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Synthesis of novel 2*H*,5*H*-dihydrofuran-3-yl ketones via ISNC reactions

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ABSTRACT

Unique 1-[2*H*,5*H*-dihydrofur-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 MNDO 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.

1. 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 Wierenga,[2] the cyclic 2,5-derivatived furan polyether macrocycles reported by Bradshaw,[3] and the macrocyclic furan ligands developed by Kobuke.[4] Some investigators, however, found little to no effect when compared to similarly sized macrocycles without furan-based components as discovered by Tarroago[5] and Jackels.[6] 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 that of 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 toward cations with a lower energy of complexation requirement for the novel macrolide.[7]

Scheme 1 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]

2. 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 2 (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 conditions,[10] which we refer to as an

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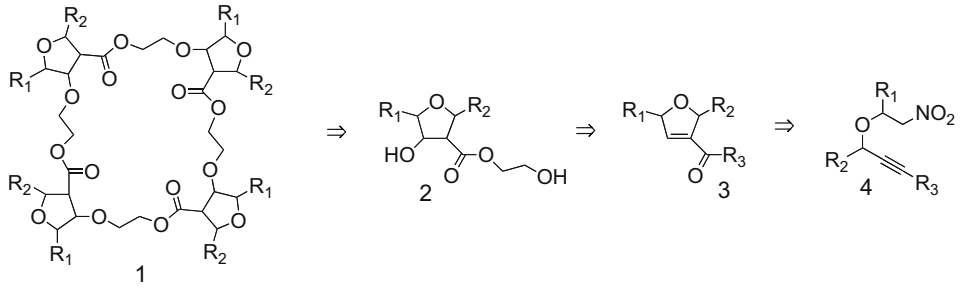
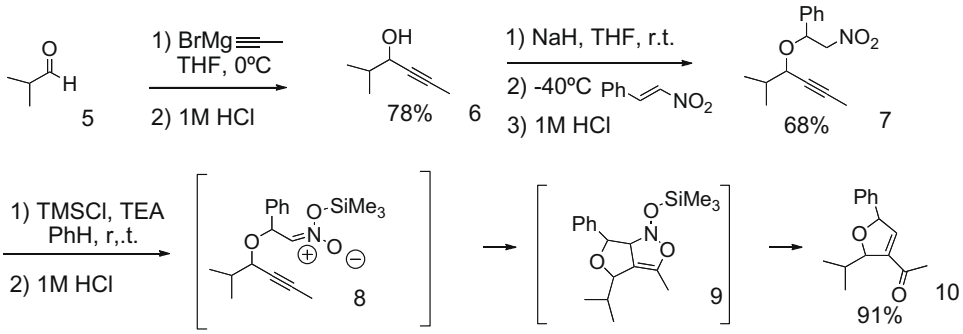


Scheme 1.



Scheme 2.

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-2*H*,5*H*-dihydrofuran-3-yl]ethanone].

Table 1 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 h of reaction time,[8] 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 (6 M) than that of the published dihydrofuranals (1 M).

3. Discussion

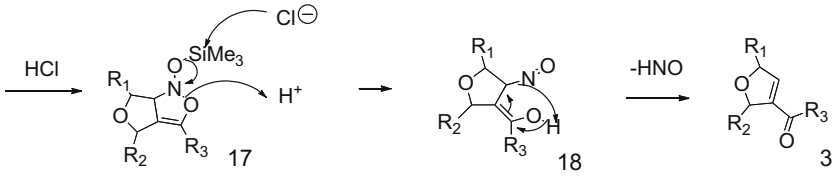
The tentative mechanism put forth by Kurth and Duffy-Matzner[8] suggested a β-nitroso-carbaldehyde intermediate with subsequent lost of HNO to form the dihydrofuranals. We now suggest the following mechanism, which entails a second intramolecular reaction during acidic work up of the 1*H*-isoxazoline intermediate **17** as depicted in Scheme 3. 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 ^{4}J and ^{5}J 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

Table 1

#	R_1	R_2	R_3	% Yield	Ratios[a]	Rxn time (days)	
10	Ph	*i*-Propyl	Me	91	10:1	4.5	
11	*t*-Butyl	Me	Me	46	2:1	3.5	
12	H	Ph	Me	63		5	
13	*i*-Propyl	H	Me	83		3	
14	Ph	H	Me	64		3.5	
15	H	Et	Me	64		4	
16	Ph	Me	Et	96	3:1	7	

[a] Ratios determined by gas chromatography and confirmed by ^{1}H NMR.



Scheme 3.

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 H_2 and H_5) 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 (MM2[13]) using the CONFLEX method,[14] where only the conformation lowest in energy was saved. The thermodynamic calculations were carried out at the MNDO[15] PM5[16] 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.

4. 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.

5. Experimental section—general procedure to make dihydrofuro-ketones

To a stirred solution of nitroether (1 equiv) in dry benzene (0.20 M) under nitrogen was added triethylamine (3.5 equiv) and trimethylsilyl chloride (3.6 equiv). After stirring overnight, thin layer chromatography (TLC) revealed the presence of some starting material so more triethylamine (0.5 equiv) and trimethylsilylchloride (0.5 equiv) were added. The reaction was followed every 12 h until no more starting material was detected (2–5 days). The reaction was quenched with 6 M HCl (18 equiv) 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 3× with 5 mL of ether. The combined organic layers were washed with 5% sodium bicarbonate, followed by brine, dried over magnesium sulfate, and filtered. Removal of the solvent under reduced pressure gave dihydrofuranyl-ethanone[17] as a clear colorless oil that turns yellow over time.

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Supplementary data

Supplementary data (experimental for compounds **10**–**16** and spectral information (FTIR, MS, ^{1}H NMR, ^{13}C NMR) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.08.110.

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17. *Compound characterization*: *(±)(±)-1-[2-[1-methylethyl]-5-phenyl-2H,5H-dihydrofuran-3-yl]ethanone* (**10**): R_f (1:6 EtOAc/hexane) **I** = 0.363, **II** = 0.272; FTIR (neat) 3064, 3031, 2963, 2929, 2872, 1674; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.85 (**I** d, J = 9.2 Hz, 3H); 0.89 (**II** d, J = 9.6 Hz, 3H), 1.12 (**I** d, J = 9.2 Hz, 3H), 1.35 (**II** d, J = 9.6 Hz, 3H), 2.18 (**II** s, 3H), 2.37 (**I** s, 3H), 2.25 (**I&II** pd, J = 9.2, 2.8 Hz 1H), 5.28 (I&**II** ddd (apparent dt), J = 7.6, 2.8, 2.8 Hz, 1H), 5.93 (**I&II** dd, J = 8.4, 2.8 Hz, 1H), 6.71 (**I** dd (apparent t), 2.4, 2.4 Hz, 1H), 6.85 (**II** m, (apparent s), 1H), 7.34 (**I&II** m,

5H); ^{13}C NMR (500 MHz, $CDCl_3$): 14.3 (**II**), 15.3 (**I**), 20.3 (**I**), 20.9 (**II**), 29.6 (**II**), 29.9 (**I**), 31.1 (**II**), 31.6 (**I**), 88.1 (**I&II**), 90.6 (**I&II**), 126.6, 128,5, 128.9, 142.3 (**I&II0**, 140.7 (**I&II**), 142.1 (**I&II**), 194.9 (**I**), 195.0 (**II**); GC–MS (initial temp: 80 °C, final temp: 250 °C, hold 2 min, ramp 12 °C/min) R_t**I** = 7.446, R_t**II** = 7.511, M^+ = 230, *m*/*z* = 187.

(±)(±)-1-[2-Methyl-5-[1,1-dimethylethyl]-2H,5H-dihydrofuran-3-yl]-ethanone (**11**): R_f (1:6 EtOAC/hexane) **I** = 0.94, **II** = 1.0; FTIR (neat) 2961, 2872, 1672; ^{1}H NMR (60 MHz, $CDCl_3$): δ = 0.83 (**I** s, 9 H), 0.85 (**II** s, 9 H), 1.20 (**I** d, *J* = 6.2 Hz, 3H), 1.26 (**II** d, *J* = 7.4 Hz, 3H), 4.36 (**II** dd, *J* = 1.7, 4.8 Hz), 4.48 (**I** dd, *J* = 1.6, 6.0 Hz,), 4.90 (**I&II** m, 1H), 6.0 (**II** m(apparent s), 1H), 6.45 (**I** m, 1H); ^{13}C NMR (60 MHz, CCl_4): 20.8 (**I&II**), 25.5 (**I**), 26.0 (**II**), 28.9 (**I&II**), 35.8 (**I&II**), 80.5 (**II**), 81.3 (**I**), 92.4 (**I**), 92.8 (**II**), 137.8 (**I**), 138.6 (**II**), 146.6 (**I&II**), 183.6 (**I&II**); GC–MS (initial temp: 75 °C, final temp: 200 °C, hold 2 min, ramp 10 °C/min) R_t**I** = 7.049, R_t**II** = 7.319, *m*/*z* = 183 (M^+−H), 126, 43.

(±)-1-[2-Phenyl-2H,5H-dihydrofuran-3-yl]-ethanone (**12**): R_f (1:12 EtOAc/hexane) = 0.080; FTIR (neat) 3064, 3032, 2619, 2851, 1671; ^{1}H NMR (60 MHz, $CDCl_3$) δ = 1.83 (s, 3H), 4.84 (ddd, 2, 2, 5 Hz, 2H), 5.84 (ddd, 2, 4, 5 Hz, 1H), 6.70 (dt, 2,2 Hz, 1H), 7.21 (s, 5H); ^{13}C NMR (60 MHz, $CDCl_3$) δ = 26.9, 86.4, 96.0, 127.7, 127.4, 126.7, 130.3, 136.3, 182.3; GC–MS M^+ = 188, *m*/*z* = 145, 77.

(±)-1-[2-[1-Methylethyl]-2H,5H-dihydrofuran-3-yl]ethanone (**13**): R_f = 0.34 (1:6 EtOAc/hexane); FTIR 3080, 2962, 2931, 2873, 1672, 1095; ^{1}H NMR (60 MHz, $CDCl_3$) δ = 0.90 (d, *J* = 6.5 Hz, 6H), 1.26 (m, 1H), 2.36 (s, 3H), 4.80 (d, *J* = 2.0 Hz, 1H), 4.82 (s, 2H), 6.65 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (60 MHz, $CDCl_3$) δ = 17.7, 17.9, 26.8, 33.0, 73.8, 92.0, 139.3, 141.9, 194.1; GC–MS (initial temp: 75 °C, final temp: 200 °C, hold 2 min, ramp 10 °C/min) R_t = 4.50, M^+ = 154, *m*/*z* = 111, 95, 69.

(±)-1-[2-Phenyl-2H,5H-dihydrofuran-3-yl]ethanone (**14**): R_f = 0.29 (1:4 EtOAc/hexane); FTIR 3063, 3031, 2958, 2922, 2859, 1672, 1096; ^{1}H NMR (60 MHz, $CDCl_3$) δ = 2.35 (s, 3H, CH_3–CO), 4.91 (ddd (apparent td), *J* = 5.0, 2.0, 2.0 Hz, 2H), 5.89 (td, *J* = 5.0, 2.0 Hz, 1H), 6.61 (dt (apparent q), *J* = 2.0, 2.0 Hz, 1H), 7.33 (s, 5H); ^{13}C NMR (60 MHz, $CDCl_3$) δ = 27.9, 75.3, 89.5, 126.8, 127.0, 129.1, 129.5, 142.3, 141.1, 195.5; GC–MS (initial temp: 75 °C, final temp: 200 °C, hold 2 min, ramp 10 °C/min) R_t = 9.17, M^+ = 188, *m*/*z* = 145, 105, 77, 43.

(±)-1-(4-Ethyl-2H,5H-dihydrofuran-3-yl)ethanone (**15**): R_f = 0.12 (1:10 EtOAc/hexane); FTIR 3091, 2967, 2933, 2877, 1672; ^{1}H NMR (60 MHz, $CDCl_3$) δ = 0.87 (t, *J* = 7.3 Hz, 3H), 1.83 (m, 2H), 2.36 (s, 3H), 4.83 (d, *J* = 1.7 Hz, 2H), 5.05 (m, 1H), 6.81 (d, *J* = 2 Hz, 1H); ^{13}C NMR (60 MHz, $CDCl_3$) δ = 8.6, 26.7 26.9, 74.3, 85.8, 139.1, 143.0, 194.0; GC–MS M^+ = 140 ($C_8H_{12}O_2$), *m*/*z* = 111, 43.

(±)(±)-1-[2-Methyl-5-phenyl-2H,5H-dihydrofuran-3-yl]propanone (**16**): R_f (1:6 EtOAC/hexane) **I** & **II** = 0.37; FTIR (neat) 3065, 3031, 2976, 2931, 1673; ^{1}H NMR (200 MHz, $CDCl_3$) δ = 1.08 (**I** t, *J* = 7.4 Hz, 3H), 1.16 (**II** t, *J* = 7.0 Hz, 3H), 1.44 (**I** d, *J* = 6.2 Hz, 3H), 1.52 (**II** d, *J* = 6.2 Hz, 3H), 2.68 (**I** q, *J* = 7.1 Hz, 2H), 2.76 (**I** q, *J* = 7.0 Hz, 2H), 5.22 (**II** qdd, *J* = 6.2, 3.9, 2.0 Hz, 1H), 5.36 (**I** qdd (apparent pd), *J* = 6.2, 6.2, 1.6 Hz, 1H), 5.83 (**II** dd, *J* = 3.9, 2.0 Hz, 1H), 5.95 (**I** dd, *J* = 6.2, 1.6 Hz, 1H), 6.62 (**I** dd (apparent t), *J* = 1.6, 1.6 Hz, 1 H), 6.85 (**II** m, 1 H), 7.33 (**I&II** m); ^{13}C NMR (60 MHz, $CDCl_3$) δ = 7.6 (**I&II**), 20.8 (**I**), 21.6 (**II**), 29.3 (**II**), 32.59 (**I**), 81.8 (**I&II**), 86.2 (**I**), 86.6 (**II**), 126.1, 127.6,127.9, 128.5 (**I&II**), 139.2 (**I&II**), 140.5 (**I&II**)143.5 (**I&II**), 197.3 (**I&II**); GC–MS (initial temp: 75 °C, final temp: 250 °C, hold 2 min, ramp 12 °C/min) R_t**I** = 10.60, R_t**II** = 10.73 (3.4:1), *m*/*z* = 159, 105, 91, 77, 57.