Highly regioselective ring opening of quinolinic [2,3] anhydrides under mild conditions

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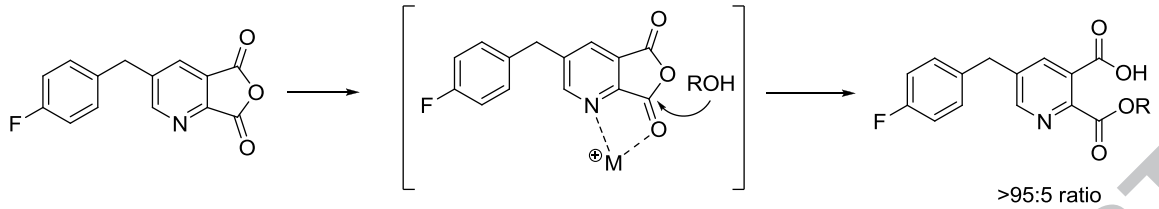

We report a study of the influence of Lewis acids upon the regioselectivity of ring opening of quinolinic [2,3] anhydrides to provide 2-(isopropoxycarbonyl)-nicotinic acids. In the presence of stoichiometric amounts of indium trifluoromethanesulfonate or lanthanum trifluoromethanesulfonate, the desired 2-position ester was generated with greater than 95:5 regioselectivity. This methodology was also applied to 6-methyl-[2,3]-quinoline to provide similar results.

Keywords: regioselective; ring opening; quinolinic [2,3] anhydrides; naphthyridines; Lewis-acid catalysis.

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Introduction

Quinolinic anhydrides have been used extensively as versatile intermediates in the synthesis of various heterocyclic systems including naphthyridines,[1] nicotinamides[2] and isotoic derivatives.[3] Recently, they have been exploited in antiviral,[4] dementia,[5] anti-allergy[6] and antitumor targets.[7]

Quinolinic anhydrides are readily generated from the corresponding pyridine-2,3-dicarboxylic acids **1** (Scheme 1) via heating at reflux in acetic anhydride.[8] Pioneering work by Kenyon and Thaker fifty years ago established that treatment of the resultant anhydride **2** with an alcohol furnishes mixtures of the regioisomeric acid-esters **3** and **4**,

and this remains the most common method to access these valuable intermediates.[9] In favorable cases, crystallization enables the separation of the isomers, albeit in low yield.[10] It is then possible to recycle the undesired isomer. However, this requires several synthetic steps (hydrolysis of undesired regioisomer to **1,** followed by repetition of the sequence). This is particularly disadvantageous when more elaborate anhydrides are utilized.[11]

Scheme 1. Thermal ring opening of quinolinic anhydrides with alcohols. For R=*i*Pr, ratio of **3**:**4** is 67:33.

Chelation as a means of influencing the regioselectivity of synthetic transformations of cyclic anhydrides has been demonstrated in a variety of contexts. Succinimides have been shown to be regioselectively reduced using sodium borohydride in the presence of a chelating metal complex.[12] Little and Cochran have demonstrated the use of a Lewis acid to catalyze the Friedel-Crafts regioselective opening and acylation of anhydrides.[13] Goto and co-workers have shown that coordination with a metal Lewis acid can help promote the subsequent sodium borohydride reduction of quinolinimides to provide high regioisomeric ratios.[14] Baruah reported that metal complexes could be utilized to effect formation of dicarboxylate metal complexes.[15]

We have previously reported that substituted quinolinic anhydrides serve as useful synthetic intermediates for an HIV integrase active site inhibitor program.[16] As expected from literature precedent, the thermal ring opening of these intermediates with various alcohols proceeds to provide the corresponding acid-esters as mixtures of regioisomers.[17] We were interested in developing a more efficient method for the generation of the desired 2-position ester, and herein report the regioselective ring opening esterification of a quinolinic anhydride via a Lewis acid metal chelate complex under mild conditions.

Results

The synthesis of anhydride **5** was recently reported.[18] We explored the ring opening of **5** with isopropanol in the presence of various Lewis acids (Scheme 2; Table 1) to obtain the two isomers **6a** and **6b**.

Scheme 2. a) Lewis acid (1 equiv.), THF, 0 ˚C b) isopropanol, 0 ˚C to rt.

Table 1. Results obtained when anhydride **5** is exposed to isopropanol and methanol in the presence of different Lewis acids. [19] Ratio of isomers determined by ^{1}H NMR analysis of crude reaction mixtures. [a] Also contains 18% of diacid. [b] also contains 9% of diacid. [c] 1.1 equiv. used for each reagent.

In all cases, the rate of reaction was enhanced by the Lewis acid such that the ring-opening could conveniently be carried out at ambient temperature. The results in Table 1 indicate that the reaction outcome is influenced both by the metal and the counterion in the additive. The monochelating metals Li^+ and Ag^+ provided little differentiation from

the regioselectivity observed under thermal conditions (entries 3-5 versus 1 and 2), with incomplete reaction (as indicated by the generation of the diacid upon quenching) with LiOTf. The results with magnesium salts were more encouraging with $Mg(ClO_4)_2$ (entry 6) in particular providing a significant enhancement in the formation of the desired isomer. $Sc(OTf)_3$ (entry 12) improved the regioselectivity further providing a 81:19 ratio of isomers. One of the best outcome was obtained with $In(OTf)_3$ (entry 10) which provided only a single isomer of the desired isomer in high yields and high regioselectivity (>95:5).[19] When catalytic amounts of $In(OTf)_3$ were used (entry 11), an erosion of the selectivity was observed (79:21). Lanthanide metals also provided high regioselectivity comparable to those shown with stoichiometric $In(OTf)_3$ with $La(OTf)_3$ and $Yb(OTf)_3$ provided >95:5 and 93:7 ratios respectively.

Less coordinating counterions tended to favor the formation of the desired isomer **6a**, with perchlorate superior to triflate in the case of magnesium (6 versus 7). However, the improved regioselectivity observed with magnesium perchlorate and triflate was negated with magnesium bromide and even reversed, relative to the thermal conditions, with magnesium chloride. A similar reversal in selectivity was observed with indium chloride (entry 13). We speculate that the nucleophilic character of the chloride anion is involved in reducing chelation of the cation to the pyridyl nitrogen. However, this might also be due to reduced Lewis acidity of the counterion. Interestingly, when $In(OTf)_3$ was used together with LiCl (entry 14), high regioselectivity was still attained.

We next looked at a different anhydride (6-methyl-[2,3]-quinoline, **7**). Under thermal conditions the regioselectivity was similar to that seen for **5** (**8a**:**8b**, 64:36; Scheme 3). Here also the use of $In(OTf)_3$ was extremely effective, providing the desired **8a** in high regioselectivity (>95:5). The results were similar when methanol was used instead of isopropanol (**9a** and **9b**).

Scheme 3. Ring opening of 6-methyl-[2,3]-quinolin. 1. a. isopropanol, 80 ˚C, 64:36 ratios of **8a:8b**. b. $In(OTf)_3$ (1.1 equiv.), IPA, THF, 0 ˚C to rt. >95: 5 **8a:8b, R = *i*Pr.** 2. c. methanol, 80 ˚C, 65:35 ratios of **8c:8d**. b. $In(OTf)_3$ (1.1 equiv.), MeOH, THF, 0 ˚C to rt. >95: 5 **9a:9b R = Me.**

Summary and Conclusions

In summary, we have demonstrated a practical, regioselective and high yielding method for generation of nicotinic acid 2-carboxy esters by the ring-opening of quinolinic-[2,3] anhydrides using indium (III) trifluoromethanesulfonate or lanthanum (III) trifluoromethanesulfonate.

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Supplementary Material

Supplemental data (spectroscopic data) of selected entries from Table 1 are attached.

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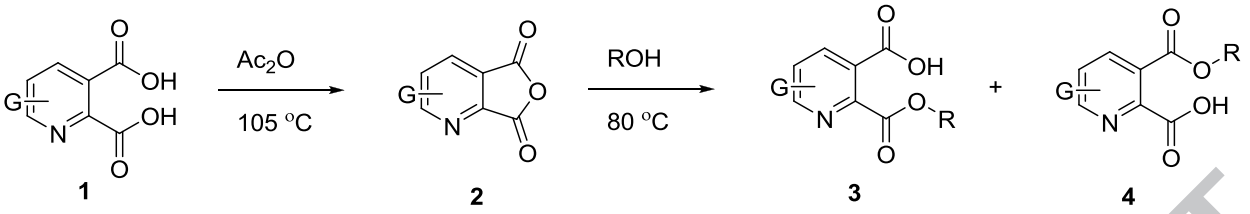
[19] The anhydride **5** (100 mg, 1 equiv., 0.39 mmol) is dissolved in THF (6 mL) and cooled to 0 ˚C. To this was added the Lewis acid (0.42 mmol, 1.1 equiv.) followed by IPA (6 mL). The reaction was allowed to warm up and stir overnight at room temperature. After the reaction was complete, it was diluted with water and ethyl acetate. The organic layer was washed with water and saturated NH_4Cl before being dried over $MgSO_4$, filtered and

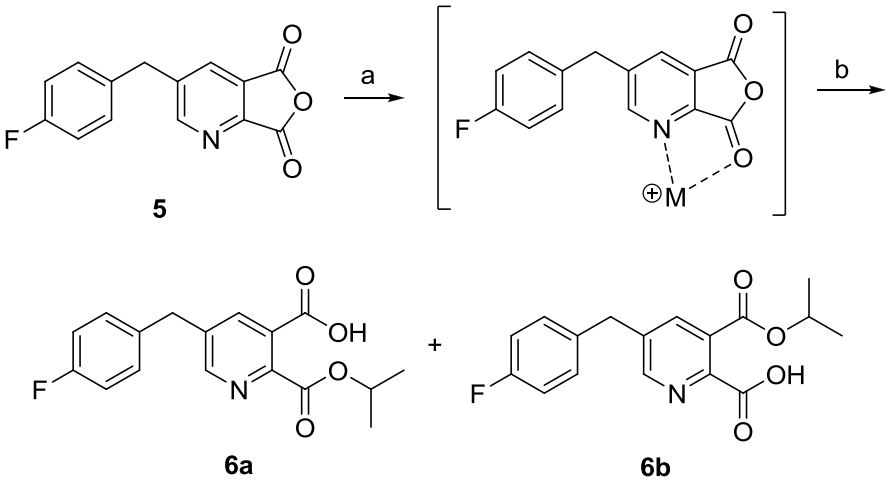
concentrated *in vacuo*. Silica gel chromatography was the carried out with Hexanes : EtOAc to obtain **6a.** (For entry 9, 112 mg, 91%).

Scheme 1



1 **2** **3** **4**

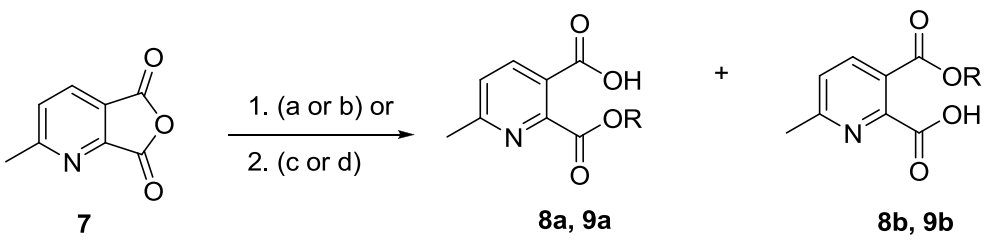
Scheme 2



5

6a **6b**

Scheme 3



7 **8a, 9a** **8b, 9b**