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Synthesis of novel 2H,5H-Dihydrofuran-3-yl Ketones via ISNC reactions

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Abstract

Unique 1-[2H,5H-dihydrofuran-3-yl]ketones have been synthesized from propargylic nitroethers via intramolecular cycloadditions involving silyl nitronates. Various substituent groups were placed on the 2 and 5 positions of the dihydrofuran rings. We examined the scope of the long-range coupling in proton NMR of the oxo-dihydrofuran products. The identities of the diastereomers resulting from the Michael Addition/cycloaddition reactions were tentatively assigned for the first time. CAChe MND0 PM5 and CONFLEX programs were engaged to assist with the identification of these stereoisomers. The reaction times and conditions for these oxo-dihydrofurans were found to be different than that of the published dihydrofuranals, which led us to propose a different mechanism.

Keywords

CAChe; CONFLEX; ISNC; propargylic nitroethers; oxo-dihydrofurans; dihydrofuranyl ketones; dihydrofuranones

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Supplementary Data The supplementary data is available online with the paper in ScienceDirect. This section contains the experimentals for compounds **10-16** and spectral information (FTIR, MS, ¹H NMR, ¹³C NMR).

Introduction

We are interested in the synthesis of a novel tetraester macrocycle (see **1** in Scheme 1) that may possibly exhibit antibiotic properties such as those of the established ionophoric antibiotic, nonactin. To our knowledge these 3,4-furan macrocycles have not been extensively investigated as compared to the 2,3-, 2,4- and 2,5-furan derivatives.¹ Many of these macromolecules have exhibited efficient cation transport as in the case of the noncyclic 2,5-dioxytetrahydrofuran ligands studied by Wierenga², the cyclic 2,5-derivatized furan polyether macrocycles reported by Bradshaw³ and the macrocyclic furan ligands developed by Kobuke⁴. Some investigators, however, discovered showed little to no effect when compared to similarly sized macrocycles without furan based components as discovered by Tarroago⁵ and Jackels⁶. The former paper stated that the lack of extraction capability of the macromolecules for an alkali atom is due to the lower donor character of the furan oxygen atom compared to an alkyl ether oxygen atom. The latter reports that the steric interactions due to the twisting of the macrocycle to accommodate a divalent metal cation were increased when the donor oxygen atom was part of a furan derivatized system and resulted in little evidence in binding. The proposed polyester series would not rely upon the furanyl oxygen for coordination to the metal and thus avoids these donor or steric strain problems. Computational analysis has found that nonactin and the proposed macrocycle have similar binding capabilities towards cations with a lower energy of complexation requirement for the novel macrolide.⁷

Scheme I shows a brief retrosynthetic analysis of the macrocycle **1**. The tetraester could be derived from a difunctional tetrahydrofuran monomer such as **2**. This in turn could be prepared from the dihydrofuran carbonyl compounds **3**. The synthesis of the related carbaldehydes has been briefly reported.⁸ The appropriate nitroethers **4** can be prepared in good yields from nitroalkenes and propargylic alcohols.⁹

Results

It was decided to explore the reactions to produce the oxo-dihydrofurans, since these compounds have not been reported in the literature. An example of the synthesis of these novel dihydrofuranyl ketones is provided in Scheme II (compounds **10-16**). 2-Methylpropanal **5** was treated under Grignard conditions to provide 2-methyl-4-hexyn-3-ol **6**. This propargylic alcohol was then converted to the secondary alkoxide and nitrostyrene was slowly added. Racemic **7** [(±)(±)-5-methyl-4-[1-nitro-2-phenyleth-2-yloxy]hex-2-yne] was isolated after work up and purification by column chromatography. This nitroether was then treated under silyl nitronate cycloaddition conditions¹⁰, which we refer to as an ISNC (Intramolecular Silyl Nitronate Cycloaddition) so as not to limit the unsaturated carbon system to alkenes (vs. ISOC which refers to olefins only). The anion of the N-trimethylsilyloxy nitronate **8** is prepared *in situ* and then undergoes a 1,3-dipolar cycloaddition to form intermediate **9**, which upon quenching with acid affords target compound **10** [(±)(±)-1-[2-[1-methylethyl]-5-phenyl-2H, 5H-dihydrofuran-3-yl]ethanone].

Table I displays the oxo-dihydrofurans that were completed. Ratios of diastereomers were determined via GC analysis of the crude products. We found that the time involved for the cycloaddition was dependent on the carbonyl substituent. The previously reported dihydrofuranals require less than 24 hours of reaction time⁸, with very little time needed for the acidic workup. In contrast, the reaction times for the α,β -unsaturated ketones was greatly influenced by the length of the carbonyl's alkyl chain. The novel oxo-dihydrofurans need a much longer reaction time (four to eight days) in comparison to their carbaldehyde counter parts. They also require an increase in the equivalents of both trimethylamine and trimethylsilylchloride, with additions of these compounds during the reaction. The acidic work

up demanded a higher concentration of acid for the ketones (6M) than that of the published dihydrofuranals (1 M).

Discussion

The tentative mechanism put forth by Kurth and Duffy-Matzner⁸ suggested a β -nitroso-carbaldehyde intermediate with subsequent loss of HNO to form the dihydrofuranals. We now suggest the following mechanism, which entails a second intramolecular reaction during acidic work up of the 1H-isoxazoline intermediate **17** as depicted in Scheme III. This negates the need for a base under acidic conditions and explains the reaction time differences due to the reduced activity of the enol **18**. This enol intermediate also explains why the propargylic nitroethers give dihydrofuro-carbonyl products under ISNC, while the vinylic nitroethers give the expected isoxazole derivatives under ISOC (Intramolecular Silyl Nitronate Olefin Cycloaddition) conditions.¹¹ There is currently work in progress to address the regioselectivity of these two cycloaddition reactions.¹²

NMR analysis of the final oxo and carbaldehydes dihydrofurans showed interesting coupling constants. We noticed that several of the final ethanones displayed 4J and 5J coupling constants in the proton spectra while several did not. It was found that phenyl and *t*-butyl substituents would provide the necessary spatial interactions to afford this longer distance coupling while methyl, ethyl and *iso*-propyl groups do not. The diastereomers of the cyclic products had different 5J coupling constants for the major (6 Hz) and minor (5 Hz) isomers. We calculated the pseudo dihedral bond-bond angles (apparent angle between H₂ and H₅) present in the cis and trans isomers of **10**. For the entirety of the calculations, the CAChe 5.1 software system was used. All the initial structures were equilibrated by executing a conformational search (MM213) using the CONFLEX method¹⁴, where only the conformation lowest in energy was saved. The thermodynamic calculations were carried out at the MNDO15 PM516 level of theory using MOPAC. The trans isomer resulted in a pseudo-bond angle of 160° and 5° for the cis isomer. Applying Karplus logic to this data allows us to assign the major diastereomer as the trans isomer.

We tried to exploit the carbonyl present in our products to make solid derivatives that could be analyzed via X-ray diffraction to provide an exact diastereomer assignment. Two attempts were made with compound **10** to produce the 2,4-dinitrophenylhydrazone and semicarbazone derivatives. Both resulted in the formation of fine powders that did not lead to crystal formation.

Conclusion

This paper represents the synthesis of a novel class of ketones. These oxo-dihydrofurans can be prepared in the hands of undergraduates via intramolecular silyl nitronate cycloaddition reactions of propargylic nitroethers in good to excellent yields. We found that the time involved for the cycloaddition was dependent on the carbonyl substituent, with drastically longer time needed for bulkier groups. This led us to propose a new mechanism for this reaction. We also found that long range coupling constants (5J) are observed in compounds with bulky substituents placed in either the 2 or 5 positions. The stereochemistry of these carbonyl dihydrofuran derivatives was also explored, as expected the transformation proceeds with a preference for the trans orientation. It is not known whether the diastereomeric ratios of these compounds are set completely during the Michael Addition step. We are currently examining the possibility of epimerization/retro Michael Addition of the N-trimethylsilyloxy nitronate intermediate (**8**) during the ISNC reaction. Our group intends to continue the work on an exact assignment of the stereoisomers produced in this process.

Experimental Section

general procedure to make dihydrofuro-ketones.

To a stirred solution of nitroether (1 eq.) in dry benzene (0.20M) under nitrogen was added triethylamine (3.5 eq.) and trimethylsilyl chloride (3.6 eq.). After stirring overnight, thin layer chromatography (TLC) revealed the presence of some starting material so more triethylamine (0.5 eq) and trimethylsilylchloride (0.5 eq.) was added. The reaction was followed every 12 hours until no more starting material was detected (2-5 days). The reaction was quenched with 6M HCl (18 eq.) and allowed to stir until no silyl intermediate was found by TLC (1-2 days). The aqueous and organic layers were separated. The aqueous layer was extracted 3X with 5mL of ether. The combined organic layers were washed with 5% sodium bicarbonate, followed by brine, dried over magnesium sulfate and filtered. Removal of solvent under reduced pressure gave dihydrofuranyl-ethanone as a clear colorless oil that turns yellow over time.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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- 17.

Scheme I.

Scheme II.

Scheme III.

Table I

#	R ₁	R ₂	R ₃	% Yield	Ratios ^a	Rxn Time
10	Ph	<i>i</i> -propyl	Me	91	10:1	4.5 days
11	<i>t</i> -butyl	Me	Me	46	2:1	3.5 days
12	H	Ph	Me	63		5 days
13	<i>i</i> -propyl	H	Me	83		3 days
14	Ph	H	Me	64		3.5 days
15	H	Et	Me	64		4 days
16	Ph	Me	Et	96	3:1	7 days

^aRatios determined by Gas Chromatography and confirmed by ¹H NMR.