## STEREOSELECTION IN THE REACTION OF ACID HALIDES AND VINYLOGOUS URETHANES

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**SUMMARY:** Acid halides which carry either an  $\alpha$ -phenyl or  $\alpha$ -alkoxy residue show fascinatingly high and useful diastereoselection on condensation with the vinylogous urethane derived ketene acetal enamine **3**. Optically active halides of this type undergo reaction with **3** accompanied by very high diastereofacial selectivity.

We have reported acylation reactions of straight-chained or symmetrically substituted  $\alpha$ -branched acid halides with either lithium enolates of vinylogous urethanes or their trimethylsilylketene acetal enamine analogues. *In situ* reduction of these acylation products with hydride, gave lactones with excellent (99:1) *anti*-stereochemistry.<sup>2</sup> These findings prompted us to examine the behavior of unsymmetrical  $\alpha$ -branched acid chlorides with these nucleolphiles, since in marked contrast to aldehydes, essentially nothing was known about their diastereoselection behavior.<sup>3</sup> The results of this study reveal some novel and useful trends in diastereoselection.

Deprotonation of the vinylogous urethane 1 with lithium diisopropylamide (LDA) generates the enolate 2, which, on reaction with trimethylsilyl chloride, affords the ketene acetal enamine 3.<sup>4</sup> The behavior of 2 and 3 with 2-phenylpropionyl bromide or chloride 4 was examined first. Reaction of 2 (0.5 M, THF, -78°C, 5 h) with either derivative of 4 gave two C-4 acylated products 5 and 6. These substances were normally reduced *in situ* with lithium triethylborohydride (-22°C) to afford a 3:1 ratio of the lactones 7 and 8 (80% yield). Significantly greater diastereoselection accrued on reaction of the ketene acetal enamine 3 (0.5 M, THF, -78°C, 12 h) with 4, since hydride reduction of the C-4 acylated products 5 and 6 led to a 12: 1 ratio of lactones 7 and 8 (84% yield).

Lactones 7 and 8, either separately or as a mixture, were degraded with  $H_5IO_6$  into the acids 9 and 10, respectively.<sup>5</sup> The <sup>1</sup>H NMR spectrum (300 MHz) of acids 9 and 10 were compared, on the same instrument, to a sample of acid 10 known to possess *anti-syn*-stereochemistry.<sup>6</sup> This comparison clearly indicated that our acid 10 was identical to the authentic sample of 10, and hence, it and lactone 8 must possess *anti-syn*-stereochemistry. In addition, the major acid 9, derived from lactone 7, proved identical to the minor acid isomer present in the authentic sample of 10; and therefore, acid 9 and lactone 7 must possess the rare *anti-anti-stereochemistry* indicated for them.

To rule out involvement in this reaction of the ketene derived from the acid halide, as well as to examine the enantioselective potential of the reaction, we acylated the (R) form of the bromo-derivative of 4 with 3, and after hydride reduction, again obtained a 12:1 ratio of lactones 7 and 8. Degradation of the major lactone, 7, into 9 followed by



esterification (CH<sub>2</sub>N<sub>2</sub>), and hydroxyl group derivatization with the acid chloride  $11^7$  gave 12. <sup>1</sup>H NMR examination (300 MHz) of 12 indicated that <1% racemization had occurred through the sequence leading to its formation. *The diastereofacial selectivity of this reaction coupled with the transformable nature of the phenyl moiety into alternative functionality augurs well for the synthetic potential of this system.*<sup>6</sup>

In an effort to probe the influence of the phenyl ring on the diastereoselection of **4**, we examined the behavior of the acid chloride **13**-the cyclohexyl analogue of **4**. Reaction of **13** with either **2** or **3** followed by hydride reduction afforded the lactones **14** and **15**. In both cases, the *anti-syn*-stereoisomer **15** predominated in a ratio of **3**:1. The structures of lactones **14** and **15** were correlated with lactones **7** and **8** by reduction of the phenyl rings present in latter (Ru/Al<sub>2</sub>O<sub>3</sub>/CH<sub>3</sub>OH/H<sub>2</sub>-1900 psi/ 36 h) which gave **14** and **15**, respectively.

We then examined the racemic lactic acid derivative 16. Condensation of 3 with 16 resulted in the formation of two C-4 acylated products, 17 and 18, which on reduction afforded a 10:1 mixture of the lactones 19 and 20, respectively (86% yield). The enolate 2, on reaction with 16, gave a 4:1 ratio of the lactones 19 and 20. Lactones 19 and 20 were treated, individually, with a mixture of KOH/H<sub>2</sub>O<sub>2</sub>/Na<sub>2</sub>WO<sub>4</sub>·H<sub>2</sub>O/CH<sub>3</sub>OH to give (78% yield) the amides 21 and 22, respectively.<sup>8</sup> Treatment of these amides with 2 N HCl caused their reformulation (41% yield) into the butyrolactones 23 (from 21) and 24 (from 22). Careful <sup>1</sup>H NMR (300 MHz) comparison of the methine proton coupling constants at C-2, C-3, and C-4 of 23 and 24 to butyrolactones with known stereochemistry<sup>9</sup> clearly showed 23 and 24 to possess the structures indicated for them-hence, the lactone 19 and the amide 21 carry *anti-syn*-stereochemistry.

The above condensation was repeated using 3 and the (S) form of 16 (94% optical purity)<sup>10</sup> to obtain 19 and 20 (10:1, 86% yield). Degradation of 19 to the amide 21 followed by derivatization with the acid chloride  $11^7$  gave 25. <sup>1</sup>H NMR (300 MHz) examination of 25 indicated a 1% loss of optical purity during the sequence leading from 16 to 25.

Other acid chlorides containing oxygen substitutents in the  $\alpha$  position, the  $\alpha$  and  $\beta$  positions, and the b position have been examined. The *t*-butyldimethyl-silyl protected lactic acid chloride **26** on reaction with **3** showed better diastereoselection than its O-benzyl analogue **16** in that a 12:1 ratio of the lactones **27** and **28**, respectively, were obtained (71% yield). The structures of **27** and **28** were proven by desilylation followed by benzylation to give the lactones **19** and **20**, respectively.<sup>11</sup> The acid chloride **29** which contains oxygen atoms in both the  $\alpha$  and  $\beta$  positions also was reacted with **3**.<sup>12</sup> In this instance, a 4:1 ratio of the lactone products **30** and **31**, respectively, were obtained from the reaction. The structure of the major lactone product, **30**, was determined by single crystal X-ray analysis (Figure 1) to carry the *anti-syn*-stereochemistry indicated for it. Lastly, the acid chlorides **32** and **33**, which carry oxygen in the  $\beta$  position, show no stereoselection whatever on reaction with **3** followed by reduction–they each give two lactone products which are 1:1 mixtures of diastereoisomers with respect to side chain stereochemistry as determined by <sup>1</sup>H NMR spectroscopy.

Clearly, the acid halides 4, 16, and 26, in their reactions with the ketene acetal enamine 3, exhibit striking and useful stereoselectivity when contrasted with their aldehyde analogues.<sup>13</sup> Lacking any clear notion of the transition-state orientation between 3 and these various acid halides, we offer the suggestion that 4, 16, and 26 react in a conformation similar to the Felkin conformation observed for aldehydes. The need for an examination of  $\sigma^*-\pi^*$  interactions in acid halides of this type, along the lines so richly developed by Anh for aldehydes, is apparent.<sup>14</sup> It seems apparent that the stereoselection observed for acid halides, as described in this manuscript, might be general for the reaction of these species with nucleophiles.<sup>2f</sup> We are examining some of these transformations, in particular, reactions with organotin nucleophiles.

Acknowledgment. We gratefully acknowledge financial support from the NIH. We also acknowledge very helpful conversations with Professor J. P. Dinnocenzo (University of Rochester).

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- 13. For some of the acid halide condensation hydride reduction examples reported herein, we have also carried out their aldol counterparts using the lithium enolate 2 at essentially the same concentrations and the same temperatures. These results are tabulated below.
  - 1) aldehyde analogue of 4
  - 2) aldehyde analogue of 13
  - 3) aldehyde analogue of 16
  - 4) aldehyde analogue of 26

14.

- 1:2.5 ratio of lactones 7 to 8
- 1:30 ratio of lactones 14 to 15
- 1:2 ratio of lactones 19 to 20
- 1:1.5 ratio of lactones 27 to 28

(Received in USA 3 September 1987)

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