

# A Simple Preparation of 2-Silylated 3-Furoic Acids and 2-Silylated 3-Thiophenecarboxylic Acids

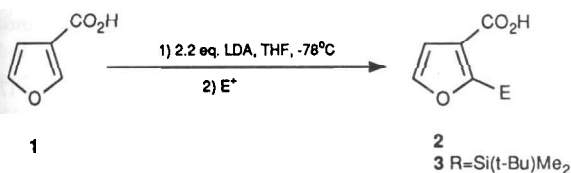
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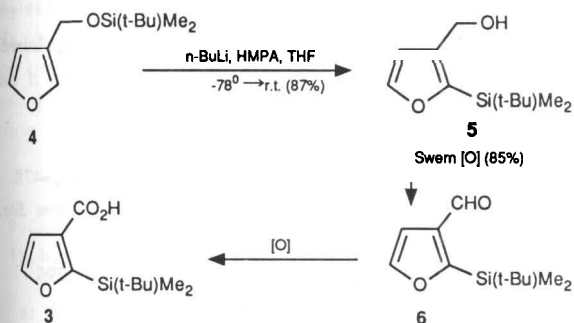
**Abstract:** A variety of 3-(silyloxycarbonyl)furans and -thiophenes undergo 1,4 O→C silyl migration to provide the corresponding 2-silylated 3-carboxy heterocycles in moderate to good yield when treated with a mixture of lithium diisopropylamide and hexamethylphosphoric triamide in tetrahydrofuran at -78°C.

We recently required 2-(*t*-butyldimethyl)silyl-3-furoic acid **3** as a starting material for the synthesis of some furan containing natural products. Knight<sup>1</sup> has reported that 2-substituted 3-furoic acids **2** can be simply prepared by treating 3-furoic acid **1** with two equivalents of LDA (THF, -78°C) followed by a quench with a suitable electrophile (Scheme 1). In our hands, employing *t*-butyldimethylsilyl chloride as the electrophile, the desired acid **3** was only formed in 5% yield.



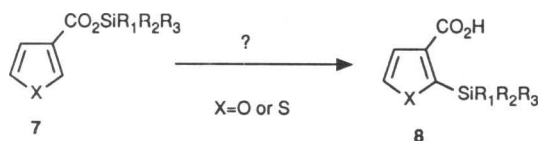
SCHEME 1

We have reported a facile preparation of 2-silylated 3-(hydroxymethyl)furans **5** from 3-(silyloxymethyl)furans **4** involving a 1,4 O→C silyl migration (Scheme 2).<sup>2</sup> Swern oxidation of **5** provided the corresponding aldehyde **6** (85%).<sup>3</sup> Unfortunately the oxidation of aldehyde **6**, employing mild oxidation reagents such as sodium hypochlorite,<sup>4</sup> AgO/NaCN,<sup>5</sup> Ag<sub>2</sub>O/NaOH,<sup>6</sup> or nickel peroxide,<sup>7</sup> provided furoic acid **3** in poor yields (0-15%).



SCHEME 2

Since the above procedures did not produce compound **3** in sufficient quantities we explored the possibility that 2-silylated 3-carboxylic acid heterocycles **8** could be produced via a 1,4 O→C silyl migration of 3-(silyloxycarbonyl)heterocycles **7** (Scheme 3).<sup>8</sup> The synthetic approach was based on the fact that furan **4** provided compound **5** via a 1,4 O→C silyl migration in good yield (87%, Scheme 2). The results from this study are reported herein.



SCHEME 3

A variety of silyl esters of both 3-furoic acid and 3-thiophenecarboxylic acid were prepared (Table 1) in moderate to good yield by heating (60°C) a mixture of the acid, silyl chloride (1.2 eq.) and imidazole (2.5 eq.) in dimethylformamide (2 mL/g of acid) for 48 hours.<sup>9,10</sup> A standard DMF workup followed by a flash silica gel column and distillation afforded the silyl esters **9-16** (Table 1).<sup>11,12</sup>

TABLE 1. 1,4 O→C Silyl Migrations of Silyl Esters

Entry	Silyl Ester (% Yield)		Product (% Yield)
1	9 (84)	X=O; R <sub>1</sub> =R <sub>2</sub> =methyl; R <sub>3</sub> = <i>t</i> -butyl	3 (72) <sup>a</sup>
2	10 (63)	X=O; R <sub>1</sub> =R <sub>2</sub> =R <sub>3</sub> = <i>i</i> -propyl	17 (56) <sup>a</sup>
3	11 (61)	X=O; R <sub>1</sub> =R <sub>2</sub> =R <sub>3</sub> = <i>n</i> -butyl	18 (51) <sup>a</sup>
4	12 (57)	X=O; R <sub>1</sub> =R <sub>2</sub> =R <sub>3</sub> =ethyl	19 (57) <sup>a</sup>
5	13 (76)	X=O; R <sub>1</sub> =R <sub>2</sub> =phenyl; R <sub>3</sub> = <i>t</i> -butyl	20 (43) <sup>a</sup>
6	14 (74)	X=S; R <sub>1</sub> =R <sub>2</sub> =R <sub>3</sub> = <i>i</i> -propyl	21 (57) <sup>b</sup>
7	15 (60)	X=S; R <sub>1</sub> =R <sub>2</sub> =methyl; R <sub>3</sub> = <i>t</i> -butyl	22 (47) <sup>b</sup>
8	16 (89)	X=S; R <sub>1</sub> =R <sub>2</sub> =phenyl; R <sub>3</sub> = <i>t</i> -butyl	23 (64) <sup>b</sup>

a) 3-Furoic acid was also isolated.

b) 3-Thiophene carboxylic acid was also isolated.

Addition of the (*t*-butyldimethyl)silyl ester **9**<sup>13</sup> to a mixture of LDA (1.2 eq.) and HMPA (1.2 eq.) in THF at -78°C resulted in an immediate deep green coloration. Acidic workup (1 N HCl) after 15 minutes at -78°C afforded 2-(*t*-butyldimethyl)silyl-3-furoic acid **3** in 72% yield.<sup>14</sup> The loss of an α-furan proton coupled with the appearance of a carboxylic acid proton and the presence of the *t*-butyldimethylsilyl group in the <sup>1</sup>H NMR spectrum indicated a disubstituted furoic acid had been prepared. A coupling constant of 1.76 Hz between the two furan protons indicated they were vicinal. Further proof that a 2,3-disubstituted compound had been produced was obtained when the spectra of the compound from the reaction with LDA/HMPA were compared with the spectra from the compound obtained via Knight's procedure (Scheme 1); both sets of spectra were identical. To our knowledge, this is the first example of a 1,4 O→C silyl migration involving silyl esters.

The silyl migration is a general reaction and is not limited to either the t-butyl dimethylsilyl group or furans. Table 1 summarizes our results to date. A variety of silyl ester furans **10-13** (entries 1-5) afforded the migrated products **17-20** respectively in moderate yields (43-72%) when treated under the optimized conditions developed for compound **9**.<sup>15</sup> Concomitant formation of 3-furoic acid reduced the yields. This was not unexpected since earlier nucleophilic studies with silyl esters had shown that nitrogen nucleophiles can attack the silicon atom of silyl esters.<sup>16</sup>

The migration reaction with thiophene silyl esters **14-16** provided the expected rearranged acids **21-23** respectively in moderate yields (entries 6-8).

Crossover experiments indicated that the silyl migration occurs by an intramolecular process. Thus an equimolar mixture of compounds **10** and **15** when subjected to the migration conditions provided acids **17** and **22**; no crossover products were detected (by <sup>1</sup>H NMR) or isolated. Similar intramolecular mechanisms have been proposed recently for other 1,4 O→C silyl migrations.<sup>2,17</sup>

We have therefore shown that 3-substituted silyl esters of furans and thiophenes undergo a 1,4 O→C silyl migration in moderate to good yields when treated at -78°C with a mixture of LDA/HMPA. Synthetic applications of this methodology are currently being explored.

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- (11) The following silyl esters could not be isolated via this procedure: (a) dimethylisopropyl; (b) dimethylphenyl; (c) triethyl; (d) tribenzyl; and (e) methyl diphenyl.
- (12) All new compounds provided analytical and/or spectroscopic data consistent with their structures.
- (13) Compound **9**: oil; bp 40-45°C (0.09 mm Hg); IR (neat) 1713, 1400, 739 cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 0.35 (s, 6H), 0.99 (s, 9H), 6.71 (dd, 1H, J=0.6, J=1.8 Hz), 7.41 (t, 1H, J=1.8 Hz), 7.97 (dd, 1H, J=0.6, J=1.8 Hz); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>) δ -4.91, 17.56, 25.45, 110.09, 120.97, 143.57, 147.98, 162.50; mass spectrum (EI) 169 (M<sup>+</sup>- t-Bu); HRMS calcd. for C<sub>7</sub>H<sub>9</sub>O<sub>3</sub>Si: 169.0321. Found: 169.0325.
- (14) Compound **3**: solid; mp 83-88°C, bp 100-110°C (0.04 mm Hg); IR (KBr) 3250-2250, 1686, 1293 cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 0.37 (s, 6H), 0.97 (s, 9H); 6.80 (d, 1H, J=1.76 Hz), 7.63 (d, 1H, J=1.76 Hz), 12.2 (bs, 1H); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>) δ -5.9, 18.0, 26.7, 111.0, 128.0, 146.5, 168.0, 170.3; Mass spectrum (EI) 169 (M<sup>+</sup>- t-Bu, 100); Elemental Analysis calcd. for C<sub>11</sub>H<sub>18</sub>O<sub>3</sub>Si: C, 58.37; H, 8.02. Found: C, 58.61; H, 8.15.
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