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Oxidation products of 2-acyl-4,5-dihydrofurans

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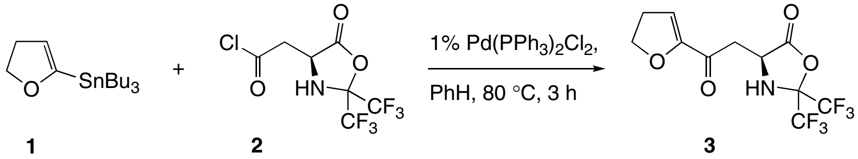
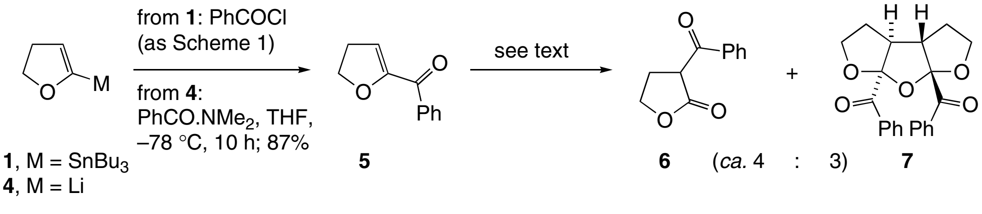
Abstract—2-Benzoyl-4,5-dihydrofuran (**5**) readily undergoes oxidation in air, during chromatography on silica, or following exposure to oxidising agents (MCPBA, DMDO), to give 2-benzoylbutyrolactone (**6**) and tricycle **7** as the major products.

As part of a project to develop enantiospecific routes to pyrrolizidine alkaloids, we had occasion to study the Stille cross-coupling of 2-(tributylstannyl)dihydrofuran **1**[1] and the aspartate-derived acid chloride **2**.[2] Under the standard conditions,[3] this reaction proceeded smoothly to give 2-acyldihydrofuran **3** in admixture with Bu_3SnCl (Scheme 1). We noticed decomposition and a low mass recovery following attempted chromatographic purification and therefore assayed some of the well-known procedures for removal of tin residues from reaction mixtures: (1) partitioning between petrol and acetonitrile[4] gave only a partial separation; (2) stirring a petrol/ethyl acetate solution with NaOH and filtration through silica [5] gave no recovery of coupled product; (3) stirring with aq KF and filtration[6] to remove precipitated polymeric Bu_3SnF resulted in an inseparable mixture of products; (4) column chromatography on KF-impregnated silica[7] succeeded in producing tin-free product but only in trace quantities.

In an attempt to identify reliable conditions for producing this type of compound in a pure form, free of tin residues, we focused on the synthesis and purification of a simple model (**5**, Scheme 2) rather than waste further acid



Scheme 1.



Scheme 2.

Keywords: Dihydrofuran; Dihydropyran; Oxidation; Rearrangement; Lactones.

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chloride **2**. The choice of benzoyl as the acyl substituent was based on the expectation that this would impart non-volatility to the sample. Interestingly, benzoyldihydrofuran **5**, prepared analogously to compound **3**, was found to be converted, either during chromatography, or on stirring with silica in ethyl acetate for 7 h, into two major products, **6** and **7** (83% combined yield), in addition to a very minor component that has so far not been isolated and identified. Whilst butyrolactone **6**[8] was readily identified following routine spectroscopic analysis (e.g., ν_{max}/cm^{-1} 1769s, 1682s), the identity of the tricyclic bisacetal **7** was less obvious; fortunately, the compound crystallised out of ethyl acetate and the structure was solved by X-ray crystallography (Fig. 1).[9]

A survey of the literature revealed no suggestions of a particular instability of 2-acyldihydrofurans[10] and, in a separate study,[11] we had prepared 2-formyl-4,5-dihydrofuran[12] without complication. Therefore, in order to confirm that this reactivity was not an artefact induced by residual reagents from the cross-coupling reaction, substrate **5** was prepared directly from 2-lithiodihydrofuran according to Meyers' method.[13] Once more, the product was initially obtained reasonably cleanly but was found to evolve into the two major products **6** and **7** as before.

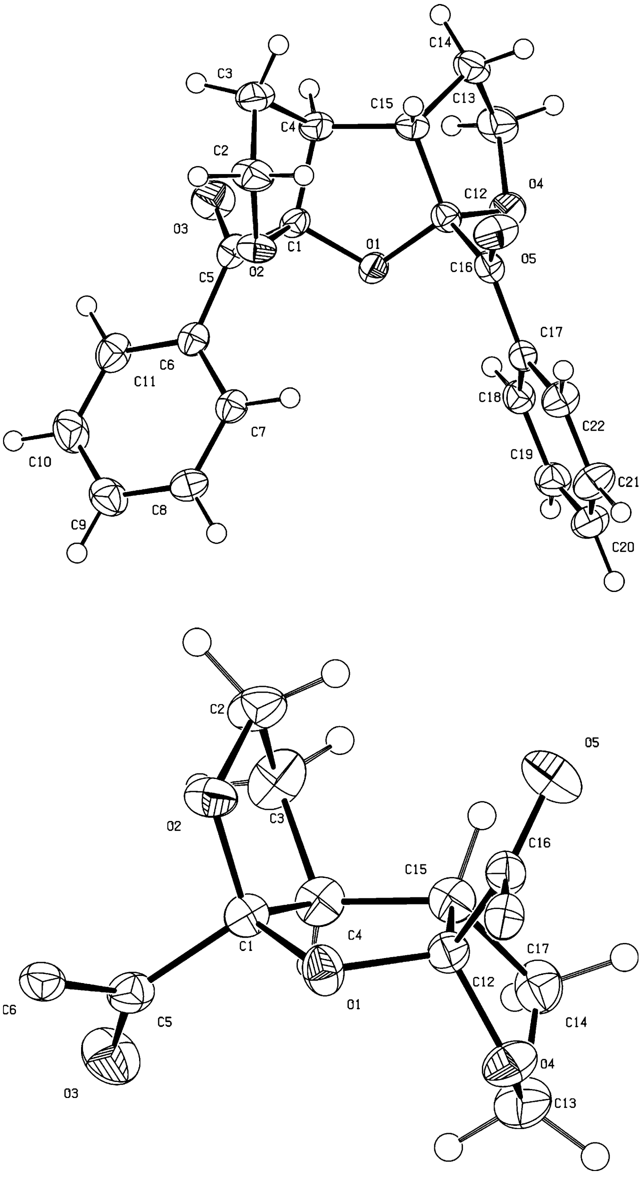
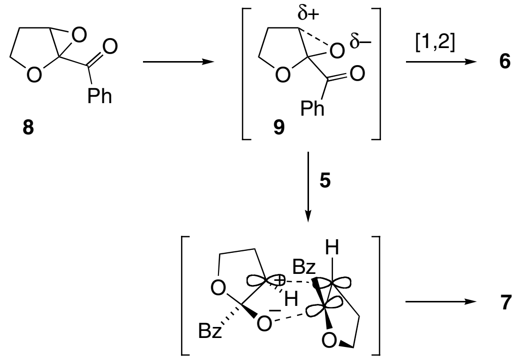


Figure 1. (Upper): ORTEP view of tricycle **7**; (lower): rotated view highlighting the step-like ring system (phenyl groups omitted for clarity).[9]

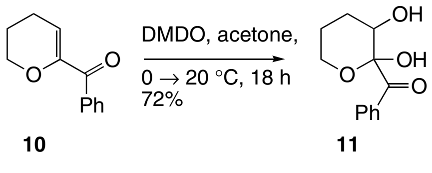
Clearly, these results reflect an inherent propensity for 2-benzoyldihydrofuran (**5**) to undergo aerial oxidation. The same behaviour could be induced deliberately by exposing dihydrofuran **5** to either MCPBA (CH_2Cl_2, 0 → 20 °C, 1 h) or DMDO (acetone, 0 → 20 °C, 1 h). On this basis, it is reasonable to propose that the enol ether double bond is epoxidised[14] (→**8**, Scheme 3), that the epoxide then has a tendency to ring-open (→**9** or a protonated analogue) to place a partial positive charge remote from the acyl group, and that benzoyl group migration[15] completes the formation of butyrolactone **6** in a formal dyotropic rearrangement[16] (i.e., **8**→**6**). In this scenario, tricycle **7** would arise by the trapping of polarised intermediate **9** by the starting dihydrofuran (**5**).

2-Acetyldihydrofuran[17] also proved to be unstable towards chromatography on silica, and 2-acetylbutyrolactone was observed in the product mixture; however, this compound showed a reduced tendency towards air-oxidation and chromatography using deactivated silica (triethylamine) was sufficient to obtain pure product. 2-Benzoyl-4,5-dihydro-6*H*-pyran (**10**)[13] showed no tendency to undergo such oxidation and rearrangement; treatment of the latter with DMDO resulted in diol **11** after chromatography (Scheme 4).

In summary, 2-benzoyldihydrofuran (**5**) exhibits a previously unrecognised proclivity towards oxidation to give



Scheme 3.



Scheme 4.

rearranged and dimeric products (**6** and **7**, respectively). Although we have not yet studied other 2-aroyldihydrofurans we expect that a similar reactivity pattern will be observed. This reactivity does not extend to the dihydropyran analogue **10** nor to the simple 2-alkanoyldihydrofurans, such as 2-formyl- and 2-acetyldihydrofuran, which show merely the expected instability towards acidic conditions.

Acknowledgements

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9. Crystal data for **7**: $C_{22}H_{20}O_5$, $M = 364.40$, colourless fragment, monoclinic, $a = 10.6044(2)$, $b = 11.9077(2)$, $c = 14.7870(3)$ Å, $V = 1807.82(6)$ Å^3, $T = 150$ K, space group $P2_1/n$, $Z = 4$, $\mu(\text{Mo K}\alpha) = 0.095\ \text{mm}^{-1}$, 19,769 reflections measured, 4330 unique ($R_{\text{int}} = 0.043$), final $wR = 0.0377$. Crystallographic data for this structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 609602. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ [fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
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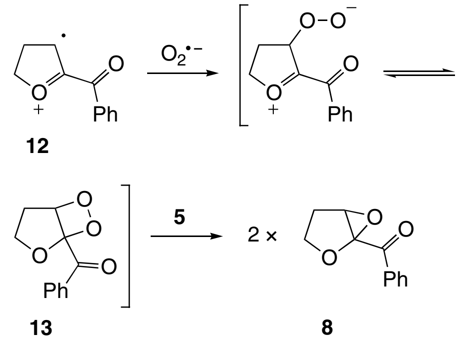

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