New Methods for the Preparation of 3-Substituted Furans[1)]

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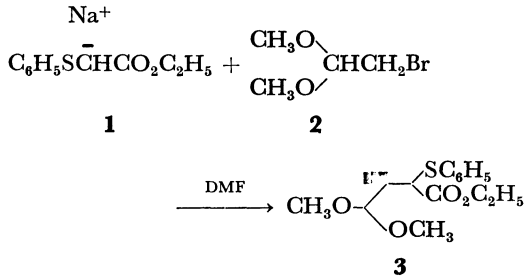
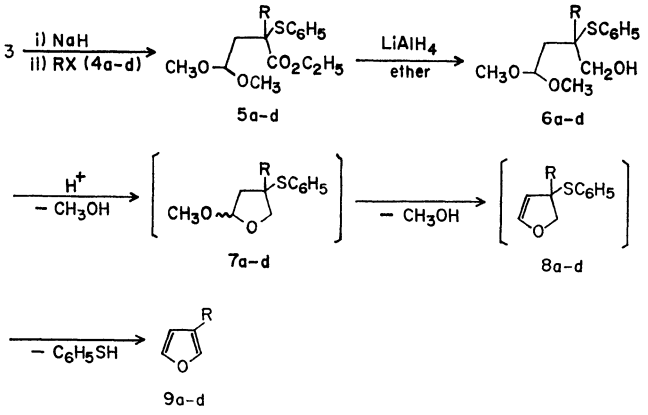
It was found that ethyl 4,4-dimethoxy-2-(phenylthio)butyrate and 3-tosylpropanal ethylene acetal are useful starting materials for the preparation of 3-substituted furans. Several 3-substituted furans, including dendrolasin [3-(4,8-dimethyl-3,7-nonadienyl)-furan], were prepared by the reaction of these compounds with alkyl halides in good yields.

It is known that a number of furan derivatives occurring in nature are 3-substituted furans such as dendrolasin [3-(4,8-dimethyl-3,7-nonadienyl)-furan]. Although some methods for the preparation of 3-substituted furan derivatives were recently reported,[2)] they require many steps or considerably complicated pathways with low overall yields. In this paper we wish to describe new convenient methods for the preparation of 3-substituted furans in three steps starting from ethyl 4,4-dimethoxy-2-(phenylthio)butyrate (Method A) and 3-tosylpropanal ethylene acetal (Method B).

Method A. The starting material, ethyl 4,4-dimethoxy-2-(phenylthio)butyrate (**3**), was readily prepared by the reaction of sodium salt of ethyl (phenylthio)acetate (**1**) with 2-bromoacetaldehyde dimethyl acetal (**2**).



The desired 3-substituted furans were synthesized from **3** and alkyl halide **4** according to the following scheme.



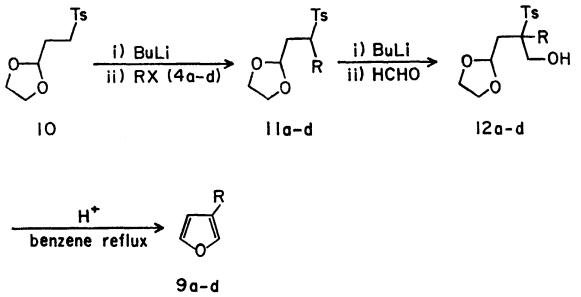
In the first place the sodium salt of **3** was allowed to react with alkyl halide in DMF at 60 °C to give the alkylated ester **5**, which was then reduced to alcohol **6** by the reaction with lithium aluminium hydride in ether at room temperature in almost quantitative yield. Finally, a benzene solution of **6** was refluxed in the presence of a catalytic amount of *p*-toluenesulfonic acid for 2 h to give the expected 3-alkylfuran **9** in good yield.

Preparation of 3-benzylfuran (**9a**), 3-octadecylfuran (**9b**), 3-geranylfuran (**9c**, nordendrolasin), and dendrolasin (**9d**) was carried out by this method (Table 1).

From the fact that the cyclic intermediate **7a** was isolated by the reaction of **6a** with an acidic catalyst at room temperature, the conversion of **6** into the corresponding 3-alkylfurans **9** appears to proceed as follows. First the cyclic intermediate **7** is formed by elimination of one molecule of methanol. By increasing temperature, another methanol is eliminated to form 3-alkyl-3-(phenylthio)dihydrofuran **8**, which has a labile phenylthio group at an allylic position and is finally converted into 3-alkylfuran **9** by elimination of benzenethiol.

Consequently, the method can be characterized by the formation of the intermediate, 4-hydroxybutanal dimethyl acetal derivative **6** having phenylthio group on C-3 as a leaving group, which is an important precursor of 3-substituted furan. This consideration provided an alternate method for the preparation of 3-substituted furans starting from crystalline 3-tosylpropanal ethylene acetal (**10**) which is accessible from acrylaldehyde, ethylene glycol, and *p*-toluenesulfinic acid.[3)]

Method B. The reduction process in Method A is not required as shown in the following scheme.



The readily available **10** was converted into lithium salt by stirring with an equimolar amount of butyllithium in tetrahydrofuran at −78 °C for 10 min under nitrogen atmosphere. Treatment of the salt with alkyl halide at −78 °C and then at room temperature gave the alkylation product **11**. Similar lithiation of **11** in tetrahydrofuran and subsequent reaction with formaldehyde gave alcohol **12** corresponding to the key intermediate **6** in Method A. In a similar way to that for **6**, a benzene solution of **12** was refluxed in the presence of a catalytic amount of *p*-toluenesulfonic acid for 3.5 h to afford 3-alkylfuran **9** in good yield. The results are given in Table 2.

Table 1. Synthesis of 3-substituted furans by method A

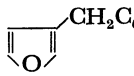
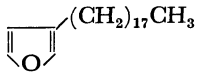
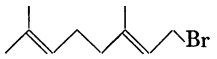
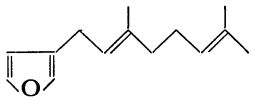
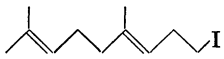
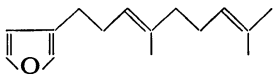
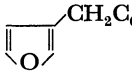
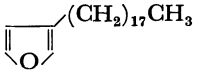
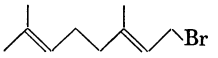
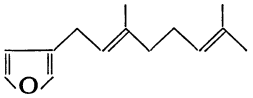
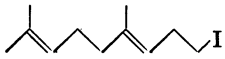
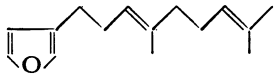
RX		Isolated yield (%) 5a—d	9a—d	
4a,	$C_6H_5CH_2Br$	82		89
4b,	$CH_3(CH_2)_{17}I$	82		83
4c,		78		83
4d,		79		81

Table 2. Synthesis of 3-substituted furans by method B

RX		Isolated yield (%) 11a—d	12a—d	9a—d	
4a,	$C_6H_5CH_2Br$	88	86		88
4b,	$CH_3(CH_2)_{17}I$	82	80		85
4c,		88	81		85
4d,		85	83		86

Experimental

All the melting points were taken with a micro melting point apparatus (Yanagimoto-Seisakusho) and are uncorrected. The proton NMR spectra were recorded on a JEOL JNM-MH 60 spectrometer. Chemical shifts are reported in terms of the δ scale relative to TMS as an internal standard. The IR spectra were taken with a JASCO IRA-1 diffraction grating infrared spectrometer.

Materials. All the solvents were distilled according to general methods and were stored over molecular sieves or sodium metal as a drying agent. Homogeranyl iodide (4,8-dimethyl-3,7-nonadienyl iodide, **4d**, bp 58—61 °C/0.002 Torr [lit,[4] bp *ca.* 80 °C/0.04 Torr]) and 3-tosylpropanal ethylene acetal (**10**, recrystallized from ethanol. mp 83—84 °C [lit,[3] mp 83—85 °C]) were prepared by the reported procedures,[3,4] respectively. Butyllithium (about 15% in hexane) was obtained from Wako Pure Chemical Industries Co. Thin-layer chromatography (TLC) was performed on Merck's Kieselgel 60 PF_{254} (Art. 7749) using a mixture of benzene and ethyl acetate as an eluent, unless otherwise stated.

*Ethyl 4,4-Dimethoxy-2-(phenylthio)butyrate (**3**).* To a suspension of sodium hydride (33 mmol) in DMF (20 ml) was added dropwise a DMF solution (10 ml) of ethyl (phenylthio)acetate (6.10 g, 31 mmol) at room temperature under nitrogen atmosphere. After 15 min, a solution of 2-bromoacetaldehyde dimethyl acetal (**2**, 5.41 g, 32 mmol) in DMF (10 ml) was added at 60 °C. The reaction mixture was then allowed to stand at 60 °C for 3.5 h. Precipitates were removed by filtration and the filtrate was concentrated under reduced pressure. The residue was treated with a pH 7.2 buffer solution, followed by extraction with ethyl acetate. The organic extract was dried over Na_2SO_4, concentrated, and distilled, giving 6.10 g (69%) of **3**: Bp 138—141 °C/1 Torr; IR 1720, 1145, 1115, 1060 cm^{-1}; NMR (CCl_4) δ 1.15 (t, 3H), 2.02 (dd, 2H), 3.23 (s, 6H), 3.63 (t, 1H), 4.04 (q, 2H), 4.42 (t, 1H), 7.24 (m, 5H).

*Ethyl 2-Benyl-4,4-dimethoxy-2-(phenylthio)butyrate (**5a**).* To a suspension of sodium hydride (1.25 mmol) in DMF (3 ml) was added dropwise a DMF solution (1 ml) of **3** (299 mg, 1.05 mmol) at 60 °C under nitrogen atmosphere. After 5 min, a solution of benzyl bromide (**4a**, 180 mg, 1.06 mmol) in DMF (1 ml) was added at 60 °C. The reaction mixture was allowed to stand at 60 °C for 3 h and then worked up according to the above procedure. The resulting residue was separated by preparative TLC to afford **5a** (322 mg, 82%) as an oil: IR 1718, 1182, 1115, 1070, 1040 cm^{-1}; NMR ($CDCl_3$) δ 1.17 (t, 3H), 2.14 (d, 2H), 3.27 (s, 2H), 3.31 (s, 3H), 3.37 (s, 3H), 4.03 (q, 2H), 4.88 (t, 1H), 7.32 (m, 10H).

In a similar way, the corresponding alkylation products **5b**, **5c**, and **5d** were obtained by the reaction of **3** with octadecyl iodide (**4b**), geranyl bromide [(*E*)-3,7-dimethyl-2,6-octadienyl bromide, **4c**], and homogeranyl iodide [(*E*)-4,8-dimethyl-3,7-nonadienyl iodide, **4d**], respectively. Spectral data of the products are as follows.

5b: Oil, IR 1725, 1145 cm^{-1}; NMR ($CDCl_3$) δ 1.17 (t, 3H), 1.22 (s, 37H), 2.03 (d, 2H), 3.21 (s, 6H), 4.01 (q, 2H), 4.67 (t, 1H), 7.23 (m, 5H).

5c: Oil, IR 1720, 1180, 1120, 1090, 1075, 1040 cm^{-1};

NMR ($CDCl_3$) δ 1.17 (t, 3H), 1.57 (s, 6H), 1.66 (s, 3H), 2.04 (m, 6H), 2.41 (d, 2H), 3.17 (s, 6H), 4.00 (q, 2H), 4.60 (t, 1H), 5.04 (broad, 1H), 5.32 (t, 1H), 7.23 (m, 5H).

5d: Oil, IR 1720, 1180, 1120, 1095, 1060, 1045 cm^{-1}; NMR ($CDCl_3$) δ 1.22 (t, 3H), 1.60 (s, 3H), 1.64 (s, 3H), 1.66 (s, 3H), 2.00 (m, 10H), 3.28 (s, 6H), 4.09 (q, 2H), 4.75 (t, 1H), 5.06 (m, 2H), 7.34 (m, 5H).

*3-Benzyl-4-hydroxy-3-(phenylthio)butanal Dimethyl Acetal (**6a**).* The ester **5a** (390 mg, 1.04 mmol) was reduced with lithium aluminium hydride (38 mg, 1.00 mmol) in ether (7 ml) at room temperature for 30 min followed by treatment with concd NaOH. The ethreal extract dried over Na_2SO_4 was evaporated and the residue was separated by preparative TLC to afford **6a** (338 mg, 98%) as an oil: IR 3460, 1112, 1038 cm^{-1}; NMR ($CDCl_3+D_2O$) δ 1.78 (d, 2H), 2.90 (s, 2H), 3.12 (s, 6H), 3.35 (s, 2H), 4.77 (t, 1H), 7.14 (m, 10H).

In other cases, the reduction products **6b—d** were not isolated. The crude products were used in the subsequent cyclization reaction.

*3-Benzylfuran (**9a**).* A benzene solution of **6a** (332 mg, 1 mmol) was refluxed in the presence of a catalytic amount of *p*-toluenesulfonic acid (*ca.* 5 mg) for 2 h. The reaction mixture was washed with 1 M NaOH and dried over Na_2SO_4. After removal of the solvent, the residue was separated by preparative TLC using hexane as an eluent to afford **9a** (143 mg, 91%) as an oil: IR 1578, 870 cm^{-1}; NMR ($CDCl_3$) δ 3.61 (s, 2H), 6.08 (m, 1H), 7.05 (m, 1H), 7.07 (s, 5H), 7.16 (t, 1H).

In a similar way, other 3-alkylfurans **9b—d** were prepared from **6b—d**. Their spectral data are as follows.

9b: Melts at near 35 °C, IR 1555, 865 cm^{-1}; NMR ($CDCl_3$) δ 0.88 (t, 3H), 1.25 (s, 32H), 2.32 (t, 2H), 6.15 (m, 1H), 7.12 (m, 1H), 7.23 (t, 1H).

9c: Oil, IR 1555, 863 cm^{-1}; NMR ($CDCl_3$) δ 1.62 (s, 3H), 1.67 (s, 6H), 2.08 (m, 4H), 3.17 (d, 2H), 5.25 (broad, 1H), 5.39 (t, 1H), 6.33 (m, 1H), 7.28 (m, 1H), 7.42 (t, 1H).

9d: Oil, The following spectra are almost identical with the published ones.[5] IR 1560, 870 cm^{-1}; NMR ($CDCl_3$) δ 1.56 (s, 6H), 1.66 (s, 3H), 1.98 (m, 4H), 2.34 (m, 4H), 4.8—5.3 (m, 2H), 6.18 (m, 1H), 7.12 (m, 1H), 7.22 (t, 1H).

*4-Benzyl-2-methoxy-4-(phenylthio)oxolane (**7a**).* A benzene solution (20 ml) of **6a** (200 mg, 0.6 mmol) was stirred in the presence of a catalytic amount of *p*-toluenesulfonic acid for 30 min at room temperature. The reaction mixture was neutralized with Na_2CO_3, washed with water, and dried over Na_2SO_4. After evaporation of the solvent, the residue was separated by preparative TLC to afford **7a** (168 mg, 93%) as an oil: IR 1100, 1025 cm^{-1}; NMR ($CDCl_3$) δ 1.9—2.2 (m, 2H), 2.85 and 2.99 (s, 2H, *ca.* 1 : 3), 3.18 and 3.21 (s, 3H, *ca.* 1 : 3), 3.79 and 3.86 (s, 2H, *ca.* 3 : 1), 4.7—5.1 (m, 1H), 7.15 (m, 10H).

*3-Benzyl-3-tosylpropanal Ethylene Acetal (**11a**).* 3-Tosylpropanal ethylene acetal (**10**, 1.31 g, 5.00 mmol) was coverted into lithium salt by stirring with an equimolar amount of butyllithium in tetrahydrofuran (25 ml) at −78 °C for 10 min under nitrogen atmosphere. After treatment of the salt with benzyl bromide (**4a**, 0.86 g, 5.02 mmol) at −78 °C and then at room temperature, the mixture was concentrated on evaporation of the solvent under reduced pressure. The residue was treated with a pH 7.2 buffer solution, followed by extraction with ethyl acetate. The organic extract was dried over Na_2SO_4 and evaporated to dryness. Recrystallization from ethanol gave **11a** (1.55 g, 88%): Mp 97—99 °C, IR 1300, 1285, 1140 cm^{-1}; NMR ($CDCl_3$) δ 2.00 (m, 2H), 2.34 (s, 3H), 2.99 (m, 2H), 3.56 (m, 5H), 4.76 (t, 1H), 7.07 (m, 5H), 7.23 (d, 2H), 7.71 (d, 2H). Found: C, 65.80; H, 6.50%. Calcd for $C_{19}H_{22}O_4S$: C, 65.88; H, 6.40%.

Products **11b—d** were prepared in a similar way, except that **11c, d** were separated by preparative TLC. Physical properties and analytical data of the products are as follows.

11b: Mp 82—83 °C, IR 1300, 1285, 1140 cm^{-1}; NMR ($CDCl_3$) δ 0.87 (t, 3H), 1.23 (s, 36H), 2.45 (s, 3H), 3.16 (m, 1H), 3.84 (m, 4H), 4.97 (t, 1H), 7.31 (d, 2H), 7.74 (d, 2H), Found: C, 70.80; H, 10.44%. Calcd for $C_{30}H_{52}O_4S$: C, 70.83; H, 10.30%.

11c: Oil, IR 1300, 1290, 1280, 1130 cm^{-1}; NMR ($CDCl_3$) δ 1.51 (s, 3H), 1.54 (s, 3H), 1.62 (s, 3H), 1.90 (m, 6H), 2.34 (s, 3H), 2.46 (m, 2H), 3.17 (m, 1H), 3.17 (m, 4H), 4.92 (m, 3H), 7.23 (d, 2H), 7.67 (d, 2H).

11d: Oil, IR 1305, 1295, 1285, 1140 cm^{-1}; NMR (CCl_4) δ 1.55 (s, 6H), 1.65 (s, 3H), 1.93 (m, 10H), 2.40 (s, 3H), 3.10 (m, 1H), 3.74 (m, 4H), 4.85 (m, 3H), 7.21 (d, 2H), 7.60 (d, 2H).

*3-Benzyl-4-hydroxy-3-tosylbutanal Ethylene Acetal (**12a**).* 3-Benzyl-3-tosylpropanal ethylene acetal (**11a**, 352 mg, 1 mmol) was converted into lithium salt in tetrahydrofuran (10 ml) according to the above procedure. Gaseous formaldehyde (generated by heating paraformaldehyde) was bubbled through a solution of the salt at −78 °C. The reaction mixture was brought to room temperature for 30 min and then concentrated on evaporation of the solvent under reduced pressure. The residue was treated with a pH 7.2 buffer solution, followed by extraction with ethyl acetate. The organic extract was dried over Na_2SO_4 and concentrated. The resulting residue was separated by preparative TLC to afford **12a**, which was further recrystallized from ethanol to give pure **12a** (328 mg, 86%): mp 61—62 °C, IR 3520, 1280, 1140 cm^{-1}; NMR ($CDCl_3+D_2O$) δ 2.03 (t, 2H), 2.39 (s, 3H), 3.14 (dd, 2H), 3.72 (m, 4H), 3.84 (dd, 2H), 4.98 (t, 1H), 7.15 (m, 5H), 7.23 (d, 2H), 7.71 (d, 2H). Found: C, 63.66; H, 6.70%. Calcd for $C_{20}H_{24}O_5S$: C, 63.82; H, 6.43%.

Products **12b—d** were prepared in a similar way. Physical properties and analytical data of the products are as follows.

12b: mp 57—59 °C, IR 3470, 1290, 1280, 1130 cm^{-1}; NMR ($CDCl_3$) δ 0.87 (t, 3H), 1.22 (s, 34H), 2.13 (d, 2H), 2.42 (s, 3H), 3.85 (m, 7H), 5.12 (t, 1H), 7.27 (d, 2H), 7.67 (d, 2H). Found: C, 69.19; H, 10.30%. Calcd for $C_{31}H_{54}O_5S$: C, 69.11; H, 10.10%.

12c: Oil, IR 3500, 1290, 1280, 1125 cm^{-1}; NMR ($CDCl_3$) δ 1.55 (s, 3H), 1.57 (s, 3H), 1.66 (s, 3H), 1.98 (m, 6H), 2.38 (s, 3H), 2.54 (m, 2H), 3.83 (m, 6H), 5.17 (m, 3H), 7.28 (d, 2H), 7.73 (d, 2H).

12d: Oil, IR 3500, 1295, 1280, 1130 cm^{-1}; NMR ($CDCl_3$) δ 1.55 (m, 9H), 1.95 (m, 10H), 2.36 (s, 3H), 3.21 (broad s, 1H), 3.79 (m, 6H), 4.7—5.3 (m, 3H), 7.24 (d, 2H), 7.67 (d, 2H).

Cyclization of **12a—d** to the corresponding 3-alkylfurans **9a—d** was performed according to the procedure described for 3-benzylfuran (**9a**).

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