Pergamon

Tetrahedron Letters, Vol. 38, No. 44, pp. 7641-7644, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10080-6

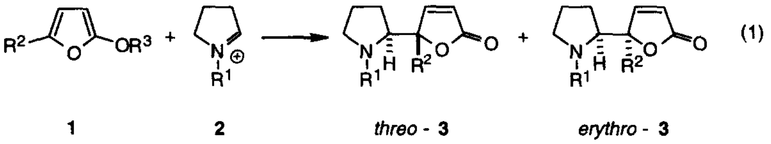
THE STEREOCHEMICAL COURSE OF INTRAMOLECULAR VINYLOGOUS MANNICH REACTIONS

Stephen F. Martin* **and Scott K. Bur**

Department of Chemistry and Biochemistry, The University of Texas, Austin, Texas 78712, USA

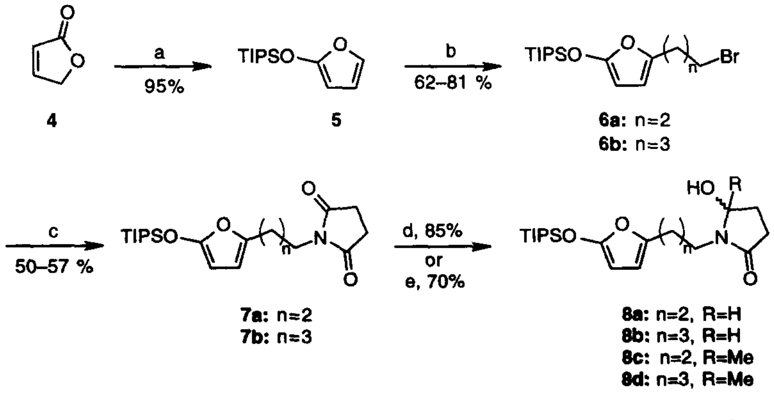
Abstract. Substituted furans **8a-d** underwent cyclizations via vinylogous Mannich reactions to give the *threo*-adducts **9a-d** as the major products (1.3 - 20:1); the effects of solvent, Lewis acid and temperature were examined. © 1997 Elsevier Science Ltd.

Recent investigations from our laboratories[1-4] as well as those of others[5] have illustrated the synthetic utility of vinylogous Mannich reactions. One useful example of such a process is found in the addition of nucleophilic trialkylsilyloxyfurans **1** to cyclic iminium ions **2** to give an isomeric mixture of adducts *threo*-**3** and *erythro*-**3** in which the former typically predominates (eqn 1). Because the stereochemical outcome of intramolecular reactions may differ from the corresponding intermolecular reactions, we decided to explore the stereochemistry of intramolecular vinylogous Mannich additions and now report the results of these investigations.



The substituted furans **8a-d** were identified as substrates for preliminary studies of the intramolecular vinylogous Mannich reaction, and these were prepared by a straightforward sequence of transformations (Scheme 1). The known furan **5** was first metallated by the action of *sec*-butyllithium in the presence of tetramethylethylene-

Scheme 1



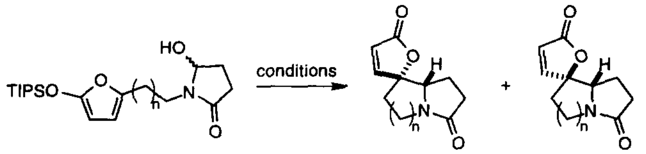
(a) TIPSOTf, DIEA, CH_2Cl_2, 0 °C to RT. (b) *sec*-BuLi, TMEDA, THF, 0 °C, 2 h; $Br(CH_2)_{n+1}Br$.
(c) KH, 18-Crown-6, succinimide, benzene, 80 °C. (d) $NaBH_4$, MeOH, -5 °C. (e) MeMgBr, THF, RT.

diamine and then alkylated with either 1,3-dibromopropane or 1,4-dibromobutane to furnish the alkylfurans **6a,b** respectively in 62-81% yield.[6] Subsequent reaction of **6a,b** with the potassium salt of succinimide in benzene with catalytic 18-Crown-6 gave the diimides **7a,b** in 50-57% yield. Reduction of **7a,b** with $NaBH_4$ in methanol at -5 °C produced the 5-hydroxypyrrolidin-2-ones **8a,b** in 85% yield,[7] whereas reaction of **7a,b** with MeMgBr gave the 5-hydroxypyrrolidin-2-ones **8c,d**.[8-9]

Several methods for generating acyliminium ions from precursors related to **8a,b** are known. For example, reaction of **8a** with trifluoroacetic anhydride in acetonitrile in the presence of Hünig's base gave a mixture (4.5:1) of the tricyclic adducts **9a** and **10a** in 80% yield. Reaction of **8b** under the same conditions provided a mixture (1.5:1) of **9b** and **10b** in 42% yield. On the other hand, use of TsCl, MsCl, and Tf_2O as activating agents returned complex mixtures, and only starting material was recovered upon treating **8a** with Ac_2O.

The cyclizations of **8a,b** could also be promoted with different Lewis acids, and the results of experiments in which the Lewis acid, temperature and solvent were varied are summarized in Table 1. Although several Lewis acids effected the cyclization, Et_2AlCl emerged as the superior reagent. The diastereomeric ratio of **9a** and **10a** was moderately affected by the choice of temperature and solvent with acetonitrile appearing to be the best solvent of those examined. Other Lewis acids, including TMSOTf and $(i\text{-PrO})_3TiCl$, led to complex reaction mixtures with no isolable products. While $ZnBr_2$ and ZnI_2 gave results similar to those obtained using $ZnCl_2$, $MgCl_2$ did not

Table 1. The Effects of Different Lewis Acids, Temperature, and Solvent.



8a: n=2
8b: n=3

9a: n=2
9b: n=3

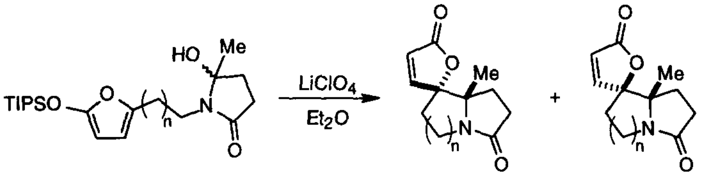
10a: n=2
10b: n=3

Entry	Substrate	Lewis acid	Solvent	Temp (°C)	**9**:**10**[a]	Yield (%)[b]
1	**8a**	$ZnCl_2$	CH_2Cl_2	20	8.8:1	62
2	**8a**	$ZnCl_2$	CH_3CN	20	4:1	51
3	**8a**	$BF_3{\bullet}OEt_2$	CH_3CN	20	6:1	64
4	**8a**	Et_2AlCl	CH_3CN	-20	8:1	72
5	**8a**	Et_2AlCl	CH_3CN	0	7:1	81
6	**8a**	Et_2AlCl	CH_3CN	20	6:1	83
7	**8a**	Et_2AlCl	CH_3CN	40	5:1	77
8	**8a**	Et_2AlCl	CH_2Cl_2	20	8.8:1	50
9	**8a**	Et_2AlCl	THF	20	7:1	63
10	**8a**	3.0 M $LiClO_4$	Et_2O	20	11:1	53
11	**8b**	Et_2AlCl	CH_3CN	20	1.3:1	58
12	**8b**	$BF_3{\bullet}OEt_2$	CH_3CN	20	1.5:1	53
13	**8b**	3.0 M $LiClO_4$	Et_2O	20	2:1	47

(a) Ratio of diastereomers determined by ^1H NMR. (b) Isolated Yield.

promote the cyclization of **8a** in acetonitrile. For reasons that are not presently understood, cyclizations promoted by 3.0 M $LiClO_4$ in ether[10,11] proceeded with slightly higher diastereoselectivity, but the yields in these reactions were generally somewhat lower than in those where Et_2AlCl was employed.

In a typical experiment, the Lewis acid (1.0 eq) was added to a solution of 5-hydroxypyrrolidin-2-one **8a** or **8b** (100 mg) in the appropriate solvent (10 mL), and the reaction mixture was stirred at the indicated temperature for 12–16 h. Aqueous NaOH (0.2 ml, 1 M) was then added, the resulting mixture was filtered through celite, and the filtrate was concentrated. The diastereomeric ratios of **9a/10a** and **9b/10b** were determined by integration of the signals for the vinyl protons in the ^1H NMR spectra of the crude reaction mixtures. Purification of the crude reaction mixtures by flash column chromatography provided mixtures of the diastereomers, which were separated by HPLC. The structures of the major products **9a** and **9b** were established by X-ray crystallography, and the structures of **10a** and **10b** were then assigned based upon a comparison of their NMR spectra with those of **9a** and **9b**.



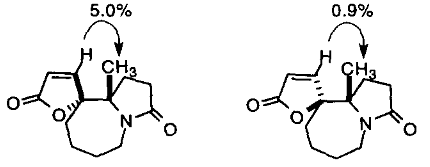
8c: n=2
8d: n=3

9c: n=2
9d: n=3

10c: n=2
10d: n=3

(2)

Attempts to effect the cyclization of the tertiary acyliminium ion precursors **8c** and **8d** by *O*-acylation with trifluoroacetic anhydride were unsuccessful. Reaction of **8c** and **8d** with Lewis acids such as Et_2AlCl, $BF_3{\cdot}OEt_2$, and $ZnCl_2$ also gave complex mixtures. On the other hand, ionization of **8c** with 2.0 M $LiClO_4/Et_2O$ gave a mixture (20:1) of **9c**, the structure of which was established by X-ray crystallography, and **10c** in 58% yield; treatment of **8d** with 2.5 M $LiClO_4/Et_2O$ gave a mixture (2:1) of **9d** and **10d** in 32% yield (eqn 2). The structures of **9d** and **10d** were assigned by NMR in combination with NOE difference spectroscopy in which the enhancements between the β-vinyl proton of the butenolide moiety and the quaternary methyl group were compared (Figure 1). Thus, when the β-proton of the butenolide ring was irradiated, the bridgehead methyl showed a 5.0% enhancement in **9d** while only a 0.9% enhancement was observed in **10d**. Similar NOE enhancements as seen for **9d** were observed for **9c**.



9d **10d**

Figure 1. NOE Enhancements for **9d** and **10d**.

Previous studies of *intermolecular* vinylogous Mannich reactions suggest that such additions generally proceed diastereoselectively to give *threo*-adducts with the observed levels of diastereoselection being influenced by substitution patterns on the reactants. On the other hand, the *intramolecular* variants of this reaction that were examined in the present study proceeded selectively to give the adducts having the opposite, *erythro* stereochemical relationship between the two newly constructed stereocenters. These cyclizations may be used to construct six- and seven-membered rings, but several preliminary attempts to fashion an eight-membered ring were unsuccessful. Current efforts are directed toward applying intramolecular Mannich reactions to the synthesis of natural products, and the results of these investigations will be reported in due course.

Acknowledgments. We thank the National Institutes of Health and the Robert A. Welch Foundation for supporting this research. We also thank Dr. Vincent M. Lynch for performing X-ray crystallographic analyses of compounds **9a–c**.

REFERENCES AND NOTES

1. Martin, S. F.; Corbett, J. W. *Synthesis* **1992**, 55-57.
2. Martin, S. F.; Liras, S. *J. Am. Chem. Soc.* **1993**, *115*, 10450-10451.
3. Martin, S. F.; Clark, C. C.; Corbett, J. W. *J. Org. Chem.* **1995**, *60*, 3236-3242.
4. Martin, S. F.; Barr, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 3299-3300.
5. For a review of the reactions of trialkylsilyloxyfurans with electrophiles, see: (a) Casiraghi, G.; Rassu, G. *Synthesis* **1995**, 607-626. See also (b) Casiraghi, G.; Rassu, G. *Tetrahedron* **1990**, *46*, 5807-5824. (c) Pelter, A.; Ward, R. S.; Sirit, A. *Tetrahedron: Asym.* **1994**, *5*, 1745-1762. (d) Morimoto, Y.; Nishida, K.; Hayashi, Y. *Tetrahedron Lett.* **1993**, *34*, 5773-5776. (e) Hanessian, S.; Raghavan, S. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1697-1702. (f) Morimoto, Y.; Iwahashi, M. *Synlett* **1995**, 1221-1222. (g) Hanessian, S.; McNaughton-Smith, G. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1567-1572. (h) Pichon, M.; Figadère, B.; Cavé, A. *Tetrahedron Lett.* **1996**, *37*, 7963-7966. (i) Harding, K. E.; Coleman, M. T.; Liu, L. T. *Tetrahedron Lett.* **1991**, *32*, 3795-3798.
6. The structure assigned to each compound is in accord with its spectral (^{1}H and ^{13}C NMR, IR, mass) characteristics; molecular composition of new compounds was established by high resolution mass measurements of purified materials. All yields are based on isolated, purified material judged >95% pure by ^{1}H NMR spectroscopy; the structures of compounds **9a-c** were determined by X-ray crystallography.
7. Miller, S. A.; Chamberlin, A. R. *J. Am. Chem. Soc.* **1990**, *112*, 8100-8112.
8. Speckamp, W. N.; Dijkink, J. *Heterocycles* **1979**, *12*, 1147-1152.
9. Compounds **8c,d** were unstable and were not purified.
10. For examples of $LiClO_4/Et_2O$ promoted Mannich reactions, see: Saidi, M. R.; Heydari, A.; Ipaktschi, J. *Chem. Ber.* **1994**, *127*, 1761-1764.
11. For other applications of $LiClO_4/Et_2O$ in synthesis, see: Grieco, P. A.; Clark, J. D.; Jagoe, C. T. *J. Am. Chem. Soc.* **1991**, *113*, 5488-5489 and references therein.

(*Received in USA* 11 *July* 1997; *accepted* 29 *August* 1997)