**4,5-Diamino-1-(*p*-nitrobenzyl)-3-[(*p*-nitrobenzyl)thio]-pyridazinium Bromide (20). Method A.** 4,5-Diaminopyridazine-3-thione (12; 284 mg, 2 mmol) was dissolved in 10 mL of 0.5 N KOH, and to this solution was added *p*-nitrobenzyl bromide (1.08 g, 5 mmol). The reaction mixture was stirred at room temperature for 20 h. The resulting precipitate was collected by filtration, washed with ethanol (2 × 5 mL), and crystallized from 95% ethanol to provide 500 mg (50%) of **20** as yellow needles: mp 255–256 °C dec; $^1$H NMR[28] ($Me_2SO$-$d_6$) δ 4.73 (s, 2, $SCH_2C_6H_4NO_2$), 5.97 (s, 2, $NCH_2C_6H_4NO_2$), 7.00 (br s, 2, $NH_2$).

Anal. Calcd for $C_{18}H_{17}N_6O_4SBr$: C, 43.82; H, 3.47; N, 17.03. Found: C, 44.04; H, 3.43; N, 16.89.

**Method B.** *p*-Nitrobenzyl bromide (32.4 mg, 0.15 mmol) was added to a solution of **19** (27.7 mg, 0.1 mmol) in 0.3 mL of 0.5 N KOH, and the mixture was stirred at room temperature for 20 h. The precipitated solid was removed by filtration, washed with absolute ethanol (5 mL), and crystallized from 95% ethanol to give 32 mg (65%) of **20** as needles. This heterocycle was identical (chromatographic mobility, UV, IR, and mixture melting point) with **20** prepared by method A.

**4,5-Dichloro-2-methylpyridazin-3-one (21).** To a three-necked, round-bottomed flask (500 mL), fitted with a condenser and dropping funnel, were added mucochloric acid (50 g, 300 mmol; Aldrich) and absolute ethanol (255 mL). The resulting solution was mechanically stirred and cooled to 5 °C. To this cooled solution was added methylhydrazine (21 mL, 300 mmol) dropwise, while the temperature was carefully maintained at 5 °C. After the addition of the methylhydrazine was complete, the reaction mixture was allowed to stir at 5 °C for 1 h and come to room temperature, and it was then heated at reflux for 4 h. After cooling to room temperature, the solution was concentrated under diminished pressure to ca. 150 mL. When the mixture was allowed to stand, pale yellow crystals formed. The crystalline material was collected by filtration and recrystallized from ethanol–water (9:1) to furnish 39 g (72.4%) of pure **21**: mp 88–89 °C (lit. mp 78–79 °C,[12a] 134–144 °C,[12b] 89–90 °C[13e]); $^1$H NMR ($Me_2SO$-$d_6$) δ 3.75 (s, 3, $NCH_3$), 8.20 (2, 1, H6).

(28) The signal of the other amino group was buried among the signals of the aromatic protons. This was confirmed by $D_2O$ exchange. We were unable to assign the chemical shifts of the *p*-nitrobenzyl moiety protons. The low-field (δ 7.62, 8.43) doublets of both sets were visible ($J$ = 9.5 Hz); however, the high-field signals of each quartet were merged together.

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**Registry No.** **1**, 22121-15-9; **2a**, 22121-14-8; **2b**, 76756-49-5; **2c**, 76756-50-8; **2d**, 76756-51-9; **3a**, 76756-52-0; **3b**, 76756-53-1; **3c**, 76756-54-2; **4**, 4725-76-2; **5**, 76756-55-3; **6**, 76756-56-4; **7**, 76756-57-5; **8a**, 76756-58-6; **8b**, 76756-59-7; **9a**, 76756-60-0; **9b**, 76756-61-1; **10a**, 76756-62-2; **10b**, 76756-63-3; **11**, 28682-73-7; **12**, 28682-74-8; **13**, 28682-75-9; **14**, 76756-64-4; **15**, 76756-65-5; **16**, 76756-66-6; **17**, 76756-67-7; **18**, 76756-68-8; **19**, 76756-69-9; **20**, 76756-70-2; **21**, 933-76-6; methyl iodide, 74-88-4; allyl bromide, 106-95-6; *p*-nitrobenzyl bromide, 100-11-8; 5-chloro-4-nitro-1-methylimidazole, 4897-25-0; mucochloric acid, 87-56-9; methylhydrazine, 60-34-4.

**Supplementary Material Available:** Ultraviolet spectral data of compounds 4–10 and 14–21 (4 pages). Ordering information is given on any current masthead page.

# A General Approach to 4-Substitution of 2-Alkylfurans

Steven M. Nolan and Theodore Cohen*

*Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260*

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Treatment of 2-alkylfurans with butyllithium followed by diphenyl disulfide yields 2-(phenylthio)-5-alkylfurans. When the 2-(phenylthio)-3-bromo-5-alkylfurans arising by bromination of the latter are treated with *tert*-butyllithium, the corresponding 3-lithio derivative is produced and it can be trapped by electrophiles such as alkyl iodides, aldehydes, trimethylsilyl chloride, and carbon dioxide. Raney nickel desulfurization of the product of such trapping produces 4-substituted-2-alkylfurans.

The substitution behavior of 2-alkylfurans has been known for many years.[1] Electrophilic substitution gives the product of attack at the 5-position as the major product, if problems of polysubstitution and destruction of the furan nucleus can be overcome.[1,2] Alternatively 2,5-disubstituted furans can be prepared by removal of the acidic 5-furyl hydrogen by an alkyllithium reagent followed by quenching of the resulting carbanion with a suitable electrophile.[3]

In cases where a different substitution pattern has been sought, recourse is usually made to synthesis of the furan ring from acyclic precursors[4a] or lactones[4b] in which the desired groups (or suitable equivalents) are already present. It was our desire to develop a convenient method of

Scheme I

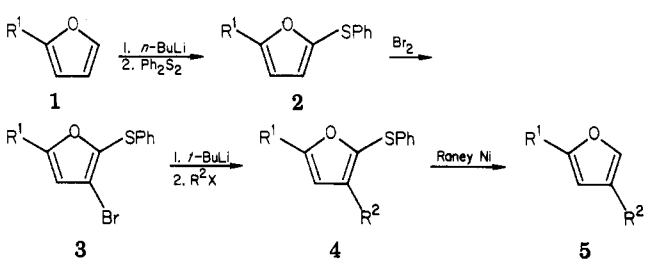



Table I. Phenylsulfenylation of Furans (1 → 2)

| $R^1$ | % yield | $R^1$ | % yield |
|---|---|---|---|
| $n$-$C_6H_{17}$ | 95 | $CH(OC_2H_5)_2$ | 71 |
| $CH_3$ | 85 | H | 42 |
| $n$-$C_4H_9$ | 61 | SPh | 0 |

(1) Dunlop, A. P.; Peters, F. N. "The Furans"; Reinhold: New York, 1953; p 29. (b) Paquette, L. A. "Modern Heterocyclic Chemistry"; Benjamin: Reading, MA, 1968; pp 102–149.

(2) Friedel–Crafts alkylation, for instance, is generally unsuccessful as the furan ring is destroyed by the harsh conditions.[1]

(3) (a) Ramanathan, V.; Levine, R. *J. Org. Chem.* **1962**, *27*, 1216. (b) Buchi, G.; Wuest, H. *Ibid.* **1966**, *31*, 977. (c) Lie Ken Jie, M. S. F.; Lam, C. H. *Chem. Phys. Lipids* **1978**, *21*, 275.

0022-3263/81/1946-2473$01.25/0 

Table II. Bromination of 2-Alkyl-5-(phenylthio)furans (2 → 3)

| $R^1$ | % yield | $R^1$ | % yield |
|---|---|---|---|
| $n$-$C_8H_{17}$ | 78 | $n$-$C_4H_9$ | 79 |
| $CH_3$ | 86 | $CH(OC_2H_5)_2$ | 0 |

Table III. Replacement of Bromine (3 → 4)

| $R^1$ | $R^2X$ | % yield |
|---|---|---|
| $C_4H_9$ | $CH_3I$ | 57 |
| $C_4H_9$ | $C_8H_{17}I$ | 76 |
| $CH_3$ | $(CH_3)_3SiCl$ | 91 |
| $CH_3$ | $CH_3CH_2CH_2CHO$ | 68 |
| $CH_3$ | $CO_2$ | 52[a] |
| $C_8H_{17}$ | $(CH_3)_3SiCl$ | 86 |

[a] Some material was lost inadvertently during workup.

introducing a new substituent in the 4-position of a 2-alkylfuran. Scheme I summarizes our approach.

The key to the strategy is the introduction of the phenylthio group at the 5-position in the first step. It serves two purposes: it blocks the 5-position during subsequent steps and it also activates the 4-position to electrophilic attack.[5]

Those 2-alkylfurans which are not commercially available were prepared from 2-lithiofuran and the appropriate alkyl iodide.[3a,c] These compounds were lithiated by using butyllithium and the 5-lithio derivative was quenched with diphenyl disulfide.[7] In simple cases, where $R^1$ = H or alkyl, the reaction proceeded at −20 °C without difficulty. In the case of $R^1$ = SPh the anion proved to be unstable and in that of $R^1 = CH(OC_2H_5)_2$ the anion could only be formed if hexamethylphosphoric triamide (HMPA) was present in the reaction solvent. The yields in the sulfenylation reactions are shown in Table I.

The products were brominated in methylene chloride and, whereas the simple alkyl-substituted furans gave high yields, the compound carrying the acetal group again gave problems, this time insuperable. The result of all attempts to substitute this furan with a variety of reagents ($Br_2$, $I_2$, pyridinium bromide perbromide, nitronium tetrafluoroborate) was either recovered starting material if a base was present or hydrolyzed starting material (aldehyde), if not. The yields in the bromination step are displayed in Table II.

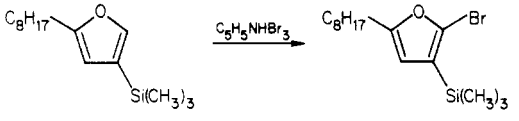
The subsequent step, lithium–bromine exchange using *tert*-butyllithium,[8] was generally successful. The yields of product, which varied with electrophile, were for the most part satisfactory and often high (Table III).

Table IV. Desulfurization of Furans (4 → 5)

| $R^1$ | $R^2$ | % yield |
|---|---|---|
| $C_8H_{17}$ | H | 85 |
| $C_4H_9$ | $C_8H_{17}$ | 83 |
| $C_8H_{17}$ | $(CH_3)_3Si$ | 68 |
| $CH_3$ | $(CH_3)_3Si$ | 50 |
| $CH_3$ | $CH_3CH_2CH_2CHOH$ | 74 |
| $CH_3$ | $CO_2H$ | 78 |

For the final step, we originally envisaged removing the sulfur group in a reductive lithiation step to produce a versatile 2-lithiofuran intermediate. We were encouraged in this by the successful replacement of sulfur by lithium in a ketene hemithioacetal using lithium dimethylaminonaphthalenide,[9] a powerful one-electron donor. Unfortunately, the desired cleavage did not occur in this case and starting material was recovered.[10] The color of the reaction mixture changed from intense green to intense red, possibly indicating that an electron transfer occurs, however, without effecting C–S bond cleavage. Following the failure of this approach we had recourse to the standard desulfurization conditions, Raney nickel[11] in ethanol, which proved successful (Table IV).

The trimethylsilyl group was deliberately chosen as one of the groups to be introduced since it has been shown that it can be replaced on aromatic rings by a variety of other functional groups under electrophilic conditions.[12] As some of these, such as halogen, are labile under Raney nickel desulfurization conditions, this could have been a way of introducing them at the end of the synthesis in a regiospecific manner. When 2-octyl-4-(trimethylsilyl)furan was treated with bromine at −20 °C, a mixture of compounds was obtained. When it was treated instead with pyridinium bromide perbromide in THF, a bromine atom was cleanly introduced at the 5-position of the furan ring with retention of the trimethylsilyl group. Apparently, the oxyallylic stabilization of the positive charge in the $\sigma$ complex intermediate obtained when electrophilic bromine attacks the 5-position is greater than the well-known stabilization of a $\beta$-positive charge by silicon which would be manifested in the cationic intermediate for brominative desilanization.




## Experimental Section

The melting points and boiling points are uncorrected. Ele-

(4) For examples see: (a) Mukaiyama, T.; Ishihara, J. I.; Inomato, K. *Chem. Lett.* **1975**, 527; Kotake, H.; Inomato, K.; Aoyama, S.; Kinoshita, H. *Ibid* **1975**, 853; Spencer, T. A.; Garst, M. E. *J. Am. Chem. Soc.* **1973**, *95*, 250; Harris, C. M.; Cleary, J. J.; Harris, T. M. *J. Org. Chem.* **1974**, *39*, 72; Yoshisato E.; Tsutsumi, S. *J. Chem. Soc., Chem. Commun.* **1968**, 33; Ibragimov, I. I.; Guseinov, M. M.; Ghazhily, R. A.; Dzhafarov, V. G.; Godzhaev, S. P. *Chem. Heterocycl. Compd. (Engl. Transl.)* **1973** *9*, 1300; Taguchi, T.; Okamura, H.; Takei, H. *Chem. Lett.* **1975**, 853; Gotthardt, H.; Weisshuhn, C. M.; Doerhofer, K. *Chem. Ber.* **1978**, *111*, 3336. (b) Grieco, P. A.; Pogonowski, C. S.; Burke, S. *J. Org. Chem.* **1975**, *40*, 542.

(5) (a) During the writing of this manuscript, we became aware of a Russian article which describes acylation of 2-(alkylthio)-5-substituted-furans at the 3- and 2-positions.[6] (b) For other examples in which 2,4-disubstituted furans are prepared from other furanoid precursors see: Van Tamelen, E. E.; Whitesides, T. H. *J. Am. Chem. Soc.* **1971**, *93*, 6129; Naoi, Y.; Nakano, T.; Sakai, K.; Fujii, K.; Wakaomi, M. *Nippon Kagaku Kaishi* **1977**, 1365; *Chem. Abstr.* **1978**, *88*, 50565.

(6) Danushevskii, Y. L.; Marakatkina, M. A.; Gol'dfarb, Y. L. *Isv. Akad. Nauk. SSSR, Ser. Khim. (Eng. Transl.)* **1968**, 2397.

(7) Although we have not found any reports of the reaction of 2-lithiofurans with diphenyl disulfide, their reaction with elemental sulfur is known: (a) Niwa, E.; Aoki, H.; Tanaka, H.; Munakata, K. *Chem. Ber.*, **1966**, *99*, 3215; (b) Cederlund, B.; Lantz, R.; Hornfeldt, A. B.; Thorsted, O.; Undheim, K. *Acta Chem. Scand., Ser. B* **1977**, *31*, 198.

(8) (a) Gilman, H.; Melstrom, D. S. *J. Am. Chem. Soc.* **1946**, *68*, 103. (b) Jones R. G.; Gilman H. *Org. React.* **1951**, *6*, 339. (c) Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 7210. (d) Neumann, H.; Seebach, D. *Chem. Ber.* **1978**, *111*, 2785. (e) Kojima, Y.; Wakita, S.; Kato, N.; *Tetrahedron Lett.* **1979**, 4577.

(9) Cohen, T.; Matz, J. R. *J. Am. Chem. Soc.* **1980**, *102*, 6900.

(10) The probable explanation for the success in the reductive lithiation of the ketene hemithioketal is that the oxygen atom attached to the vinyl radical in the putative intermediate[9] can arrange itself for maximum stabilization of this radical whereas the 2-furyl radical must enjoy only marginal overlap with the nonbonding $\sigma$ electrons of the neighboring oxygen atom.

(11) (a) Pizey, I. S. "Synthetic Reagents"; Wiley: New York, 1974; Vol. II, Chapter 4. (b) Pettit, G. R.; Van Tamelen, E. E. *Org. React.* **1962**, *12*, 356.

(12) (a) Colvin, E. W. *Chem. Soc. Rev.* **1978**, *7*, 15. (b) Felix, G.; Dunoguès, J.; Pisciotti, F.; Calas, R. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 488.

(13) Kinlin, T. E.; Muralidhara, R.; Pittet, A. O.; Sanderson, A.; Walradt, J. P. *J. Agric. Food Chem.* **1972**, *20*, 1021.

mental analyses were performed by Galbraith Laboratories, Knoxville, TN. The spectroscopic analyses were for samples which were homogeneous by TLC. Mass spectra were obtained on an LKB 9000 mass spectrometer. $^1H$ NMR spectra were recorded on a Varian EM 390 spectrometer. IR spectra were taken on a Perkin-Elmer Model 137B Infracord spectrophotometer.

**2-Octylfuran.**[4f,14] Furan (5.0 g, 73 mmol) in 300 mL of THF was metalated by using butyllithium (46 mL of 1.6 M solution in hexane, 73 mmol) at −20 °C. After the solution was stirred for 2 h, 1-iodooctane (17.5 g, 73 mmol) in 40 mL of THF was added. The solution was stirred at −20 °C for 1 h and then at 22 °C for 1 h. The reaction mixture was quenched with 40 mL of water and the aqueous layer extracted (1:1 diethyl ether–pentane). The combined organic layer was washed with 5% sodium bisulfite solution, water, and brine. The crude organic layer was dried ($MgSO_4$) and the solvents were removed under vacuum. The crude product was purified by column chromatography (silica gel, hexanes) followed by Kugelrohr distillation (75–90 °C, 14 mm) to yield 10.2 g (78%) of a mobile colorless oil (lit.[14] $bp_{12}$ 103–104 °C): $^1H$ NMR ($CCl_4$) $\delta$ 7.25 (d, $J$ = 2 Hz, 1 H, C5-H of furan), 6.20 (dd, $J$ = 2, 3 Hz, 1 H, C4-H of furan), 5.90 (d, $J$ = 3 Hz, 1 H, C3-H of furan), 2.57 (t, $J$ = 7 Hz, 2 H, $CH_2C_7H_{15}$), 1.60 (m, 2 H, $CH_2CH_2C_6H_{13}$), 1.28 (m, 10 H, $(CH_2)_5CH_3$), 0.88 (br t, $J$ = 6 Hz, 3 H, $CH_3$); IR (neat) 2910, 2840, 1595, 1500, 1460, 720 $cm^{-1}$; mass spectrum, $m/e$ 180 ($M^+$), 95 ($C_4H_3OCH_2CH_2^+$), 82, 81 (100%, $C_4H_3OCH_2^+$).

**2-Butylfuran**[3a,4f] was prepared in the same manner [bp 144–146 °C (lit.[3a] bp 137 °C)] in 69% yield: $^1H$ NMr ($CCl_4$) $\delta$ 7.30 (d, $J$ = 2 Hz, 1 H, C5-H of furan), 6.26 (dd, $J$ = 2, 3 Hz, 1 H, C4-H of furan), 5.95 (d, $J$ = 3 Hz, 1 H, C3-H of furan), 2.60 (t, $J$ = 7 Hz, 2 H, $CH_2C_3H_7$), 1.50 (m, 2 H, $CH_2C_2H_5$), 1.26 (m, 2 H, $CH_2CH_3$), 0.90 (br t, $J$ = 7 Hz, 3 H, $CH_3$); IR (neat) 2940, 1580, 1480, 1000, 730 $cm^{-1}$; mass spectrum, $m/e$ 124 ($M^+$), 82, 81, (100%, $C_4H_3OCH_2^+$).

**5-Butyl-2-(phenylthio)furan.** 2-Butylfuran (1.65 g, 13.3 mmol) in 50 mL of THF was metalated by using butyllithium (8.5 mL of 1.6 M solution in hexane, 13.6 mmol) at −20 °C. After the solution was stirred for 3 h, diphenyl disulfide (2.94 g, 13.5 mmol) in 10 mL of THF was added. The dark solution was stirred at −20 °C for 1 h and then at 22 °C for 3 h. The reaction mixture was quenched with 30 mL of water, and the aqeous layer was extracted (1:1 diethyl ether–pentane, 2 × 40 mL). The combined organic layer was washed with 2 N aqueous sodium hydroxide solution (3 × 30 mL), water, and brine. The organic layer was dried ($MgSO_4$) and the solvents were removed under vacuum. The crude product was purified by Kugelrohr distillation (110 °C, 0.5 mm) to yield 1.87 g (61%) of a colorless oil: $^1H$ NMR ($CCl_4$) $\delta$ 7.12 (br s, 5 H, Ph), 6.60 (d, $J$ = 4 Hz, 1 H, C3-H of furan), 6.03 (d, $J$ = 4 Hz, 1 H, C4-H of furan), 2.67 (br t, $J$ = 7 Hz, 2 H, $CH_2C_3H_7$), 1.55 (m, 2 H, $CH_2C_2H_5$), 1.28 (m, 2 H, $CH_2CH_3$), 0.95 (br t, $J$ = 7 Hz, 3 H, $CH_3$); IR (neat) 2950, 2910, 1580, 1480, 1005, 780, 735, 690 $cm^{-1}$; mass spectrum, $m/e$ 232 ($M^+$), 188 (100%, $M^+ - C_3H_6$); exact mass calcd for $C_{14}H_{16}OS$ 232.0922, found 232.0921.

**5-Methyl-2-(phenylthio)furan** was prepared in the same manner as a colorless oil: $^1H$ NMR ($CCl_4$) $\delta$ 7.23 (s, 5 H, Ph), 6.68 (d, $J$ = 3 Hz, 1 H, C3-H furan), 6.07 (d, $J$ = 3 Hz, 1 H, C4-H of furan), 2.38 (s, 3 H, $CH_3$); IR (neat) 3050, 2900, 1585, 1468, 1434, 1010, 790, 730 $cm^{-1}$; mass spectrum $m/e$ 190 (100%, $M^+$), 147, 43. Anal. Calcd for $C_{11}H_{10}OS$: C, 69.53; H, 5.26. Found: C, 69.76; H, 5.41.

**5-Octyl-2-(phenylthio)furan** was prepared in the same manner as a colorless oil: $^1H$ NMR ($CCl_4$) $\delta$ 7.07 (m, 5 H, Ph), 6.53 (d, $J$ = 4 Hz, 1 H, C3-H, of furan), 5.97 (d, $J$ = 4 Hz, 1 H, C4-H of furan), 2.61 (t, $J$ = 7 Hz, 2 H, $CH_2C_7H_{15}$), 1.60 (br m, 2 H, $CH_2C_6H_{13}$), 1.27 (m, 10 H, $(CH_2)_5CH_3$), 0.90 (br t, $J$ = 7 Hz, 3 H, $CH_3$); IR (neat) 2930, 2850, 1583, 1488, 730 $cm^{-1}$; mass spectrum, $m/e$ 288 ($M^+$), 204, 190 (100%, $M^+ - C_7H_{14}$). Anal. Calcd for $C_{18}H_{24}OS$: C, 75.00; H, 8.33. Found: C, 75.31; H, 8.19.

**2-(Phenylthio)-5-(diethoxymethyl)furan** was prepared in a similar fashion except on a smaller scale (5.8 mmol) in a solvent of 10:1 THF–HMPA (110 mL) and the product, a light orange oil, was purified by column chromatography on triethylamine-washed silica gel with hexane elution: $^1H$ NMR ($CCl_4$) $\delta$ 7.16 (s, 5 H, Ph), 6.64 (d, $J$= 3 Hz, 1 H, C3-H of furan), 6.34 (d, $J$ = 3 Hz, 1 H, C4-H of furan), 5.45 (s, 1 H, $CH(OEt)_2$), 3.50 (q, $J$ = 7 Hz, 4 H, $CH_2$), 1.12 (t, $J$ = 7 Hz, 6 H, $CH_3$); IR (neat) 2950, 2860, 1580, 1475, 1100, 1040, 730 $cm^{-1}$; mass spectrum, $m/e$ 278 ($M^+$), 234 (100%, $M^+ - C_2H_4O$), 204 ($M^+ - C_4H_{10}O$); exact mass calcd for $C_{15}H_{18}O_3S$ 278.0977, found 278.0980.

**2-(Phenylthio)-3-bromo-5-butylfuran.** To 2-(phenylthio)-5-butylfuran (0.569 g, 245 mmol) in $CH_2Cl_2$ (20 mL) at −22 °C was added bromine (0.390 g, 2.44 mmol) in $CH_2Cl_2$ (10 mL) by addition funnel. The mixture was stirred for 1 h at −22 °C and at 0 °C for 1 h. Excess (2 g) diisopropylamine was added and the solution was warmed to room temperature. Aqueous 5% sodium sulfite solution (5.0 mL) was added, the resulting mixture was partitioned, and the organic layer was washed with 2 N hydrochloric acid solution (4 × 20 mL), 5% sodium bicarbonate solution (2 × 20 mL), and brine. The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure. Column chromatography (silica gel, hexanes) yielded a colorless oil (0.59 g, 77%): $^1H$ NMR ($CCl_4$) $\delta$ 7.07 (br s, 5 H, Ph), 6.10 (s, 1 H, C4-H of furan), 2.61 (br t, $J$ = 7 Hz, 2 H, $CH_2C_3H_7$), 1.13–1.83 (m, 4 H, $CH_2CH_2CH_3$), 0.93 (br t, $J$ = 7 Hz, $CH_3$); IR (neat) 3050, 2950, 2915, 2850, 1580, 1479, 1438, 970, 795, 691 $cm^{-1}$; mass spectrum, $m/e$ 312 ($M'^+$ with $^{81}Br$), 310 ($M^+$ with $^{79}Br$), 269 ($M'^+ - C_3H_7$), 267 ($M^+ - C_3H_7$), 147, 85; exact mass calcd for $C_{14}H_{15}O^{79}BrS$ 310.0027, found 310.0025.

**2-(Phenylthio)-3-bromo-5-methylfuran** was prepared in the same manner as a colorless oil: $^1H$ NMR ($CCl_4$) $\delta$ 7.13 (m, 5 H, Ph), 6.07 (s, 1 H, C4-H of furan), 2.22 (s, 3 H, $CH_3$); IR (neat) 2900, 1580, 1480, 1000, 740 $cm^{-1}$; mass spectrum, $m/e$ 270 ($M'^+$ with $^{81}Br$), 268 ($M^+$ with $^{79}Br$), 189 ($M^+ - Br$), 58, 43 (100%); exact mass calcd for $C_{11}H_9O^{79}BrS$ 267.9555, found 267.9557.

**2-(Phenylthio)-3-bromo-5-octylfuran** was prepared in the same manner as a colorless oil: $^1H$ NMR ($CCl_4$) $\delta$ 7.17 (m, 5 H, Ph), 6.13 (s, 1 H, C4-H of furan), 2.56 (t, $J$ = 7 Hz, 2 H, $CH_2C_7H_{15}$), 1.60 (m, 2 H, $CH_2C_6H_{13}$), 1.26 (m, 10 H, $(CH_2)_5CH_3$), 0.88 (br, t, $J$ = 7 Hz, 3 H, $CH_3$); IR (neat) 2920, 2850, 1580, 1480, 990, 740 $cm^{-1}$; mass spectrum, $m/e$ 368 ($M'^+$ with $^{81}Br$), 366 ($M^+$ with $^{79}Br$), 269 ($M'^+ - C_7H_{15}$), 267 (100%, $M^+ - C_7H_{15}$), 189, 147; exact mass calcd for $C_{18}H_{23}O^{79}BrS$ 366.0658, found 366.0660.

**2-(Phenylthio)-3-octyl-5-butylfuran.** To 2-(phenylthio)-3-bromo-5-butylfuran (0.503 g, 1.62 mmol) in 30 mL of THF was added *tert*-butyllithium (1.80 mL of 2 N solution in pentane, 3.60 mmol) at −22 °C via syringe. After 2 h of stirring, HMPA (2 mL) was added followed by 1-iodooctane (0.411 g, 1.71 mmol) in THF (5 mL). After 1 h of being stirred the reaction mixture was quenched ($H_2O$) and warmed to room temperature, and the layers were partitioned. The aqueous layer was washed with 1:1 diethyl ether–pentane and the combined organic layer was washed with 1 N hydrochloric acid solution (20 mL), 5% sodium bicarbonate solution, and brine. The solution was dried ($MgSO_4$) and filtered, and the solvent removed under vacuum. Column chromatography (silica gel, hexane) yielded 0.43 g (76%) of a colorless oil: $^1H$ NMR ($CCl_4$) $\delta$ 7.10 (br s, 5 H, Ph), 5.97 (s, 1 H, C4-H of furan), 2.60 (br t, $J$ = 7 Hz, 2 H, $ArCH_2C_3H_7$), 2.50 (br t, $J$ = 7 Hz, 2 H, $CH_2C_7H_{15}$), 1.23 (m, 16 H, $(CH_2)_2CH_3$ and $(CH_2)_6CH_3$), 0.93 (t, 6 H, $C_3H_6CH_3$ and $C_7H_{14}CH_3$); IR (neat) 2945, 2905, 2840, 1580, 1480, 1455, 1020, 728, 680 $cm^{-1}$; mass spectrum, $m/e$ 344 ($M^+$, 100%); exact mass calcd for $C_{20}H_{32}OS$ 344.2174, found 344.2150.

**2-(Phenylthio)-3-methyl-5-butylfuran** was prepared as a colorless oil by an analogous procedure: $^1H$ NMR ($CCl_4$) $\delta$ 7.00 (m, 5 H, Ph), 5.87 (s, 1 H, C4-H of furan), 2.58 (t, $J$ = 7 Hz, 2 H, $CH_2C_3H_7$), 2.25 (s, 3 H, $ArCH_3$), 1.53 (m, 4 H, $(CH_2)_2CH_3$), 0.90 (t, $J$ = 7 Hz, $CH_2CH_3$); IR (neat) 2900, 1580, 1475, 730 $cm^{-1}$; mass spectrum, $m/e$ 246 ($M^+$), 203 (100%, $M^+ - C_3H_7$); exact mass calcd for $C_{15}H_{18}OS$ 246.1078, found 246.1078.

**2-(Phenylthio)-3-(1-hydroxybutyl)-5-methylfuran** was prepared as a colorless oil in a similar fashion except that butanal was used as electrophile and chloroform as the eluent in the chromatography: $^1H$ NMR ($CDCl_3$) $\delta$ 7.24 (m, 5 H, Ph), 6.15 (s, 1 H, C4-H of furan), 4.80 (t, $J$ = 7 Hz, 1 H, CHOH), 2.33 (s, 3 H, $ArCH_3$), 1.73 (m, 4 H, $(CH_2)_2CH_3$), 1.00 (t, $J$ = 7 Hz, 3 H, $CH_2CH_3$); IR (neat) 3300, 2900, 1580, 1180, 1110, 950, 890 $cm^{-1}$; mass spectrum, $m/e$ 262 ($M^+$), 245 ($M^+ - OH$), 219 (100%, $M^+ - C_3H_7$); exact mass calcd for $C_{15}H_{18}O_2S$ 262.1028, found 262.1025.

**2-(Phenylthio)-3-(trimethylsilyl)-5-methylfuran.** 2-(Phenylthio)-3-bromo-5-methylfuran (1.00 g, 3.72 mmol) in 40 mL of

(14) Buchta, E.; Huhn, C. *Justus Liebigs Ann. Chem.* **1965**, *686*, 77.

THF was treated with *tert*-butyllithium (3.8 mL of 2.0 M solution in pentane, 7.6 mmol) at −78 °C. After the mixture was stirred for 90 min, trimethylsilyl chloride (0.60 mL, 0.52 g, 4.8 mmol) was injected by syringe. The reaction mixture was stirred for 4.5 h and then transferred at 0 °C in air to a one-neck flask. The solvent was removed under vacuum. Column chromatography (base-washed silica gel, hexane) yielded 0.88 g (91%) of a colorless oil: $^1$H NMR ($CCl_4$) δ 7.20–7.32 (m, 5 H, Ph), 6.13 (s, 1 H, C4-H of furan), 2.31 (s, 3 H, $ArCH_3$), 0.21 (s, 9 H, $Si(CH_3)_3$); IR (neat) 2950, 1590, 1485, 1435, 1242, 832, 730 cm$^{-1}$; mass spectrum, *m/e* 262 ($M^+$, 100%), 187, 173; exact mass calcd for $C_{14}H_{18}OSSi$ 262.0848, found 262.0850.

**2-(Phenylthio)-3-(trimethylsilyl)-5-octylfuran** was prepared by an analogous procedure as a colorless oil: $^1$H NMR ($CCl_4$) δ 7.13 (m, 5 H, Ph), 6.04 (s, 1 H, C4-H of furan), 2.65 (t, $J$ = 7 Hz, $CH_2C_7H_{15}$), 1.67 (br m, 2 H, $CH_2C_6H_{13}$), 1.30 (m, 10 H, $(CH_2)_5CH_3$), 0.90 (br t, $J$ = 7 Hz, $CH_2CH_3$), 0.21 (s, 9 H, $Si(CH_3)_3$); IR (neat) 2930, 1585, 1480, 1255, 840 cm$^{-1}$; mass spectrum, *m/e* 360 ($M^+$), 345 ($M^+ - CH_3$), 262 (100%, $M^+ - C_7H_{14}$), 261 ($M^+ - C_7H_{15}$), 73; exact mass calcd for $C_{21}H_{32}OSSi$ 360.1946, found 360.1949.

**2-(Phenylthio)-5-methylfuran-3-carboxylic Acid.** To 2-(phenylthio)-3-bromo-5-methylfuran (0.69 g, 2.5 mmol) in THF (40 mL) at −78 °C was added *tert*-butyllithium (2.6 mL of 2.0 M solution in pentane, 5.1 mmol). After the solution was stirred for 1 h, carbon dioxide from a cylinder was passed in for 5 min. The solution was warmed to room temperature and partitioned between 2 N sodium hydroxide solution and pentane. The organic layer was extracted with more sodium hydroxide solution. The combined aqueous layer was shaken with 1:1 diethyl ether–pentane, acidified with excess 2 N hydrochloric acid solution, and extracted with diethyl ether (5 × 20 mL). The ether layer was washed with brine, dried ($MgSO_4$), and filtered, and the solvent removed under vacuum. Recrystallization from hexane afforded 0.413 g (52%) of colorless plates: mp 121.0–122.0 °C; $^1$H NMR ($CDCl_3$) δ 7.33 (m, 5 H, Ph), 6.47 (s, 1 H, C4-H of furan), 2.27 (s, 3 H, $CH_3$); IR (neat) 3200, 3050, 2950, 1683, 1517, 1250, 713 cm$^{-1}$; mass spectrum, *m/e* 234 ($M^+$, 100%), 191, 173, 146, 105, 43. Anal. Calcd for $C_{12}H_{10}O_3S$: C, 61.59; H, 4.27. Found: C, 61.72; H, 4.36.

**2-Butyl-4-octylfuran.** A suspension of 1.66 g of Raney nickel in 60 mL of ethanol containing 0.29 g (0.083 mmol) of dissolved 2-(phenylthio)-3-octyl-5-butylfuran was heated at reflux for 6 h. The reaction mixture was filtered through Celite and the solvent evaporated under vacuum. Kugelrohr distillation (100–115 °C, 0.15 mm) yielded 0.16 g (83%) of a colorless oil: $^1$H NMR ($CCl_4$) δ 6.95 (s, 1 H, C5-H of furan), 5.75 (s, 1 H, C3-H of furan), 2.53 (t, $J$ = 7 Hz, 2 H, $CH_2C_3H_7$), 2.30 (t, $J$ = 7 Hz, 2 H, $CH_2C_7H_{15}$), 1.29 (m, 16 H, $(CH_2)_2CH_3$ and $(CH_2)_6CH_3$), 0.91 (br t, $J$ = 7 Hz, 3 H, $CH_3$), 0.87 (t, $J$ = 7 Hz, 3 H, $CH_3$); IR (neat) 2950, 2910, 2850, 1605, 1530, 1460, 1110, 940 cm$^{-1}$; mass spectrum, *m/e* 236 ($M^+$), 138 ($M^+ - C_7H_{14}$), 74, 59 (100%). Anal. Calcd for $C_{16}H_{28}O$: C, 81.29; H, 11.94. Found: C, 81.43; H 12.25.

**2-Methyl-4-(trimethylsilyl)furan** was prepared by the same desulfurization procedure, starting from 2-(phenylthio)-3-(trimethylsilyl)-5-methylfuran. It was a colorless liquid: bp 75 °C (175 mm, Kugelrohr); $^1$H NMR ($CCl_4$) δ 7.21 (s, 1 H, C5-H of furan), 5.95 (s, 1 H, C3-H of furan), 2.25 (s, 3 H, $ArCH_3$), 0.19 (s, 9 H, $Si(CH_3)_3$); IR (neat) 2890, 1580, 1470, 1240, 835 cm$^{-1}$; mass spectrum, *m/e* 154 ($M^+$), 139 (100%, $M^+ - CH_3$ of silyl group), 73 ($SiMe_3^+$), 43; exact mass calcd for $C_8H_{14}OSi$ 154.0814, found 154.0810.

**2-Octyl-4-(trimethylsilyl)furan** was prepared as a colorless oil by a similar desulfurization of 2-(phenylthio)-3-(trimethylsilyl)-5-octylfuran: $^1$H NMR ($CCl_4$) δ 7.15 (s, 1 H, C5-H of furan), 5.91 (s, 1 H, C3-H of furan), 2.61 (t, $J$ = 7 Hz, 2 H, $CH_2C_7H_{15}$), 1.63 (m, 2 H, $CH_2C_6H_{13}$), 1.33 (m, 10 H, $(CH_2)_5CH_3$), 0.90, (t, 3 H, $CH_2CH_3$), 0.23 (s, 9 H, $Si(CH_3)_3$); IR (neat) 2920, 2850, 1580, 1250, 1110, 840 cm$^{-1}$; mass spectrum, *m/e* 252 ($M^+$), 237 ($M^+ - CH_3$ of silyl group), 168, 167, 153 (100%, $M^+ - C_7H_{15}$), 73 ($SiMe_3^+$); exact mass calcd for $C_{15}H_{28}OSi$ 252.1909, found 252.1909.

**2-Methyl-4-furoic acid** was prepared by similar desulfurization of a 2-(phenylthio)-5-methylfuran-3-carboxylic acid. It was sublimed at 100 °C (14 mm) and had mp 111.5–113.5 °C (lit.[5a] mp 114–115 °C): $^1$H NMR ($CDCl_3$) δ 7.96 (s, 1 H, C5-H of furan), 6.40 (s, 1 H, C3-H of furan), 2.32 (s, 3 H, $CH_3$); IR (Nujol) 3150–2250, 1660, 1540, 1420, 1190, 1120, 950 cm$^{-1}$; mass spectrum, *m/e* 126 (100%, $M^+$), 109 ($M^+ - CH_3$), 43. Anal. Calcd for $C_6H_6O_3$: C, 57.19; H, 4.76. Found: C, 57.37; H, 4.76.

**2-Methyl-4-(1-hydroxybutyl)furan** was prepared as a colorless oil in the same manner from 2-(phenylthio)-3-(1-hydroxybutyl)-5-methylfuran: $^1$H NMR ($CDCl_3$) δ 7.16 (s, 1 H, C5-H of furan), 5.93 (s, 1 H, C3-H of furan), 4.50 (t, $J$ = 7 Hz, 1 H, CHOH), 2.20 (s, 3 H, $ArCH_3$), 1.61 (m, 2 H, $CH_2C_2H_5$), 1.25 (m, 2 H, $CH_2CH_3$), 0.90 (t, $J$ = 7 Hz, $CH_2CH_3$); IR (Nujol) 3400, 2950, 1120, 1025, 920 cm$^{-1}$; mass spectrum, *m/e* 154 ($M^+$), 111 (100%, $M^+ - C_3H_7$), 93, 43; exact mass calcd for $C_9H_{14}O_2$ 154.0994, found 154.0994.

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**Registry No.** 1 ($R^1$ = $CH_3$), 534-22-5; 1 ($R^1$ = $C_8H_{17}$), 4179-38-8; 1 ($R^1$ = $C_4H_9$), 4466-24-4; 1 ($R^1$ = $CH(OC_2H_5)_2$), 13529-27-6; 1 ($R^1$ = H), 110-00-9; 2 ($R^1$ = $C_4H_9$), 77287-71-9; 2 ($R^1$ = $CH_3$), 77287-72-0; 2 ($R^1$ = $C_8H_{17}$), 77287-73-1; 2 ($R^1$ = $CH(OC_2H_5)_2$), 69197-87-1; 2 ($R^1$ = H), 16003-14-8; 3 ($R^1$ = $C_4H_9$), 77287-74-2; 3 ($R^1$ = $CH_3$), 77287-75-3; 3 ($R^1$ = $C_8H_{17}$), 77287-76-4; 4 ($R^1$ = $C_4H_9$; $R^2$ = $C_8H_{17}$), 77287-77-5; 4 ($R^1$ = $C_4H_9$; $R^2$ = $CH_3$), 77287-78-6; 4 ($R^1$ = $CH_3$; $R^2$ = $CH(OH)CH_2CH_2CH_3$), 77287-79-7; 4 ($R^1$ = $CH_3$; $R^2$ = $SiMe_3$), 77287-80-0; 4 ($R^1$ = $C_8H_{17}$; $R^2$ = $SiMe_3$), 77287-81-1; 4 ($R^1$ = $CH_3$; $R^2$ = $CO_2H$), 77287-82-2; 5 ($R^1$ = $C_4H_9$; $R^2$ = $C_8H_{17}$), 77287-83-3; 5 ($R^1$ = $CH_3$; $R^2$ = $SiMe_3$), 77287-84-4; 5 ($R^1$ = $CH_3$; $R^2$ = $CO_2H$), 21984-93-0; 5 ($R^1$ = $CH_3$; $R^2$ = $CH(OH)CH_2CH_2CH_3$), 77287-85-5; 5 ($R^1$ = $C_8H_{17}$; $R^2$ = $SiMe_3$), 77287-86-6; 1-iodooctane, 629-27-6; diphenyl disulfide, 882-33-7; trimethylsilyl chloride, 75-77-4; carbon dioxide, 124-38-9; methyl iodide, 74-88-4; butanal, 123-72-8.

# Intramolecular Reactions of Reissert Compounds

John A. Tyrell, III, and William E. McEwen*

*Department of Chemistry, University of Massachusetts, Amherst, Massachusetts 01003*

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2-[*o*-(Chloromethyl)benzoyl]-1,2-dihydroisoquinaldonitrile (1) upon treatment with base yielded 5,6,13,14-didehydro-8-oxoberbine (3). 6,7-Dimethoxyisoquinoline gave 2-[*o*-(chloromethyl)benzoyl]-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (4) which reacted with base to yield 2,3-dimethoxy-5,6,13,14-didehydro-8-oxoberbine (5). 2-(*o*-Formylbenzoyl)-1,2-dihydroisoquinaldonitrile (7) reacted with base to form phthalideisoquinoline (10).

Reissert compounds readily undergo base-catalyzed alkylation[1] and addition–rearrangement reactions with aldehydes.[2] Numerous examples of both types of reactions and their many applications in synthetic work have been

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