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Synthesis of Highly Functionalized Furanones via Aldol Reaction of 3-Silyloxyfurans[†]

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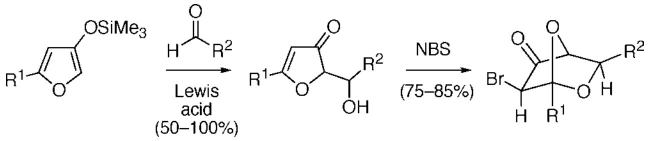
ABSTRACT

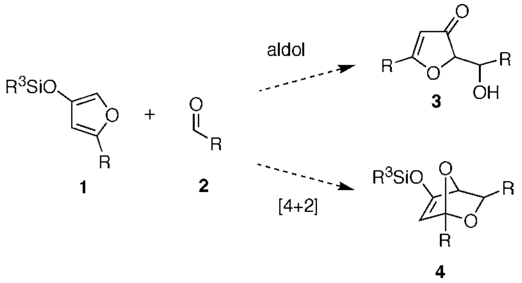


The stereoselective aldol reaction of 3-silyloxyfurans with aldehydes in the presence of a Lewis acid is described. *N*-Bromosuccinimide (NBS)-mediated cyclization of the aldol product leads to the formation of the 2,7-dioxa-bicyclo[2.2.1]heptan-3-one ring system, which represents the formal product of hetero Diels–Alder reaction of the furan with the aldehyde.

While the reactivity of 2-silyloxyfurans has been extensively studied, the chemistry of the corresponding 3-silyloxyfurans has been relatively unexplored.[1] We describe herein a general method for the preparation of 3-silyloxyfurans and the results of our preliminary study on the reactivity of these systems with carbonyl electrophiles.

The goal of these studies was to establish whether the Lewis-acid-catalyzed reaction of **1** with **2** (Scheme 1) would proceed to give the aldol adduct **3** or the [4 + 2]-cycloaddition product **4**, given that Danishefsky and others had previously found that either pathway could be followed in the analogous reactions of electron-rich dienes with aldehydes.[2] We report herein that reaction of 3-trimethylsilyloxyfurans with aldehydes leads exclusively to the formation of aldol products **3** in high yields and with excellent diastereoselectivity.

Scheme 1



The preparation of the requisite 3-trimethylsilyloxyfurans is outlined in Scheme 2. The synthesis of 3-oxygenated furans has been reported by Taddei by the reaction of the anion obtained on metalation of 3-bromofuran with bis(trimethylsilyl)peroxide.[3] We have found that silylation of the enol derived from a furanone, i.e., **7** (Scheme 2), as described by Nicholas, affords a more general route to the preparation of the requisite dienes.[4] Reaction of the conjugate base of 2-octanone (LDA, THF) with ethyl chloroacetate led

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[†] Dedicated to our friend and colleague Amos B. Smith, III, on the occasion of his 60th birthday.

(1) (a) Rassu, G.; Zanardi, F.; Battistini, L.; Casiraghi, G. *Chem. Soc. Rev.* **2000**, *29*, 109–118. (b) Rassu, G.; Auzzas, L.; Zambrano, V.; Burreddu, P.; Pinna, L.; Battistini, L.; Zanardi, F.; Casiraghi, G. *J. Org. Chem.* **2004**, *69*, 1625–1628 and references therein.

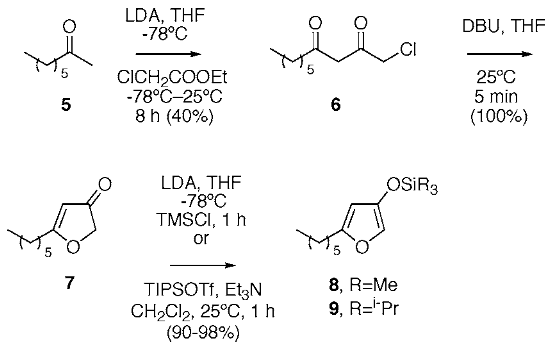
(2) (a) Danishefsky, S. J.; Larson, E.; Askin, D.; Kato, N. *J. Am. Chem. Soc.* **1985**, 107, 1246–1255. (b) Oppolzer, W. In *Comprehensive Organic Synthesis*; Pergamon: New York, 1991; Vol. 5, pp 315–399. (c) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilkogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668–1698. (d) Thorhauge, J.; Roberson, M.; Hazell, R. G.; Jorgensen, K. A. *Chem. Eur. J.* **2002**, *8*, 1888–1898.

(3) For the cycloaddition of 3-trimethylsilyoxyfuran with nonheteroatom dienophiles, see: Camici, L.; Ricci, A.; Taddei, M. *Tetrahedron Lett.* **1986**, *27*, 5155–5158.

(4) Stuart, J. G.; Nicholas, K. M. *Heterocycles* **1991**, *32*, 949–963.

10.1021/ol047810q CCC: $30.25

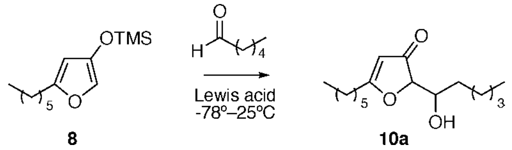
Scheme 2



to the formation of the chlorinated β-diketone **6**.[5] Exposure of **6** to DBU in THF at ambient temperature provided the furanone **7** in excellent yield.[6] Silylation of **7** could be achieved either with LDA/TMSCl in THF to generate the trimethylsilyl ether **8** or by reaction of **7** with TIPSOTf/Et_3N in dichloromethane to give the triisopropylsilyl ether **9**.[4]

As outlined in Table 1, reaction of 5-*n*-hexyl-3-trimethylsilyloxyfuran with *n*-hexanal in the presence of $TiCl_4$ or BF_3·OEt_2 led to the formation of aldol products in quantitative yield, albeit as a *ca*. 1:1 mixture of diastereomeric furanones.[7]

Table 1. Aldol Reaction of 3-Silyloxyfuran in the Presence of a Lewis Acid



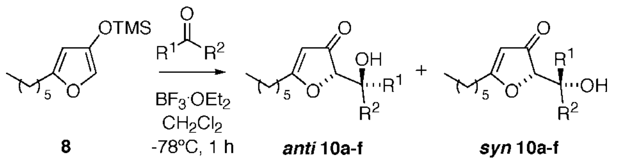
entry	Lewis acid	anti:syn[a]	reaction time (h)	yield (%)
1	$ZnCl_2$	42:58	48	23
2	$MgCl_2$	50:50	48	20
3	Et_2AlCl	50:50	8	65
4	$TiCl_4$	39:61	0.3	100
5	BF_3·OEt_2	50:50	1	100

[a] Determined by ^{1}H NMR analysis

Increasing the steric hindrance about the aldehyde led to a dramatic increase in the diastereoselectivity of the aldol reaction. While sterically unhindered aldehydes such as *n*-hexanal gave modest diastereoselectivity (Table 1), isobutyraldehyde and pivaldehyde led to the highly selective formation of syn products, i.e., **10c** and **10d** in Table 2.

The stereochemical outcome of the cyclization can be explained by the examination of the reacting conformations shown in Figure 1. The observed products result from aldol reaction via conformer **A**, which does not suffer from the unfavorable steric interaction shown in **B**. The stereochemistry of the aldol product **10d** was established unambiguously by X-ray crystallographic analysis (see Supporting Information).

Table 2. Aldol Reaction of 3-Silyloxyfuran with Carbonyl Electrophiles



entry	R^1	R^2	anti:syn	yield (%)
10a	H	$(CH_2)_4CH_3$	50:50	100
10b	H	Ph	38:62	95
10c	H	*i*-Pr	>5:95	60
10d	H	*t*-Bu	>5:95	99
10e	H	CH_2CH_2OBn	50:50	42
10f	$-CH_2(CH_2)_3CH_2-$		N/A	60

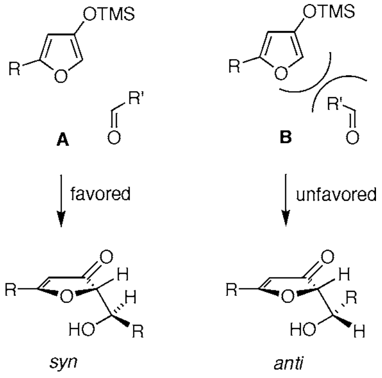
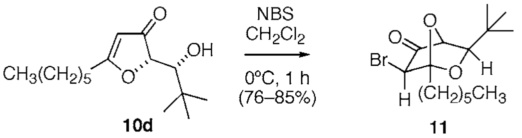


Figure 1. Stereochemical outcomes of aldol reactions.

While these results establish the proclivity of **8** to give aldol and not cycloaddition products, the dioxanorbornane nucleus **11**, which represents the formal product of hetero Diels–Alder reaction of furan with the aldehyde, could be prepared by exposure of the aldol product **10d** to NBS in dichloromethane (Scheme 3).[8]

Scheme 3



We also note that the dehydration of the aldol product **10d** occurs with remarkable facility. On standing for 48 h

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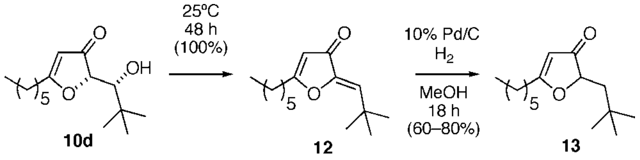
[5] Cui, J. N.; Ema, T.; Sakai, T.; Utaka, M. *Tetrahedron: Asymmetry* **1998**, *9*, 2681–2692.

[6] (a)Yamaguchi, M.; Shibato, K.; Nakashima, H.; Minami, T. *Tetrahedron* **1988**, *44*, 4767–4776. (b) Langer, P.; Thilo, K. *Chem. Eur. J.* **2001**, *7*, 1720–1727.

[7] Utilization of **9** gave results similar to those obtained with **8**.

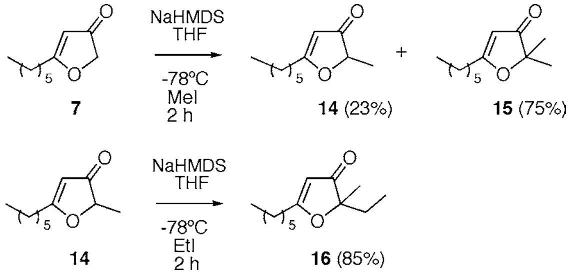
[8] Nishikawa, T.; Isobe, M. *Tetrahedron* **1994**, *50*, 5621–5632.

Scheme 4



at ambient temperature, the aldol product **10d** led to the formation of **12** (Scheme 4) in quantitative yield.[9] Selective reduction of dienone **12** could be achieved via catalytic hydrogenation (H_2, Pd/C, MeOH, 18 h) to give **13**. The selective formation of **13** is noteworthy, as direct alkylation of the conjugate base of **7** (Scheme 5) led to a ca. 1:3 mixture of monoalkylated and dialkylated products **14**[10] and **15**,[11] respectively. While the selective monoalkylation of **7** cannot be readily achieved,[12] the alkylation of monoalkylated product **14** proceeded in excellent yield to give **16**.

Scheme 5



These results establish the utility of the 3-trimethylsilyloxyfurans for the synthesis of highly functionalized furanones. The application of these results to the synthesis of biologically relevant furanone products is currently underway in our laboratory, and our results will be reported in due course.

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Supporting Information Available: Experimental procedures and spectral data for **6**−**13** and **16** and X-ray data for **10d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[9] (a) Danishefsky, S.; Etheredge, S. *J. Org. Chem.* **1978**, *43*, 4604−4605. (b) Varma, R. S.; Varma, M. *Tetrahedron Lett.* **1992**, *33*, 5937−5940. For the establishment of the alkene stereochemistry, see: Crombie, L.; Josephs, J. L. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2591−2597 and references therein.

[10] Mukerji, S. K.; Sharma, K. K.; Torsell, K. B. G. *Tetrahedron* **1983**, *39*, 2231−2236.

[11] Smith, A. B.; Levenberg, P. A.; Jerris, P. J.; Scarborough, R. M.; Wovkulich, P. M. *J. Am. Chem. Soc.* **1981**, *103*, 1501−1513.

[12] (a) Feldman, K. S. *Tetrahedron Lett.* **1982**, *23*, 3031−3034. (b) Padwa, A.; Kissell, W. S.; Eidell, C. K. *Can. J. Chem.* **2001**, *79*, 1681−1693.