moderate yields obtained were believed to be due,