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Diastereoselective Synthesis of 2,5-Dialkyl Tetrahydrofuran-3-ones by a Copper-Catalysed Tandem Carbenoid Insertion and Ylide Rearrangement Reaction

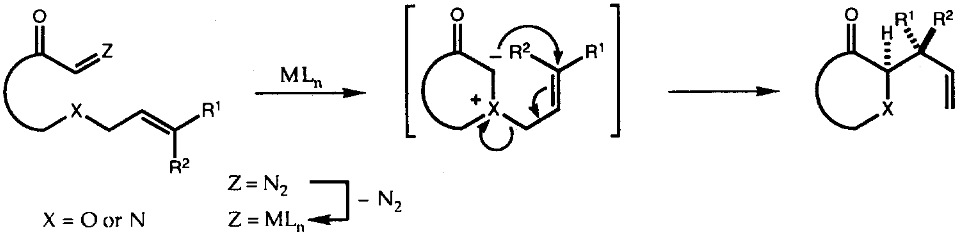
J. Stephen Clark

Department of Chemistry, University of Nottingham, Nottingham, NG7 2RD, U.K.

Abstract: Cu(acac)$_2$-catalysed cyclisations of the α-diazo ketones **3**, result in the diastereoselective formation (>97:3) of the *trans*-2,5-dialkyl tetrahydrofuran-3-ones **4**. The yields and levels of diastereoselection are catalyst, solvent, and temperature dependent.

Tetrahydrofurans occur frequently in complex natural products of structural and biological importance, such as the polyether antibiotics.[1] Although numerous methods for the preparation of these systems have been reported,[2] few allow substituted tetrahydrofurans to be prepared with high levels of diastereocontrol, and so the development of new stereoselective methods continues to be of importance.

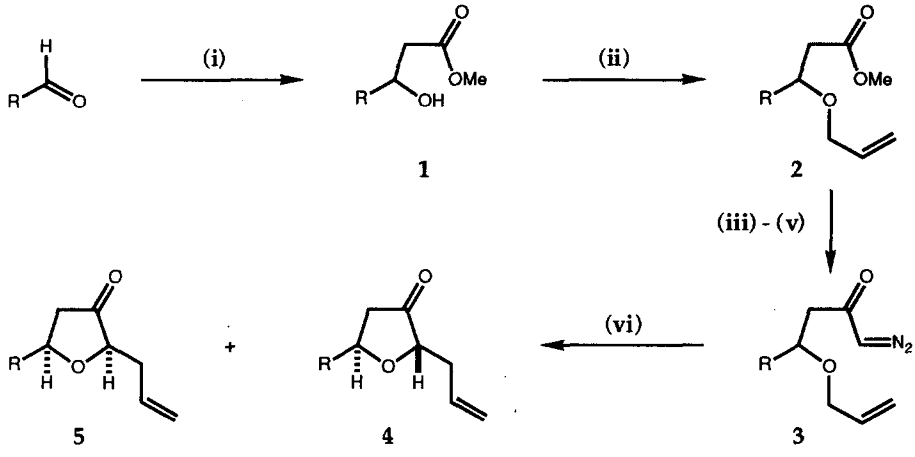
We have investigated the factors that influence diastereocontrol in the synthesis of 2,5-dialkyl tetrahydrofuran-3-ones by an *intramolecular* tandem carbenoid insertion and ylide rearrangement reaction.[3,4] This reaction, first reported by Pirrung and Johnson,[5,6] offers a potentially efficient approach to the synthesis of *O*- and *N*-heterocycles because it allows two new bonds and either one, or two, new stereocentres to be formed in a single step (**Scheme 1**).



Scheme 1

We now report preliminary results, which demonstrate that the copper-catalysed tandem carbenoid insertion and ylide rearrangement reaction affords 2,5-dialkyl tetrahydrofuran-3-ones in good yield and with high levels of diastereocontrol, and that the catalyst functions as part of a metal bound ylide-enolate species during C–C bond formation.

The preparation and cyclisation of the α-diazo ketones **3a** and **3b** were accomplished as summarised in **Scheme 2**.[7] Thus, treatment of the appropriate aldehyde with methyl bromoacetate in the presence of activated zinc powder afforded the β-hydroxy ester **1**,[8] which was transformed into the allyl ether **2** by treatment with allyl 2,2,2-trichloroacetimidate and a catalytic amount of trifluoromethane sulphonic acid.[9] Cleavage of the methyl ester was accomplished by treatment of **2** with aqueous lithium hydroxide, and the resulting acid was then converted into the corresponding acid chloride using oxalyl chloride and catalytic dimethylformamide. Subsequent treatment of the acid chloride with excess diazomethane then furnished the requisite α-diazo ketone **3**.



a R = $(CH_3)_2CH$ **b** R = $CH_3(CH_2)_2$

Scheme 2 (i) $BrCH_2CO_2CH_3$, Zn, Me_3SiCl (cat.), Et_2O, reflux (**5a** 86%, **5b** 87%); (ii) $Cl_3CC(NH)OCH_2CH{=}CH_2$, CF_3SO_3H (cat.), CH_2Cl_2-hexane, RT (**6a** 80%, **6b** 77%); (iii) 2M LiOH(aq.), MeOH, RT (**7a** 95%, **7b** 97%); (iv) $(COCl)_2$, DMF (cat.), CH_2Cl_2, 0 °C → RT; (v) CH_2N_2, Et_2O, 0 °C (**1a** 89%, **1b** 78%), (vi) catalyst (2 mol%), solvent, RT or reflux (see text)

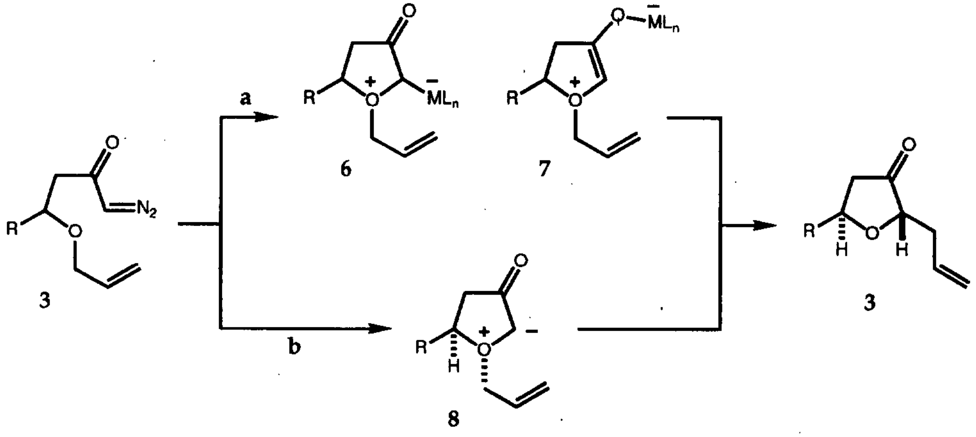
The $Rh_2(OAc)_4$-mediated cyclisation of **3a**,[10] in a variety of solvents at reflux or room temperature, afforded a mixture of **4a** and **5a** in fair yield (51-68%),[11,12] with a modest preference (65:35–81:19) for the thermodynamically disfavoured *trans*-tetrahydrofuran-3-one **4a**.[13,14] The yields and levels of diastereoselection were solvent and temperature dependent, but in all cases, the diastereoisomer ratios were inferior to the single result, previously reported by Johnson, for the $Rh_2(OAc)_4$-catalysed cyclisation of a homologous substrate.[15]

A dramatic improvement in both the yield and level of diastereoselection was achieved by employing $Cu(acac)_2$ as the catalyst in CH_2Cl_2, THF, or benzene, at reflux.[10,11] Optimum results were obtained when the reaction was performed in THF or benzene (>97:3, 83–85%). $Cu(OTf)_2$ also proved to be an effective catalyst for the reaction, but the yields (61-74%) and levels of diastereoselection (≤93:7) were less satisfactory than those of the $Cu(acac)_2$-catalysed reaction.[16]

High yields and excellent levels of diastereoselection were also obtained for the $Cu(acac)_2$-catalysed cyclisation of the isomeric precursor **3b**, bearing an *n*-propyl chain instead of the more bulky α-branched substituent present in **3a**. The best result (>97:3, 83%) was obtained when the cyclisation reaction was performed in THF at reflux.

The modest levels of diastereocontrol achieved in the $Rh_2(OAc)_4$-catalysed cyclisation reactions of **3**, contrast with the example reported by Johnson, and our results demonstrate that $Rh_2(OAc)_4$ is not the catalyst of choice for this reaction, despite the extensive use of the complex for related carbenoid transformations.[4,17]

The marked effect that the catalyst has on the level of diastereoselection suggests that rearrangement occurs via a metal-bound ylide-enolate species such as **6** or **7** (path **a**), or that there is selective insertion of one of the diastereotopic oxygen lone pairs, to form **8**, coupled with efficient transfer of stereochemical information from oxygen to carbon during rearrangement (path **b**) (**Scheme 3**). In order for path **b** to be operative, it would be necessary for the rate of rearrangement to be rapid with respect to rate of inversion at the oxonium centre. Although the rates of inversion of oxonium ylides have not been determined, it is known that the barriers to inversion of analogous oxonium ions are low.[18] It seems unlikely, therefore, that the configuration at the oxonium centre of ylide **8** would be preserved prior to rearrangement.



Scheme 3

This method promises to be of general synthetic utility and should be amenable to enantioselective synthesis, due to the availability of β-hydroxy esters, such as **1**, in non-racemic form.[19]

Further work is in progress to determine the factors that affect diastereocontrol in these reactions, and to apply this method to the construction of heterocyclic systems and the synthesis of complex natural products.

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References and Notes

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7. All new compounds exhibited satisfactory spectroscopic and either microanalytical, or mass spectrometry data.
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10. Experimental procedure: α-Diazo ketone **3** (1 mmol) was dissolved in the appropriate solvent (50 ml) and the solution added dropwise, over a period of 10–30 min, to a solution of the catalyst in the same solvent (50 ml) at either room temperature, or reflux, under an atmosphere of nitrogen. After the reaction had been stirred at the same temperature for an additional period of time (10 min to 20 h), the solvent was removed *in vacuo* and the product purified by flash column chromatography on silica gel (hexane–diethyl ether, 9:1) to afford the desired tetrahydrofuran-3-one(s). All reactions were performed on a 1 mmol scale for comparison purposes.
11. Ratios were determined by NMR (250 or 400 MHz). An isomer ratio of 97:3 was clearly visible by NMR, so we judge this to be a conservative lower limit for detection of the minor diastereoisomer.
12. Stereochemistry was determined by NMR. A 5–6% NOE was observed between the protons adjacent to the ether oxygen of **5a**.
13. Treatment of ketones **4a** and **5a** with a solution of potassium carbonate in methanol at room temperature for 3 days, afforded a thermodynamic 33:67 (**4a**:**5a**) ratio of isomers.
14. After treatment of a 93:7 (**4a**:**5a**) mixture of isomers with a solution of $Rh_2(OAc)_4$ in THF at reflux, an isomeric mixture of the same ratio was isolated. Thus, epimerisation of the stereocentre adjacent to the carbonyl group does not occur during the $Rh_2(OAc)_4$-catalysed reaction.
15. Johnson obtained a 93:7 ratio of **4**:**5** from the $Rh_2(OAc)_4$-catalysed cyclisation of **3** (R = CH_3) in benzene at room temperature (see ref. 6).
16. It is believed that Cu(OTf), produced as a consequence of the *in situ* reduction of $Cu(OTf)_2$ by the diazo compound, is the catalytic species in these reactions. See: Salomon, R. G.; Kochi, J. K. *J. Am. Chem. Soc.* , **1973**, *95*, 3300.
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