Efficient Synthesis of Substituted 2-Silylfurans from Acylsilane Dicarbonyl Compounds

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Furans[1] have enjoyed an important niche in organic synthesis as a result of their frequent occurrence in natural products[2] as well as their role as versatile synthetic intermediates in a wide variety of organic transformations.[3] Because of their importance, there exists a need for efficient methods of furan synthesis that control the regiochemistry of substituents placed about the ring.[4] Traditional methods have relied upon the acid-catalyzed dehydrative cyclization of 1,4-dicarbonyl compounds[5] or further elaboration of an existing furan nucleus.[6] Herein, we report a route to substituted 2-silylfurans **2** from acylsilane dicarbonyl compounds **1** that introduces synthetic flexibility to the more traditional dicarbonyl entry to furans (Scheme 1).

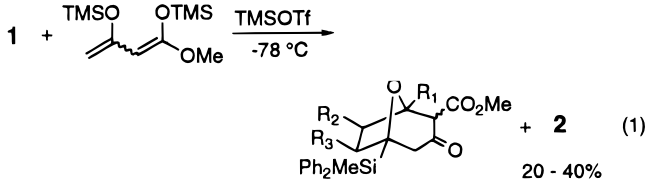
Table 1. 2-Silylfurans from Acylsilane Dicarbonyl Compounds

acysilane	silylfuran	R_1	R_2	R_3	% isoltd yield[a]
1a	**2a**	H	H	H	75
1b	**2b**	H	Me	H	87
1c	**2c**	H	H	Me	65
1d	**2d**	H	H	Ph	57
1e	**2e**	Me	H	H	81

[a] Refers to yields of purified product after Kugelrohr distillation. All of the above compounds have been fully characterized spectroscopically (^{1}H NMR, ^{13}C NMR, IR), and elemental composition has been established by combustion analysis and/or exact mass.

The synthesis of the requisite acylsilane dicarbonyl compounds **1** was accomplished by the coupling of 2-silyl-1,3-dithianes with halo acetals (Scheme 2). The details of these syntheses have previously been disclosed.[7]

While we were investigating the chemistry of **1** in Lewis acid-promoted [3 + 4] and [3 + 5] annulation reactions with bis(trimethylsilyl) enol ethers,[7,8] the instability of these dicarbonyl substrates toward both Lewis acids and protic acids became readily apparent. Annulation of **1** with the bis(trimethylsilyl) enol ether of methyl acetoacetate in the presence of catalytic trimethylsilyl triflate was sometimes contaminated by as much as 20−40% of the furan (eq 1). In fact, some furan was formed during the purification of **1** by flash chromatography on silica gel or upon allowing **1** to stand for several days at room temperature.



(1)

The ready formation of silylfurans from **1** can be attributed to the greater relative contribution of resonance form **1B** in the acylsilanes when compared to alkyl ketones.[9] Resonance form **1B** is stabilized by the inductive release of electron density from the silicon atom toward the carbonyl group. This results in an increase in nucleophilicity at the acylsilane carbonyl oxygen.[10] Intramolecular attack of this oxygen on the alkyl ketone with subsequent loss of water from the intermediate accounts for the formation of the furan.

This reactivity pattern of acylsilanes is used to advantage in the preparation of substituted 2-silylfurans **2** from acylsilane dicarbonyl compounds **1** (Table 1).

In all cases, the 2-silylfurans **2** were readily obtained in good to excellent yields under mild conditions. The yields of furans **2c** and **2d** are lowered slightly because of unfavorable steric interactions that develop upon ring formation and elimination of water in the 2,3-disubstituted furans. For these more highly substituted systems

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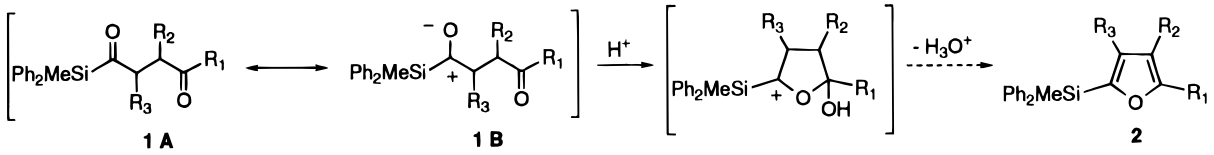
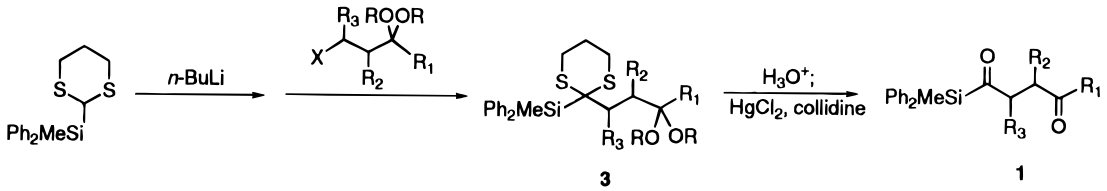
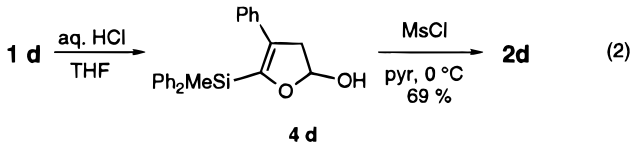
Scheme 1



Scheme 2

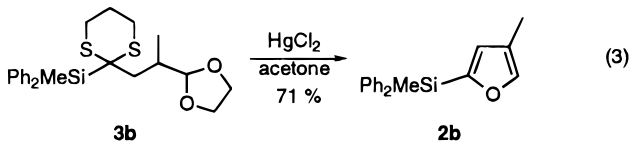


it was beneficial to use a two-step protocol for furan formation. For example, brief exposure of **1d** to aqueous acid caused rapid intramolecular cyclization. Subsequent treatment of the crude hemiacetal with methanesulfonyl chloride and pyridine at 0 °C provided furan **2d** in 69% yield (eq 2).



(2)

It is noteworthy that furans **2** could also be prepared directly from the protected dithiane acetal **3** without isolation of the acylsilane dicarbonyl compound by employing a one-pot hydrolysis/cyclization sequence. For example, when **3b** was treated with $HgCl_2$ in unbuffered medium, furan **2b** was isolated in 71% yield (eq 3). Unfortunately, this one-pot operation could not be extended to furans **2c** and **2d**, which possess the 2,3-disubstituted furan substitution pattern.



(3)

The method developed herein should find use in organic synthesis. It represents an improvement over the traditional dicarbonyl cyclization routes to furans in that the acylsilane undergoes reaction under milder reaction conditions and, in general, gives more acceptable yields than simple alkyl-substituted 1,4-diketones. Furthermore, the silyl substituent facilitates the subsequent regiospecific C_2-elaboration of the furan ring by either electrophilic substitution or metalation−addition strategies.[11]

Experimental Section

Reagents. Tetrahydrofuran (THF) was distilled immediately prior to use from benzophenone ketyl under Ar. CH_2Cl_2 was stirred over sulfuric acid, decanted, and stirred over K_2CO_3. It was distilled from CaH_2 onto 4 Å molecular sieves and stored over 4 Å molecular sieves. Standard benchtop techniques were employed for handling air-sensititve reagents,[12] and all reactions were carried out under argon.

General Procedure for the Synthesis of 2-Silylfurans from Acylsilane Dicarbonyl Compounds. A stirred solution of acylsilane dicarbonyl compound (50−100 mg) in THF (3 mL) and 1 N HCl (1 mL) was stirred at room temperature for 4−24 h. The mixture was diluted with ether, washed with saturated aqueous $NaHCO_3$ and brine, dried (K_2CO_3), and concentrated *in vacuo*. Flash chromatography of the residue on silica gel (1% ether in hexanes) followed by Kugelrohr distillation provided the silylfuran.

2-(Methyldiphenylsilyl)furan (2a). 2a was isolated in 75% yield from (1,4-dioxobutyl)methyldiphenylsilane (**1a**) after 16 h: oven temperature (ot) 90−100 °C/0.2 mmHg; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 1.6 Hz, 1H), 7.64 (m, 4H), 7.48−7.41 (m, 6H), 6.79 (d, J = 3.2 Hz, 1H), 6.48 (dd, J = 3.2, 1.6 Hz, 1H), 0.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.36, 147.70, 134.98, 134.92, 129.65, 127.89, 122.87, 109.52, −3.99; IR (neat) 3069 cm^{-1}; LRMS (EI$^+$) m/z 264 (52), 249 (100), 223 (8), 187 (8), 171 (8), 105 (25), 53 (6). Anal. Calcd for $C_{17}H_{26}OSi$: C, 77.21; H, 6.11. Found: C, 76.90; H, 6.09.

4-Methyl-2-(methyldiphenylsilyl)furan (2b). 2b was isolated in 87% yield from (3-methyl-1,4-dioxobutyl)methyldiphenylsilane (**1b**) after 16 h: ot 100 °C/0.03 mmHg; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (m, 4H), 7.53 (s, 1H), 7.47−7.38 (m, 6H), 6.61 (s, 1H), 2.08 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.46, 144.70, 135.13, 134.92, 129.60, 127.88, 125.70, 119.82, 9.33, −4.00; IR (neat) 3069, 1428, 1252, 1113, 1078, 912, 791, 676, 599 cm^{-1}; HRMS calcd for $C_{18}H_{18}OSi$ 278.1127, found 278.1118; LRMS (EI$^+$) m/z 278 (82), 263 (100), 223 (18), 197 (16), 161 (14), 145 (15), 105 (45), 91 (11), 77 (13), 53 (19), 39 (16).

4-Methyl-2-(methyldiphenylsilyl)furan (2b) from [2-[2-(1,3-dioxolan-2-yl)-1-methylethyl]-1,3-dithian-2-yl]methyldiphenylsilane (3b). A solution of [2-[2-(1,3-dioxolan-2-yl)-1-methylethyl]-1,3-dithian-2-yl]methyldiphenylsilane (**3b**) (130 mg, 0.302 mmol) and mercuric chloride (456 mg, 1.68 mmol) in 90% acetone (10 mL) was stirred at room temperature for 24 h. HCl (6N, 1 drop) was added, and stirring was continued for 2 h. The mixture was diluted with ether, filtered through Celite/neutral alumina, washed with water and brine, dried (K_2CO_3), and concentrated *in vacuo*. Flash chromatography of the residue on silica gel (petroleum ether) provided furan **2b** (60 mg, 71%), which was identical to material prepared above.

3-Methyl-2-(methyldiphenylsilyl)furan (2c). 2c was isolated in 65% yield from (2-methyl-1,4-dioxobutyl)methyldiphenylsilane (**1c**) (100 mg, 0.338 mmol) in THF (5 mL) and 1 N HCl (3 drops) for 24 h: ot 110 °C/0.1mmHg; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 1.2 Hz, 1H), 7.59 (dd, J = 7.7, 1.4 Hz, 4H), 7.46−7.38 (m, 6H), 6.31 (d, J = 1.2 Hz, 1H), 1.90 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.53, 146.91, 135.40, 135.01, 133.07, 129.54, 127.88, 112.98, 11.27, −3.28; IR (neat) 3069 cm^{-1}; LRMS (EI$^+$) m/z 278 (21), 263 (34), 185 (10), 161 (5), 141 (10), 105 (21), 84 (100), 77 (10), 47 (55). Anal. Calcd for $C_{18}H_{18}OSi$: C, 77.63; H, 6.52. Found. C, 77.23; H, 6.65.

2-(Methyldiphenylsilyl)-3-phenylfuran (2d). 2d was Isolated in 57% yield from (1,4-dioxo-2-phenylbutyl)methyldiphenylsilane (**1d**) after 16 h: ot 115 °C/0.15 mmHg; ^{1}H NMR (400

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MHz, $CDCl_3$) δ 7.70 (d, J = 1.5 Hz, 1H), 7.48 (m, 4H), 7.37−7.27 (m, 6H), 7.18−7.12 (m, 5H), 6.56 (d, J = 1.5 Hz, 1H), 0.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.17, 147.26, 139.56, 135.34, 135.04, 134.16, 133.98, 129.48, 128.80, 127.86, 127.80, 127.72, 126.95, 111.91, −3.70; IR (neat) 3068, 1558, 1503, 1428, 1373, 1254, 1111, 1048, 790, 754, 726, 697, 668 cm^{-1}; HRMS calcd for $C_{23}H_{20}OSi$ 340.1278, found 340.1283; LRMS (EI$^+$) m/z 340 (94), 325 (100), 247 (34), 223 (20), 197 (10), 165 (9), 105 (23), 77 (9), 51 (5).

Alternate Procedure for 2d. To a stirred solution of **1d** (70 mg, 0.19 mmol) in THF (10 mL) at room temperature was added 1 N HCl (1 drop), and stirring was continued for 10 min. The mixture was dried ($MgSO_4$) and concentrated *in vacuo* to provide crude 4,5-dihydro-2-hydroxy-5-(methyldiphenylsilyl)-4-phenylfuran (**4d**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (dt, J = 1.5 8.0, 1.4 Hz, 4H), 7.39−7.30 (m, 6H), 7.09 (m, 5H), 5.88 (m, 1H), 3.32 (dd, J = 16.9, 6.8 Hz, 1H), 2.98 (d, J = 4.2 Hz, 1H), 2.87 (dd, J = 16.9, 2.0 Hz, 1H), 0.52 (s, 3H). To a stirred solution of crude **4d** in dichloromethane (5 mL) cooled to 0 °C were added methanesulfonyl chloride (75 μL, 0.969 mmol) and pyridine (160 μL, 1.98 mmol), and stirring was continued for 1 h at 0 °C. The solution was washed with water and then brine, dried over $MgSO_4$, and concetrated *in vacuo*. Flash chromatography of the residue on silica gel (1% ether in hexanes) provided **2d** (46 mg, 69%), which was identical to the material prepared above.

5-Methyl-2-(methyldiphenylsily)furan (2e). **2e** was isolated in 81% yield from (1,4-dioxopentyl)methyldiphenylsilane (**1e**) after 4 h: ot 100 °C/0.1 mmHg; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (m, 4H), 7.44−7.36 (m, 6H), 6.61 (d, J = 3.0 Hz, 1H), 6.02 (d, J = 3.0 Hz, 1H), 2.36 (s, 3H), 0.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.78, 154.34, 135.40, 134.95, 1229.52, 127.83, 124.27, 105.94, 13.85, −3.91; IR (neat) 3069, 1490, 1428, 1252, 1215, 1187, 1114, 1018, 956, 787, 726, 698 cm^{-1}; LRMS (EI$^+$) m/z 278 (70), 263 (100), 237 (7), 201 (10), 185 (9), 161 (7), 141 (5), 105 (20), 77 (5), 43 (12). Anal. Calcd for $C_{18}H_{18}OSi$: C, 77.65; H, 6.52. Found: C, 77.60; H, 6.34.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds for which no elemental analysis was obtained (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of this journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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