calculations; the results are given in Table II. The rates of the isomerizations were measured in CD_3CN solution at 80.1 °C, with DMF as a reference as before.

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Supplementary Material Available: ^1H and ^{13}C NMR spectra of allyl (5-fluoroadamantylidene)methyl sulfide and of mixtures of (*RR*)- and (*RS*)-8, of (*EE*)- and (*ZE*)-9, and of (*EZ*)- and (*ZZ*)-9 (4 pages). Ordering information is given on any current masthead page.

A General Approach to 5-Substitution of 3-Furaldehydes[1]

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Herein we report the details of the conversion of 3-furaldehyde into 2-substituted 4-furaldehydes and the transformations of 2-substituted 4-furaldehydes and 4-substituted 3-furaldehydes into tri- and tetrasubstituted furans. We have developed a new disubstituted furan synthesis by applying metalation to the direct conversion of 3-substituted furans into 2,4-disubstituted furans. In situ protection of 3-furaldehyde with lithium morpholide followed by metalation at the C-5 position and quenching with several electrophiles affords 2-substituted 4-furaldehydes in 30–70% yield. The electrophiles include chlorosilanes, chlorostannanes, aldehydes, ketones, and primary iodides. This work provides a general route to a previously relatively inaccessible furan substitution pattern and is the first example of selective metalation at the C-5 position of 3-substituted furans. Other bulky α-alkoxy substituents at C-3 direct remote metalation to C-5 of furan. We examined other 3-furaldehyde metalations. The amino alkoxide intermediate derived from lithio *N,N,N'*-trimethylethylenediamine and 3-furaldehyde, when treated with BuLi and electrophiles, provided a product mixture which included metalation at the C-4 position of 3-furaldehyde. Several approaches to enhance this unusual C-4 metalation were unsuccessful. Using this amino alkoxide-metalation chemistry, 4-alkyl- or 4-phenyl-3-furaldehyde could be substituted at C-2 or C-5 selectively. Finally we converted trisubstituted furans into tetrasubstituted furans with metalation/electrophilic trapping.

Introduction

Substituted furans play an important role in the field of heterocyclic chemistry, occur widely in nature,[2] and enjoy wide application in a variety of commercially important products such as pharmaceuticals, heterocyclic polymers,[2] and flavor and fragrance compounds.[3] Moreover, furan derivatives are versatile synthetic intermediates for the preparation of a wide range of cyclic and acyclic organic compounds.[4] Although numerous synthetic routes to furans have been developed,[5] *direct* conversion of monosubstituted into 2,4-disubstituted furans has not been generally successful.

The substitution behavior of 2- and 3-substituted furans has been known for many years.[6] Electrophilic substitution of 2-substituted furans gives the product of attack at the 5-position as the major product. Likewise, metalation followed by electrophilic trapping often results in C-5 substitution[7] affording 2,5-disubstituted furans **1** although certain ortho-directing C-2 substituents yield a mixture of 2,3-disubstituted furans **2** and **1**.[7]

Only a handful of methods have been reported for the synthesis of 2,4-disubstituted furans.[5] None of these involves a direct and regiospecific conversion of a 2-substituted into a 2,4-disubstituted furan **3**. Instead, the strategies involve manipulation of acyclic precursors[8] (especially for the synthesis of 2,4-dialkylfurans), of lactones,[9] of 2-substituted furans,[10] of 3-substituted furans,[11,12a] or **1**.[13] All of these synthetic routes require many steps,

(1) (a) Part of this work was presented at the 198th National Meeting of the American Chemical Society, Division of Organic Chemistry, Miami Beach, FL, Sept 10–15, 1989; Lee, G. C. M.; Holmes, J. M.; Garst, M. E. *A Novel Synthesis of 2,4-Substituted Furans*; Abstract No. 194. (b) Lee, G. C. M. US Patent 4,935,530 issued June 19, 1990.

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(8) For examples see: (a) Ibragimov, I. I.; Guseinov, M. M.; Gadzhily, R. A.; Dzhafarov, V. G.; Godzhaev, S. P. *Khim. Geterotsikl. Soedin.* **1973**, 1434. (b) Jones, R. G. *J. Am. Chem. Soc.* **1955**, *77*, 4074. (c) Buchi, G.; Wuest, H. *J. Org. Chem.* **1969**, *34*, 857. (d) Stahle, M.; Schlosser, M. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 875. (e) Nishio, T.; Sugawara, M.; Omote, Y. *J. Heterocycl. Chem.* **1979**, 815. (f) Garst, M. E.; Spencer, T. A. *J. Am. Chem. Soc.* **1973**, *95*, 250. (g) Obrecht, D., *Helv. Chim Acta* **1989**, *72*, 447.

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(11) For examples see: (a) Goldsmith, D.; Liotta, D.; Saindane, M.; Waykole, L.; Bowen, P. *Tetrahedron Lett.* **1983**, *24*, 5835. (b) Tanis, S. P.; Head, D. B. *Tetrahedron Lett.* **1984**, *25*, 4451.

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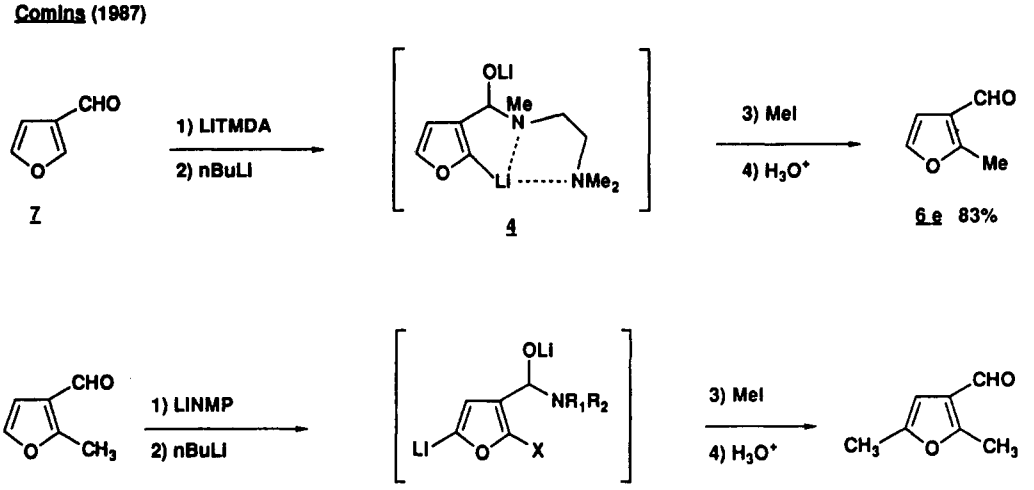
0022-3263/92/1957-3126$03.00/0

Scheme I



including discrete protection and deprotection, utilize relatively inaccessible starting materials, or proceed in low overall yield. Electrophilic reactions and metalation[7] of 3-substituted furans often give a product mixture of 1 and 3. By choosing a substituent with an ortho-directing capacity, e.g., the carboxy,[14] 1,3-dioxolane,[12] or hydroxymethyl,[15] regiospecific metalation at C-2 becomes possible. Hence, these procedures constitute reliable syntheses of 2 from a 3-substituted furan. Recently, Comins et al.[16] illustrated regiospecific metalation at C-2 of 3-furaldehyde via an α-amino alkoxide intermediate (4, Scheme I).

This observed regioselectivity is reported to be *independent* of the α-amino alkoxide group (vide infra).[16] Under the Comins' conditions, direct conversion of a 3-substituted to a 2,4-disubstituted or 3,4-disubstituted furan was not observed. Herein we describe, for the first time, the application of metalation to the direct conversion of 3-substituted to 2,4-disubstituted furans. We also report the metalation at the C-4 position of an amino alkoxide from 3-furaldehyde and that 4-phenyl- or 4-alkyl-3-furaldehyde can be selectively metalated at C-2 or C-5 of the furan. We further explored the metalation/trapping of trisubstituted furans to yield tetrasubstituted products. Thus, we have extended this chemistry to the preparation of tri- and tetrasubstituted furans.

Results and Discussion

2-Substituted 4-Furaldehyde. Metalation followed by electrophilic trapping has become a powerful method in regiospecific functionalization of aromatic and heterocyclic compounds.[7,17] Comins et al.[16] reported that regiospecific metalation occurs at C-2 of 3-furaldehyde with high regioselectivity regardless of which α-amino alkoxide was used (4, Scheme I). Metalation at the C-5 position was reported *only* when the 2-position is blocked by a substituent (Scheme I).[16] Our need for 2-(trialkylsilyl)-4-furaldehydes coupled with several observations made during the course of other metalations prompted us to reinvestigate 3-furaldehyde as a substrate for α-amino alkoxide mediated metalations, as depicted in Scheme III.

Conceptually we could not understand why 3-furaldehyde should behave differently from 3-formylthiophene,[16] methoxybenzaldehydes,[21] or *N*-(carboxyalkoxy)-1,4-dihydropyridin-3-aldehyde,[18] all of which have been converted into α-amino alkoxides that undergo metalation distal to the alkoxide.

Treatment of 3-furaldehyde (7, 3-FA) with lithium morpholide (LiMorph),[19] followed by metalation (*t*-BuLi) and trapping with chlorotrimethylsilane (TMSCl), to our delight, gave a mixture of 2-(trimethylsilyl)-4-furaldehyde (**5a**), 2-(trimethylsilyl)-3-furaldehyde (**6a**), and 7 in a ratio of 53:33:14 (entry 1, Table I). Thus, by using morpholine (Morph)[19] or *N*-methylpiperazine (NMP)[20,21] as the blocking amine component with 3-FA and then applying regioselective metalation at C-5, the formation of a 2,4-disubstituted furan should be possible.

Since the regioselectivity of metalation can depend on the directing group, solvent, metalating agent, reaction time and temperature,[16] we have investigated the effect of many parameters and summarize the critical findings in Tables I and II. For example, LiMorph or LiNMP in THF at −78 °C was used successfully to generate the α-amino alkoxide (entries 1–5, 8–11, Table I). LDA gave lower yields of silylated furaldehyde (Table I) accompanied by some furanmethanol-derived products.[22] Lithium phenoxazinide and magnesium morpholide did not afford any silated products.

In the metalation step, *s*-BuLi gave a better C_2 to C_5 product ratio than *n*-BuLi or *t*-BuLi (Table I). Usually 1–2 h at −78 °C in THF is sufficient time for metalation. When the metalation was performed in DME, very little regioselectivity was observed (entry 12, Table I). Solvent additives, e.g., TMEDA (entry 13, Table I) or lithium chloride[23] (entries 14–15, Table I) offer no advantage.

This process tolerates a wide range of electrophiles (Table II). TMSCl and triethylsilyl chloride (TESCl) have

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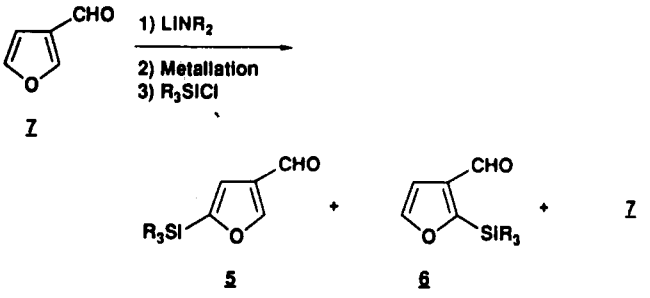
Table I



a (R = Me) b (R = Et)

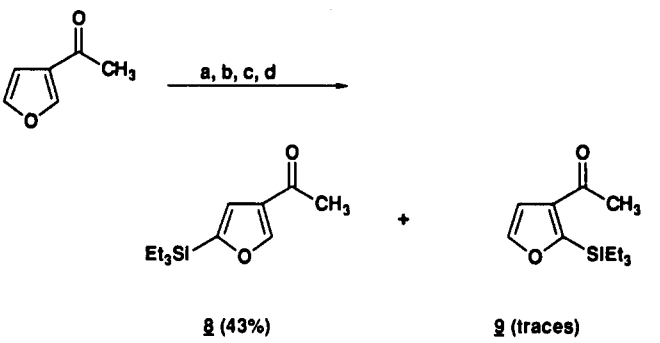
entry	amine	metalation condns	% yield[a] 5	6	7
1	Morph	1.05 *t*-BuLi, THF, −78 °C, 2 h	53 (5a)	33 (6a)	14
2		1.05 *t*-BuLi, THF, −78 °C, 1 h	46 (5a)	31 (6a)	23
3		1.05 *s*-BuLi, THF, −78 °C, 4 h	59 (5a)	5 (6a)	0
4		1.00 *s*-BuLi, THF, −78 °C, 7 h	70 (5a)	5 (6a)	0
5		1.05 *n*-BuLi, THF, −78 °C, 2 h	52 (5a)	25 (6a)	23
6	$(i\text{-Pr})_2$NH	1.05 *s*-BuLi, THF, −78 °C, 2 h	29 (5b)	0 (6b)	0
7		1.05 LDA, THF, −78 °C, 2 h	traces 5b	0 (6b)	0
8	Morph	1.00 *s*-BuLi, THF, −78 °C, 7 h	73 (5b)	traces 6b	0
9		1.05 *s*-BuLi, THF, −78 °C, 2 h	62 (5b)	traces 6b	0
10	NMP	1.05 *s*-BuLi, THF, −78 °C, 7 h	64 (5b)	traces 6b	0
11		1.05 *s*-BuLi, THF, −78 °C, 2 h	72 (5b)	traces 6b	0
12		1.05 *s*-BuLi, DME, −78 °C, 2 h	49 (5b)	33 (6b)	0
13	Morph	1.05 *s*-BuLi, 1.05 TMEDA, THF, −78 °C, 7 h	58 (5b)	6 (6b)	0
14		1.05 *s*-BuLi, 1.1 LiCl, THF, −78 °C, 2 h	68 (5b)	traces 6b	0
15		1.05 *s*-BuLi, 1.1 LiCl, THF, −78 °C, 1 h	68 (5b)	traces 6b	0

[a] Isolated yields of products after column chromatography on silica gel.

been used many times on scales from milligrams to tens of grams always providing the yields given in Table II with TESCl being more regioselective. For optimum yields of (trialkylsilyl)furans, the stoichiometry of lithium amide-/3-FA/metalation base/electrophile was found to be 1.05:1.0:1.05:1.1. Experiments with other electrophiles have been completed once or twice; hence, yields may be higher in several instances. Aliphatic aldehydes (entries 8 and 9, Table II) gave complicated reaction products, presumably arising from aldol condensation of the aldehyde. Attempted in situ oxidation (entries 11 and 12, Table II) using oxygen or MoOPH[24] led to a complicated mixture of unidentified products.

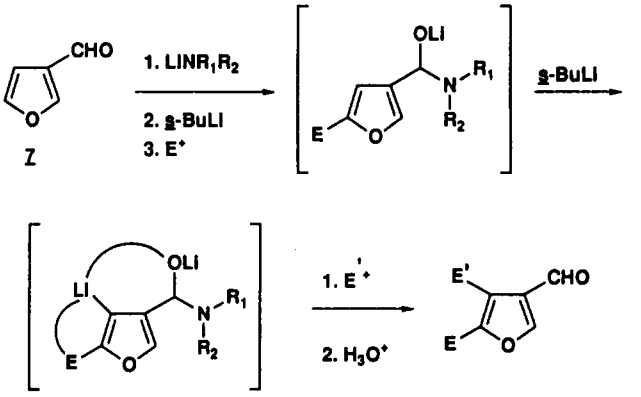
Next, we examined other applications of a bulky group to promote remote metalation. Using the reaction conditions described above, 3-acetylfuran gave the expected product 8 (43%) accompanied by traces of the isomer 9 (Scheme II). However, 3-(2-ketoheptyl)furan gave a complicated mixture containing starting material, both C-2 and C-5 substitution products, and unidentified byproducts. Presumably, enolization and subsequent reactions of the ketone under these conditions cause complications. Treatment of 4-(1-hydroxyalkyl)furans with greater than 2 equiv of alkyllithium also failed to yield metalation (data in Tables A and B, supplementary material).

Scheme II[a]



[a] Reagents: (a) LiMorph; (b) 2.0 *s*-BuLi/−78 °C/7 h; (c) Et_3SiCl; (d) H^+.

Scheme III



Other Metalations of 3-Furaldehydes. We needed gram amounts of 2-silyl-3-furaldehyde and 2-methyl-3-furaldehyde.[12,14,15,26] From all of the directed metalation options, we used lithio *N,N,N'*-trimethylenediamine (LiTMDA) to generate an α-amino alkoxide from 3-furaldehyde. In situ metalation and trapping afforded the expected product 6 accompanied by 5–15% of 2-substituted 4-furaldehyde 5 and 10–25% of 4-substituted 3-furaldehyde 16 (Table III). These volatile furans were difficult to purify without substantial losses. The formation of 16 has not been reported. To our knowledge the metalation of 2-TBDMS-3-furanmethanol at C-4 reported by Keay[29] is the only other example of metalation of a 3-substituted furan at C-4 with unsubstituted α-positions. To verify this observation 16c was prepared by adopting the methods of Reich,[26] oxazole cycloaddition,[27,28] and the metalation sequence of Keay.[29]

The formation of 4-substituted 3-furaldehydes in low yield prompted us to explore C-4 metalation by using directing/protecting groups at both C-3 and C-5 (Scheme III). We attempted to trap the C-5 lithio species with an

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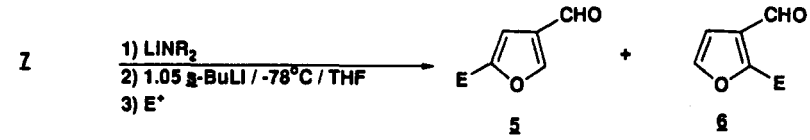
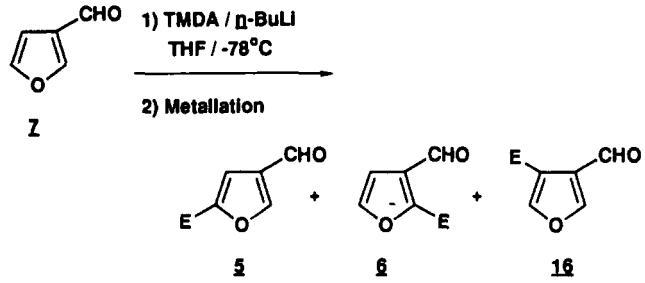
Table II



entry	HNR_2	metalation time (h)	electrophile (E^+)	E	% yield[a] 5	% yield[a] 6
1	Morph	7	Me_3SiCl	Me_3Si	70 (**5a**)	5–10 (**6a**)
2		2	Et_3SiCl	Et_3Si	73 (**5b**)	<3[b] (**6b**)
3		1	*t*-$BuMe_2SiCl$	*t*-$BuMe_2Si$	37 (**5c**)	0
4		4	Bu_3SnCl	Bu_3Sn	31 (**5d**)	0
5	NMP	2	MeI	Me	53 (**5e**)	7 (**6e**)
6	Morph	4	$Me(CH_2)_7I$	$Me(CH_2)_7$	45 (**5f**)	0
7		4	4-BrC_6H_4CHO	4-$BrC_6H_4CH(OH)$	59 (**5g**)	0
8		7	$Me(CH_2)_5CHO$	$Me(CH_2)_5CH(OH)$	30 (**5h**)	0
9		7	$Me(CH_2)_{10}CHO$	$Me(CH_2)_{10}CH(OH)$	0	0
10		7	$MeCO(CH_2)_8Me$	$MeC(OH)(CH_2)_8Me$	51 (**5i**)	0
11		7	MoOPH	O	0	0
12		6	O_2	O	0	0

[a] Isolated yield of products by distillation or column chromatography on silica gel and recrystallized (if applicable). Except for entries 1 and 2, yields were not optimized. [b] Estimated from ^1H NMR of the crude reaction mixture.

Table III



entry	metalation condns	electrophile	% yield[a,b] 5	6	7	16
1	1.1 *n*-BuLi, −78 °C, 4 h	Me_3SiCl	2 (**5a**)	29 (**6a**)	3	4 (**16a**)
2	1.05 *s*-BuLi, −78 °C, 3 h	Et_3SiCl	8 (**5b**)	37 (**6b**)	0	13 (**16b**)
3	1.05 *s*-BuLi, −78 °C, 2 h	MeI	2 (**5e**)	24 (**6e**)	<1	3 (**16c**)

[a] Yield of the combined purified products as determined by ^1H NMR. [b] Products are volatile.

initial electrophile, which could assist in stabilizing a C-4 anion, followed by an additional equivalent of organolithium and MeI. Initial electrophiles which failed to promote the second metalation and trapping include carbon dioxide, cyclohexanone, sulfur dioxide, formaldehyde, and *N*-thionylaniline.[30] We next examined blocking C-5 of 3-FA with silicon. Either LiTMDA or LiMorph gave only 2-alkyl-5-(trialkylsilyl)-3-furaldehyde (**15**) (Scheme IV). Thus, treatment of 2-(trialkylsilyl)-4-furaldehyde with LiTMDA followed by BuLi and methyl iodide or butyl iodide gave **15a** or **15b**, in 29–35% accompanied by comparable amounts of starting aldehyde. These mixtures contained less than 1% of possible C-3 products. Using LiMorph to generate **5b** in situ followed by treatment with BuLi and methyl iodide also gave only **15c** in 17% yield. Thus, we were unable to enhance the C-3 metalation by an additional directing group at C-2 or by blocking C-2 with a silyl group.

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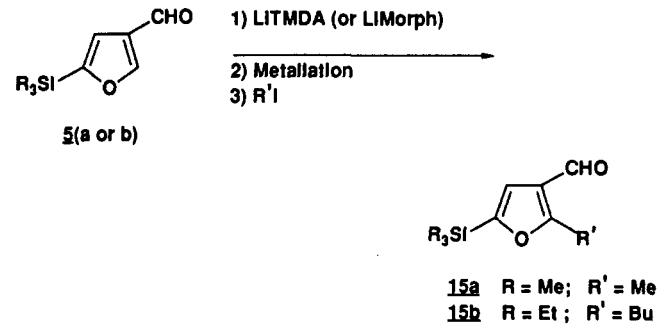
Scheme IV

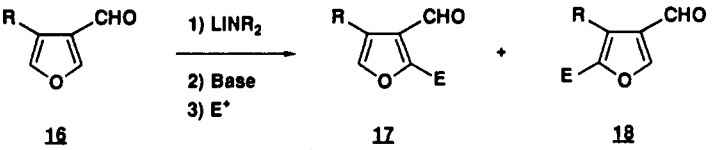


We then examined the substitution of 4-alkyl-3-furaldehyde and 4-phenyl-3-furaldehyde which proved to be straightforward (Table IV). Our experiments with 3-FA (vide supra) indicated LiNMP and LiMorph to be equivalent.[31] The methylation of **16d** with LiNMP led to a complex mixture (Table IV, entry 3). However, LiMorph and **16d** gave the expected product **18a** accompanied by 2-methyl-3-phenyl-4-furanmethanol (**19**), which must have been formed from **18a** to account for this substitution pattern. Finally, 4-benzyl-3-furaldehyde with LiTMDA or LiMorph followed by methyl iodide gave the expected products accompanied by trace amounts of benzylic alkylation (Table IV, entries 8 and 9). 4-Phenyl- (**16d**) and 4-benzyl-3-furaldehydes (**16e**) were metalated at C-2 using LiTMDA as a protecting group and at C-5 using LiMorph. The formation of **16** from 3-FA and LiTMDA while **5a** and LiTMDA gave less than 1% C-3 alkylation and while **16e** and LiTMDA gave <1% benzyllic metalation remains to be explained.

We also eventually required 2-alkyl-4-phenyl-5-(trialkylsilyl)-3-furanmethanol. We were unable to achieve alkylation of 2-(trialkylsilyl)-3-phenyl-4-furaldehyde by treatment with LiTMDA under a variety of conditions. We then examined 2-silyl-3-phenyl-4-furanmethanol, which with excess organolithium followed by methyl iodide gave extensive decomposition products. Addition of lithium

(31) We assumed Morph and NMP were equivalent. We favored NMP since it is not a controlled substance.

Table IV

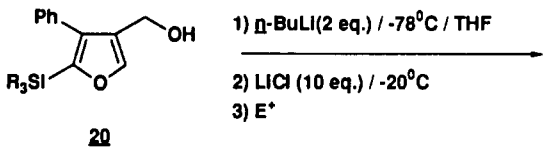


16 17 18

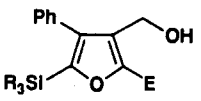
entry	HNR_2	base	E^+	R	% yield 16	17	18
1[a]	TMDA	*n*-BuLi	MeI	Ph (16d)	17	44 (17a)	6 (18a)
2[b]	Morph	*s*-BuLi	MeI	Ph (16d)	6	0	47 (18a)
3	NMP	*s*-BuLi	MeI	Ph (16d)	11	7 (17a)	25 (18a)
4	NMP	*s*-BuLi	Et_3SiCl	Ph (16d)	27	0	61 (18b)
5	Morph	*s*-BuLi	Et_3SiCl	Ph (16d)	31	0	47 (18b)
6[c]	Morph	*s*-BuLi	Me_3SiCl	Ph (16d)	traces	0	75 (18c)
7	NMP	*s*-BuLi	Me_3SiCl	Me (16c)	6	0	37 (18d)
8[a,d]	TMDA	*n*-BuLi	MeI	benzyl (16e)	42	33 (17e)	traces
9[a,d]	Morph	*s*-BuLi	MeI	benzyl (16e)	27	0	30 (18e)

[a] Trace amounts of other alkylation products were observed. [b] 17% of 5-methyl-4-phenyl-3-furanmethanol (19) was also isolated. [c] Trace amounts of other silylation products were observed. [d] Yield of the purified products was determined by ^1H NMR ratio.

Table V



20



21

a (R = Et)
b (R = Me)

entry	E^+	E	LiCl equiv	% yield 20	21
1[a-c]	DMF	CHO	10	8 (20a)	20 (21a)
2[c]	MeI	Me	10	26 (20b)	60 (21b)

[a] Reaction performed at 0 °C for 60 h. [b] 15% of 4-phenyl-5-TES-2,3-furandialdehyde (22) was also isolated. [c] Yield of purified products as determined by ^1H NMR.

chloride permits isolation of the expected products from trapping with DMF and methyl iodide (Table V).

This work on polysubstituted furans coupled with the recent reports by Keay[29] suggest that metalation–electrophilic trapping of disubstituted furans occurs readily if the furan bears vicinal substitution, but it is difficult to insert a group between 1,3 substituents.[32]

In summary, we have developed a general route to the relatively inaccessible 2,4-disubstituted furans from 3-furaldehyde. The reaction sequence represents the first example of preferential metalation at the C-5 position of 3-substituted furans. In addition, under certain metalation conditions 3-furaldehyde provided some 4-substituted 3-furaldehyde. The work in this paper with that of Comins[16] and Keay[29] illustrates the preparation of disubstituted, trisubstituted, and tetrasubstituted furans from 3-furaldehyde or 3-furanmethanol.

Experimental Section

^1H NMR (299.943 MHz) and ^{13}C NMR spectra (75.429 MHz) were obtained in $CDCl_3$, and chemical shifts are reported in δ units (parts per million) downfield from tetramethylsilane. Infrared spectra (IR) were recorded as thin films using polystyrene calibration. The frequencies are reported in cm^{-1}. Analytical thin-layer chromatography (TLC) was performed on precoated 0.25-mm silica gel 60PF-254, and the spots were visualized with UV or by spraying with a solution of 5% phosphomolybdic acid in ethanol and heated at ca. 200 °C for a few minutes. All reactions involving moisture-sensitive reagents were carried out in oven- or flame-dried apparatus under argon (Ar). THF was freshly distilled from sodium benzophenone ketyl under Ar before use. Morpholine (Morph), *N*-methylpiperazine (NMP), and *N,N,N'*-trimethylethylenediamine (TMDA) were distilled from calcium hydride or barium oxide and stored over 4-Å molecular sieves under N_2. *n*-BuLi (a 2.5 M solution in hexane) and *s*-BuLi (a 1.3 M solution in cyclohexane) were purchased from Aldrich and used as received. 3-Acetylfuran[33] and 3-(1-heptanoyl)furan[34] were prepared by methyl Grignard and hexyl Grignard addition to 3-FA followed by Swern oxidation.[35] Unless otherwise stated, all commercial reagents were used as received. All chromatography was completed on silica gel unless indicated otherwise.

General Procedure for the Preparation of 2-Substituted 4-Furaldehyde or 2-Substituted 4-Acylfuran from 3-Furaldehyde and 3-Acylfuran, Respectively (Tables I and II). *n*-BuLi (1.05 equiv) was added to a solution of Morph or NMP (1.05 equiv) in THF (ca. 0.15 M) at −78 °C under Ar. After 20 min, 3-furaldehyde (3-FA) or 3-acylfuran (1.0 equiv) was added. After another 20 min, the metalating base (1.05 equiv) was added dropwise and stirring continued at −78 °C for a noted period of time before the electrophile (1.1 equiv) was added. Stirring was then continued for 16 h while the cooling bath attained room temperature. The solution was poured into 1:10 (v/v) 10% HCl/ice, and the layers were separated. The aqueous phase was extracted with Et_2O. All the organic phases were combined, dried ($MgSO_4$), and concentrated to give the crude product, which was purified by distillation or column chromatography.

2-TES-4-furaldehyde (5b). *n*-BuLi (30.6 mL, 76.5 mmol) was added to a solution of Morph (or an equivalent amount of NMP) (6.66 mL, 76.5 mmol) in THF (500 mL) at −78 °C under Ar. After 15 min, 3-FA (6.3 mL, 72.8 mmol) was added. After another 20 min, *s*-BuLi (59.0 mL, 76.5 mmol) was added dropwise and stirring continued at −78 °C for ca. 2 h before TESCl (13.4 mL, 80.1 mmol) was added. The reaction was completed and processed as before to give an oil, which was distilled under high vacuum to yield 11.15 g (73%) of **5b** as a pale yellow oil: bp 85–90 °C (0.4 Torr); R_f = 0.28 (10% Et_2O/hexane); IR 1680, ^1H NMR 0.79 (q, 6 H, J = 7.3 Hz), 0.96 (t, 9 H, J = 7.3 Hz), 7.0 (s, 1 H), 8.26 (s, 1 H) and 9.96 (s, 1 H); ^{13}C NMR 2.9, 7.1, 117.2, 128.8, 155.6, 162.3 and 184.6;

(32) For a solution to this problem with 3-methoxybenzaldehyde see: Comins, D. L.; Brown, J. D. *J. Org. Chem.* **1989**, *54*, 3730.

(33) Heller, H. G.; Oliver, S. *J. Chem. Soc., Perkin Trans. 1* **1981**, 197.

(34) Watanabe, E.; Imai, N.; Inomata, K.; Kinoshita, H.; Kotake, H. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3225.

(35) Mancuso, A. J.; Brownfair, D. S.; Swern, D. *J. Org. Chem.* **1979**, *44*, 4148.

HRMS exact mass calcd for $C_{11}H_{18}O_2Si$ (M^+) 210.1076, found 210.1071.[36] A semicarbazone derivative was prepared: mp 146–147 °C. Anal. Calcd for $C_{12}H_{21}N_3O_2Si$: C, 53.90; H, 7.92; N, 15.71. Found: C, 54.20; H, 7.81; N, 15.55.

Less than 3% of 2-TES-3-furaldehyde (**6b**) could be seen in the ^1H NMR of the crude reaction product. A sample of **6b** was purified by chromatography: ^1H NMR 0.75–1.00 (m, 15 H), 6.75 (d, 1 H, J = 1.9 Hz), 7.59 (d, 1 H, J = 1.9 Hz) and 10.05 (s, 1 H); ^{13}C NMR 3.5, 7.1, 107.4, 138.3, 147.7, 170.2 and 186.0; HRMS exact mass calcd for $C_{11}H_{18}O_2Si$ ($M + H^+$) 211.1154, found 211.1171.

2-(Triethylsilyl)-4-acetylfuran (8). *n*-BuLi (3.63 mL, 9.08 mmol) was added to a solution of Morph (0.79 mL, 9.08 mmol) in THF (50 mL) at −78 °C under Ar. After 15 min, a solution of 3-acetylfuran (1.0 g, 9.08 mmol) in THF (2 mL) was added followed sequentially in 1 h by *s*-BuLi (13.9 mL, 18.2 mmol) and in 6 h by TESCl (9.07 mL, 27.2 mmol). Completion as before gave a residue, which was purified by chromatography using 5% Et_2O/hexane to afford 880 mg (43% yield) of **8**: ^1H NMR 0.75 (q, 6 H, J = 7.3 Hz), 0.95 (t, 9 H, J = 7.3 Hz), 2.44 (s, 3 H), 6.98 (s, 1 H) and 8.22 (s, 1 H); ^{13}C NMR 2.7, 6.8, 27.7, 111.5, 119.2, 152.0, 161.6 and 193.0; HRMS exact mass calcd for $C_{12}H_{20}O_2Si$ (M^+) 224.1232, found 224.1228.

2-TES-4-furaldehyde (5b), 2-TES-3-furaldehyde (6b), and 4-TES-3-furaldehyde (16b). *n*-BuLi (13.66 mL, 21.85 mmol) was added to a solution of TMDA (2.23 g, 21.85 mmol) in THF (100 mL) at −78 °C under Ar. After 15 min, 3-FA (2.00 g, 20.81 mmol) was added. After another 20 min, *s*-BuLi (16.81 mL, 21.85 mmol) was added dropwise and stirring continued an additional 3 h at −78 °C before TESCl (3.45 g, 22.89 mmol) was added. The reaction mixture was warmed to rt and stirred for 16 h. The usual workup yielded 3.49 g of an oil which was filtered thru silica using 5% Et_2O/hexane to give 2.53 g of a mixture of **5b** (8.1% yield), **6b** (37% yield), and **16b** (13% yield) in a ratio of 14:64:22. Flash chromatography (3% Et_2O/hexane) separated **5b** from **6b** and **16b**. Normal-phase HPLC using 1% EtOAc/hexane afforded pure **6b** (vida supra) and **16b**: IR 1684; ^1H NMR 0.77 to 0.87 (m, 6 H), 0.88 to 0.97 (m, 9 H), 7.34 (d, 1 H, J = 1.2 Hz), 8.14 (d, 1 H, J = 1.2 Hz), 9.96 (s, 1 H); ^{13}C NMR 2.9, 7.2, 114.1, 132.7, 151.1, 154.1, 185.4; HRMS exact mass calcd for $C_9H_{13}O_2Si$ ($M^+ - C_2H_5$) 181.0685, found 181.0678.

2-Methyl-5-TMS-3-furaldehyde (15a). *n*-BuLi (3.28 mmol, 2.04 mL) was added to a solution of TMDA (3.56 mmol, 0.46 mL) in THF (10 mL) at −78 °C under Ar. After 15 min, a solution of **5a** (2.98 mmol, 500 mg) in THF (2 mL) was added. After another 15 min, *n*-BuLi (5.94 mmol, 3.72 mL) was added followed in 2 h by MeI (17.9 mmol, 1.12 mL). After 30 min, the solution was processed and purified by flash chromatography with 10% Et_2O/pentane to give 159 mg (29%) of **15a**: ^1H NMR 0.29 (s, 9 H), 2.63 (s 3 H), 6.91 (s, 1 H), 9.95 (s, 1 H); LRMS ($M+ H)^+$ 183.

2-Butyl-5-TES-3-furaldehyde (15b). *n*-BuLi (0.88 mL, 2.17 mmol) was added to a solution of TMDA (222 mg, 2.17 mmol) in THF (15 mL) at −78 °C under Ar. After 45 min **5b** (415 mg, 1.98 mmol) was added. After another 45 min, *n*-BuLi (0.88 mL, 2.17 mmol) was added dropwise and stirring continued for another 3 h at −78 °C before 1-iodobutane (2.18 g, 11.86 mmol) was added. The reaction mixture was warmed gradually to rt and stirred an additional 16 h. The reaction was processed in the usual manner to give an oil which was purified by flash chromatography using 5% Et_2O/hexane to give 193 mg (36%) of **15b**: IR 1690; ^1H NMR 0.72 (q, 6 H, J = 7.2 Hz), 0.90–1.15 (m, 12 H), 1.33 (m, 2 H), 1.69 (m, 2 H), 2.94 (t, 2 H, J = 7.4 Hz), 6.89 (s, 1 H), 9.91 (s, 1 H); ^{13}C NMR 3.0, 7.2, 13.6, 22.2, 26.8, 30.4, 118.6, 122.5, 158.4, 170.2 and 184.3; HRMS exact mass calcd for $C_{15}H_{26}O_2Si$ (M^+) 266.1702, found 266.1690.

2-Methyl-5-TES-3-furaldehyde (15c). *n*-BuLi (13.8 mL, 22.1 mmol) was added to a solution of Morph (1.92 mL, 22.1 mmol) in THF (200 mL) at −78 °C under Ar. After 20 min, 3-FA (1.8 mL, 21.0 mmol) was added, followed by *s*-BuLi (17.0 mL, 22.1 mmol) after another 20 min. Stirring was continued for 2 h, and TESCl (3.7 mL, 22.1 mmol) was added. After 2 h at −78 °C, *s*-BuLi (17.0 mL, 22.1 mmol) was added, followed by MeI (3.9 mL, 63.1 mmol) after another 2 h. The reaction mixture was warmed to rt and stirred an additional 16 h before being processed and purified by flash chromatography using 5% Et_2O/hexane to give 1.01 g of a mixture of **5b** (5% yield) and **15c** (17% yield). An aliquot was further purified by normal-phase HPLC using a Whatman Partisil 10 column and a solvent mixture of 2% EtOAc/hexane to give pure **15c**: IR 1690; ^1H NMR 0.75 (q, 6 H, J = 8.0 Hz), 0.95 (t, 9 H, J = 8.0 Hz), 2.58 (s, 3 H), 6.88 (s, 1 H) and 9.90 (s, 1 H); ^{13}C NMR 2.6, 6.7, 12.5, 118.8, 122.8, 158.5, 166.2 and 185.1; HRMS exact mass calcd for $C_{12}H_{20}O_2Si$ (M^+) 224.1232, found 224.1226.

4-Benzyl-2-methyl-2-furaldehyde (17e). *n*-BuLi (1.08 mL, 1.73 mmol) was added to a solution of TMDA (180 mg, 1.73 mmol) in THF (4 mL) at 0 °C under Ar. After 15 min the solution was cooled to −78 °C, and **16e** (29 mg, 1.58 mmol) was added. This mixture was stirred for 15 min at 0 °C and then recooled to −78 °C before *n*-BuLi (1.38 mL, 2.20 mmol) was added dropwise. After 2 h at −78 °C, MeI (1.14 g, 7.87 mmol) was added and this mixture was stirred an additional 20 h at −20 °C. Processing and purification by flash chromatography using 5% EtOAc/hexane gave 230 mg of a 1:1.2 mixture composed mainly of **17e** (33%) and **16e** (42%) accompanied by <2% of **18e**. Normal-phase HPLC on a Whatman Partisil 10 column using 3% EtOAc/hexane afforded pure **17e**: IR 3032, 1679; ^1H NMR 2.55 (s, 3 H), 3.99 (s, 2 H), 6.92 (s, 1 H), 7.17–7.31 (m, 5 H), 9.67 (s, 1 H); ^{13}C NMR 12.6, 30.0, 121.2, 124.7, 126.5, 128.6, 128.9, 139.5, 163.7, 186.0; HRMS exact mass calcd for $C_{13}H_{12}O_2$ (M^+) 200.0837, found 200.0828. Less than 2% of unidentified product possessing a quartet at 4.42 ppm suggest the possibility of alkylation at the benzylic position.

3-Benzyl-2-methyl-4-furaldehyde (18e). *n*-BuLi (0.82 mL, 0.92 mmol) was added to a solution of Morph (70 mg, 0.92 mmol) in THF (5 mL) at 0 °C under Ar. After 15 min, the solution was cooled to −78 °C and **16e** (140 mg, 0.76 mmol) was added. This mixture was stirred for 15 min at 0 °C and then recooled to −78 °C before *s*-BuLi (0.82 mL, 1.07 mmol) was added dropwise. After 5 h at −78 °C, MeI (550 mg, 3.82 mmol) was added and the mixture was stirred an additional 20 h at −20 °C. Processing and purification by flash chromatography using 5% EtOAc/hexane gave 83 mg of a 1.2:1 mixture of **18e** (30%) and starting material **16e** (27%). This mixture was separated by normal-phase HPLC using 3% EtOAc/hexane to give pure **18e**: IR 3032, 1687; ^1H NMR 2.27 (s, 3 H), 3.99 (s, 2 H), 7.12–7.13 (m, 5 H), 7.87 (s, 1 H), 9.85 (s, 1 H), ^{13}C NMR 11.4, 29.2, 116.5, 126.0, 128.0, 140.2, 151.15, 151.22, 151.82, 185.18, 185.20; HRMS exact mass calcd for $C_{13}H_{12}O_2$ (M^+) 200.0837, found 200.0845.

Supplementary Material Available: ^{13}C NMR and/or ^1H NMR spectra for all compounds in Tables I–V and full experimental details for **5a**, **5c**, **6a**, **6c**, **16a**, **16c–e**, **17a**, **18a–d**, **20a,b**, and **21a,b** as well as details of metalation experiments on 3-(1-hydroxalkyl)furans with Tables A and B (72 pages). Ordering information is given on any current masthead page.

(36) We also prepared this compound from 2-bromo-4-furaldehyde (ref 25) as illustrated in ref 20. The yield was lower (ca. 50%) and the scale was limited by the sensitivity of the bromoaldehyde.

(37) For a reference to **5e** without data see: Kotsuki, H.; Monden, M.; Ochi, M. *Chem. Lett.* **1983**, 1007.