Synthesis of Butanolides *via* Intramolecular Acylative Ring-opening Reactions of 3-(Tetrahydro-2-furyl)propanoic Acid Derivatives

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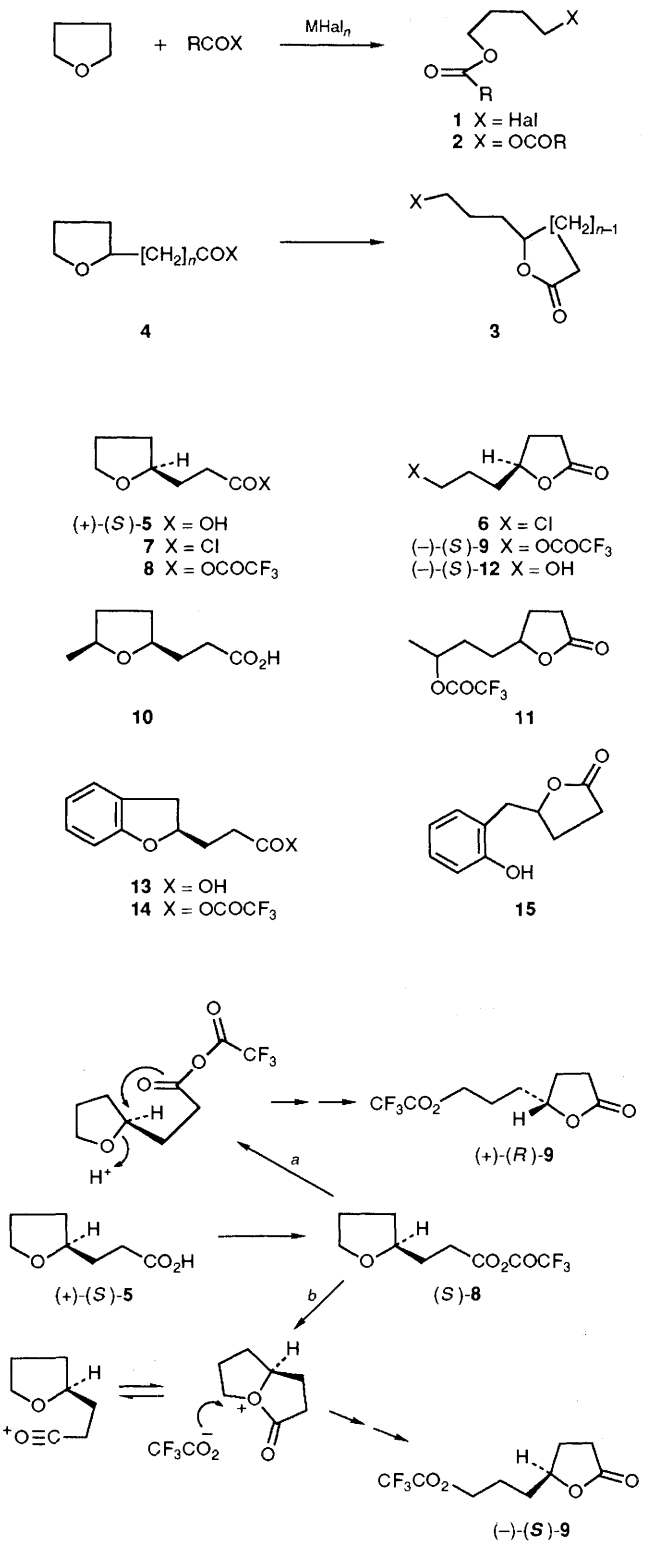
5-Substituted furan-2(3*H*)-ones are formed when mixed 3-(tetrahydro-2-furyl)propanoic trifluoroacetic anhydrides are treated with acid catalysts.

The ring-opening reactions of tetrahydrofurans which occur when they are treated with acyl halides[1] or anhydrides[2] in the presence of Lewis acids are well known, and provide convenient routes to (4-halobutyl)alkanoates **1** and to diesters of butane-1,4-diol **2**, respectively. Consideration of these reactions suggested to us that an intramolecular variant of the former should be feasible, and that this should lead to the formation of lactones **3** from appropriate tertrahydrofuryl-alkanoic acids **4**. In this communication, we report results which we have obtained from some examples of acids **4** where $n = 2$, and present evidence for the mechanism of one of the novel reactions involved.

When 3-(tetrahydro-2-furyl)propanoic acid **5**, easily prepared by catalytic hydrogenation of (*E*)-3-(2-furyl)propenoic acid, was treated with thionyl chloride the major product was 5-(3-chloropropyl)furan-2(3*H*)-one **6** (83%).† However, we were unable to obtain the acyl chloride **7** efficiently in pure form, even when attempting its preparation under essentially neutral conditions.[3]‡ In addition, it was not always easy to

† All new compounds were fully characterised and gave spectroscopic data in accord with their structures.

‡ (*a*) Lithium salt of **5**, 0.33 equiv. of PCl_3, $CHCl_3$; (*b*) PPh_3–CCl_4.



Scheme 1

separate the lactone **6** from other polar materials formed during the reaction.

More satisfactorily, treatment of the acid **5** with one equivalent of trifluoroacetic anhydride in dry chloroform at 0 °C led rapidly to the isolable mixed anhydride **8**. This, when pure, was unaffected by prolonged refluxing in that solvent, but if a small amount of trifluoroacetic acid was added to the hot solution or if the mixture in which the anhydride had been prepared was simply heated then the furanone **9** was obtained in 86% yield. Similar treatment of the propanoic acid **10**§ yielded the analogous trifluoroacetoxy lactone **11**.

Two plausible mechanisms for these reactions may be considered (Scheme 1). One of them (*a*) involves initial protonation of the tetrahydrofuryl oxygen in **8** followed by intramolecularly assisted ring cleavage with stereochemical inversion at C-2′. The other (*b*) assumes the intervention of an acylium species which ultimately leads to the product *via* a route which requires retention of configuration about that centre.

To test the issue we subjected (+)-(*S*)-3-(tetrahydro-2-furyl)propanoic acid **5**[4] to our reaction conditions. The (–)-(*S*)-5-(3-trifluoroacetoxypropyl)furan-2(3*H*)-one **9** obtained could be assigned the absolute configuration shown by virtue of its hydrolysis (MeOH–$NaHCO_3$) to the known[5] (–)-(*S*)-5-(3-hydroxypropyl)furan-2(3*H*)-one **12**. This result is consistent with mechanism (*b*) where there is retention of the original configuration at C-2′ of the acid **5**.

Supporting this finding, the 2,3-dihydrobenzofuran derivative **13**[6] reacted with trifluoroacetic anhydride to give the mixed anhydride **14** which stubbornly resisted all attempts to rearrange it to a lactone in the presence of trifluoroacetic acid. Treatment of **14** with BF_3·Et_2O also had little effect, but heating it in chloroform with $TiCl_4$ slowly yielded the lactone **15**. These results presumably reflect the consequence of an alternative reaction pathway being imposed on **14** by the inability of the dihydrobenzofuran system to undergo nucleophilic attack at C-7′a as is required in the final step of mechanism (*b*) (Scheme 1).

The availability of lactones like **6**, **9**, and **11** from the reactions which we have described makes them attractive intermediates for the synthesis of natural products such as certain insect pheromones which incorporate the dihydrofuran-2(3*H*)-one function. Work to define the limit of *n* in the acids **4** is currently in progress, and we expect that we should be able to form useful macrolides where values of *n* are large.

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§ Prepared by hydrogenation of the corresponding (*E*)-3-(2-furyl)-propenoic acid, and assumed to have mainly the *cis*-configuration. The ^{13}C NMR spectrum of **10** indicated that a minor, presumably *trans*, diastereoisomer was present (20%). The ^{13}C NMR spectrum of the derived trifluoroacetoxy lactone **11** revealed an almost identical diastereoisomeric ratio, suggesting that the formation of **11** involved S_N2 attack by trifluoroacetate on the acyloxonium intermediate.