Dimetalation of Furans and Thiophenes. One-Pot Procedures for Furan-2,5- and Thiophene-2,5-dicarboxaldehyde

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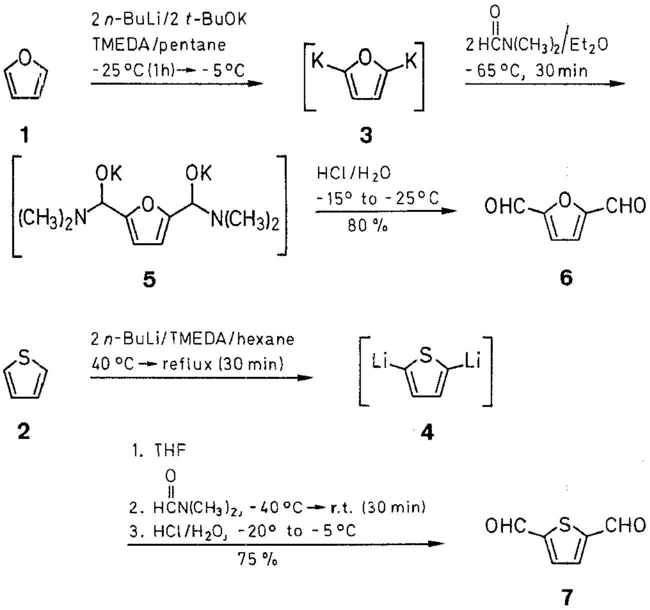
A new one-pot synthesis of furan-2,5-dicarboxaldehyde and thiophene-2,5-dicarboxaldehyde in 80% and 75% yields, respectively, via dimetalation of furan and thiophene, is described. In addition, monoprotected furan-2,5-dicarboxaldehyde was prepared in 73% yield from furfural.

Furan- and thiophene-dicarboxaldehydes have a variety of important applications,[1] for instance, in the synthesis of annulenones and polyenyl-substituted furans and thiophenes,[2] in the preparation of macrocyclic ligands of bimetallic complexes for mimicking enzymes,[3] and in crown ether chemistry.[4] Renewed interest in functionalized thiophenes and furans for natural product synthesis as well as for the synthesis of heterocyclic compounds requires quick and reliable procedures for the preparation of these starting materials.

Several routes have been developed which start from properly protected furan- or thiophene-carboxaldehydes or which are based on the oxidation of the corresponding hydroxymethyl or chloromethyl compounds.[5] A drawback of these routes is that several steps are required or low yields are obtained.[2c,5,12]

A reported three-step procedure[6] for the synthesis of furan-2,5-dicarboxaldehyde (**6**) from 2-(2-furanyl)-1,3-dimethylimidazolidine did not give reasonable yields in our hands. Efficient mono- and difunctionalization reactions have recently been achieved using strongly basic reagents.[7] In particular, use of the Schlosser-Lochmann reagent, i.e., butyllithium/potassium *tert*-butoxide, has been found to be advantageous for mono- and dimetalations. Our recent successful application of this reagent in a number of dimetalation[7,9] reactions opened an attractive possibility for a one-pot conversion of furan into 2,5-diformylfuran (**6**) according to Scheme **A**. The analogous 2,5-diformylthiophene (**7**) can be obtained from 2,5-dilithiated thiophene, generated with the butyllithium/*N*,*N*,*N'*,*N'*-tetramethylethylenediamine (TMEDA) reagent.[14]



Scheme A

In our one-pot procedure for the preparation of dialdehyde **6**, furan (**1**) was dimetalated (presumably to 2,5-dipotassiofuran, **3**) using butyllithium, potassium *tert*-butoxide (ratio 1:1), and TMEDA in hexane. Subsequent addition of dimethylformamide followed by hydrolysis of the adduct **5** with cold dilute hydrochloric acid afforded **6** in 80% yield. The mode of hydrolysis of intermediate **5** is very critical, since product **6** seems to be extremely base-sensitive; immediate neutralization of all base is essential.

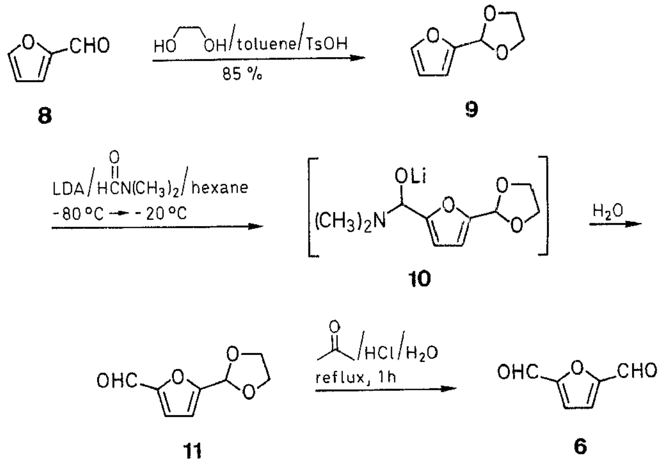
Thiophene-2,5-dicarboxaldehyde (**7**) was obtained in a similar way in 75% yield from 2,5-dilithiothiophene generated according to Ref. 14 (see also Ref. 7).

Spectroscopic and analytical data of products **6** and **7** are in full conformity with the proposed structures. In addition, both compounds were prepared independently by known procedures.[5]

The procedures described here can also be applied to the introduction of various other substituents at the 2- and 5-positions of **1** and **2**.[7] Thus, 2,5-bis(methylthio)furan is obtained in 78% yield from intermediate **3** and dimethyl disulfide while 2,5-bis(trimethylsilyl)thiophene is formed in 90% yield when intermediate **4** is treated with excess chlorotrimethylsilane.

In order to prepare the *mono-protected* furan-2,5-dicarboxaldehyde **11** and as an alternative route to **6**, a two-step sequence from furfural (**8**) was elaborated. 2-(2-Furanyl)-1,3-dioxolane (**9**) was metalated with lithium diisopropylamide at −80 °C; subsequent treatment with excess dimethylformamide afforded 2-(5-formyl-2-furanyl)-1,3-dioxolane (**11**) in 85% yield (Scheme **B**). It is essential to keep the reaction temperature below −60 °C during the whole procedure; otherwise, substantial amounts of starting material **9** will be recovered. This might be due to the temperature dependency of the metalation equilibrium.[10]

The formation of dialdehyde **6** in 66% overall yield from furfural (**8**) represents a considerable improvement as compared with reported procedures which also use furfural as starting material.[5,6]



Scheme B

Further, the mono-protected furandicarboxaldehyde **11** can be prepared in 85 % yield. The mono- and bis-metalation reactions described here should be applicable to the synthesis of various other 2,5-disubstituted furan and thiophene derivatives.

All reactions were carried out in dried glassware under a nitrogen atmosphere. Tetrahydrofuran was distilled from Na (benzophenone) under N_2. Diisopropylamine was dried with solid KOH and dry TMEDA was obtained by distillation from $LiAlH_4$ at ~136 mbar. Furan, thiophene, and furfural were distilled prior to use. For further general remarks concerning procedures, see Ref. 7, pp. 3–23.

Mass spectra were obtained on an AEI MS902 spectrometer. IR spectra were recorded on a P-Unicam Sp-200. ^{1}H- and ^{13}-C-NMR spectra were recorded on Hitachi Perkin Elmer R24B and Nicolet NT200 spectrometers, respectively.

Furan-2,5-dicarboxaldehyde (2,5-Diformylfuran, 6):

Method A, from Furan: In a 1000 mL flask (for details, see Ref. 7, p. 9) are placed pentane (80 mL), *t*-BuOK (15 g, 0.13 mol), and TMEDA (16 g, 0.13 mol). The flask is filled with N_2 whereupon the mixture is cooled to – 60 °C. To the stirred suspension is then added, via syringe, a hexane solution of butyllithium (0.13 mol in 87 mL hexane) while keeping the temperature below – 40 °C. Stirring is continued at – 40 °C for 10 min, the suspension is then cooled to – 50 °C, and a solution of furan (3.4 g, 0.05 mol) in pentane (20 mL) is added all at once. The mixture is stirred at – 25 °C for 1 h and at – 15 °C for 30 min. The temperature is then raised to – 5 °C, Et_2O (100 mL) is added, the mixture is cooled to – 65 °C, and DMF (5.57 g, 0.15 mol) is added dropwise over a 10 min period. The temperature of the mixture is raised to + 15 °C over 30 min.

A mixture of 30% aqueous HCl (110 g) and H_2O (200 mL) in a 3000 mL flask equipped with an efficient stirrer is cooled to – 20 °C under N_2. Into this stirred HCl solution, the above described mixture is injected by syringe. It is essential that the injection is done just above the surface of the aqueous solution at 2–3 cm from the wall of the vessel to ensure efficient mixing and instanteneous neutralization of the base liberated.

The temperature should be kept between – 15 and – 25 °C. Inefficient mixing results in the formation of substantial quantities of intractable brown resins. The temperature of the mixture is then raised to 0 °C and the layers are separated. The organic layer is washed with H_2O (2 × 20 mL) and the combined aqueous layers are extracted with $CHCl_3$ [35(!) × 20 mL]. The combined organic layers are dried (sufficient quantity of $MgSO_4$; the use of excess drieryte should be avoided as it leads to substantial loss due to adsorption of the dialdehyde). Removal of the solvent by rotary evaporation (temperature below 45 °C) and of traces of H_2O in vacuo (< 1.0 mbar, temperature < 40 °C) yields a light-yellow solid (7.5 g).

Crystallization from $CHCl_3/Et_2O$ (30 mL + 100 mL) at – 25 °C gives pure **6**; yield: 4.95 g (80 %); mp 109 °C. (Lit.[11] mp 109–110 °C).

$C_6H_4O_3$	calc.	C 58.07	H 3.23
(124.1)	found	57.99	3.50
		57.82	3.31

Exact Mass: calc. 124.016 found 124.017.

IR (CCl_4): ν = 1680, 1170, 1020 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 7.30 (s, 2 H); 9.75 (s, 2 H).

^{13}C-NMR ($CDCl_3$/TMS): δ = 119.30 (d); 154.00 (s); 179.00 (d).

Method B, from Furfural:

2-(2-Furanyl)-1,3-dioxolane (**9**): Prepared following the known procedure[13] with slight modifications (toluene as solvent and pyridinium tosylate as catalyst); yield of pure **9**: 85 %.

2-(5-Formyl-2-furanyl)-1,3-dioxolane (**11**): A solution of butyllithium (50 mL, 0.075 mol) in hexane is added dropwise at – 20 °C to diisopropylamine (0.080 mol) under N_2, and the mixture is stirred for 15 min. Then, THF (60 mL) is added, the solution is cooled to – 80 °C, 2-(2-furanyl)-1,3-dioxolane (**9**; 7.5 g, 0.0536 mol) dissolved in THF (25 mL) is added dropwise, and stirring is continued for 30 min. During the whole operation, the reaction temperature is kept at – 80 °C. At this temperature, DMF (50 mL) is added, and the mixture stirred for 12 h during which period the temperature is allowed to gradually rise to 20 °C. Ether (200 mL) is added, and the organic solution is washed with H_2O (3 × 150 mL), and dried ($MgSO_4$). The solvent is removed *in vacuo* and some starting material **9** is recovered at 100 °C/29 mbar. Distillation affords pure **11** as a colorless oil; yield: 7.65 g (85 %); bp 120 °C/0.06 mbar.

Exact Mass ($C_8H_8O_4$): calc. 168.042 found 168.042.

IR (CCl_4): ν = 2950, 2870, 2800, 1675, 1340, 1190, 1100 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 4.00 (m, 4 H); 5.95 (s, 1 H); 6.35 (d, 1 H, J = 4.5 Hz); 7.30 (d, 1 H, J = 4.5 Hz); 9.65 (s, 1 H).

^{13}C-NMR ($CDCl_3$/TMS): δ = 54.3 (t); 97.6 (d); 110.5 (d); 120.62 (d); 152.70 (s); 157.08 (s); 177.96 (d).

Furan-2,5-dicarboxaldehyde (**6**): The acetal **11** (2.27 g, 0.014 mol) is dissolved in a mixture of acetone (150 mL) and 6 N HCl (10 mL) and this solution is stirred and heated at reflux for 1 h. The major part of the solvent is removed *in vacuo* and to the residue is added CH_2Cl_2 (150 mL). This organic solution is washed with 15 % aq K_2CO_3 (3 × 100 mL), H_2O (100 mL), and dried ($MgSO_4$; see previous remarks). The solvent is removed *in vacuo*, and the remaining solid is crystallized from cyclohexane/$CHCl_3$ to afford pure **6** as a yellow solid; yield: 1.56 g (90 %); mp 109 °C.

Alternatively, acetal **11** (0.014 mol) is dissolved in acetone (150 mL) containing 1 % H_2O and a catalytic amount of pyridinium tosylate (1 mol%), and this mixture is stirred under reflux for 12 h. To the solution is added CH_2Cl_2 (150 mL) and the organic solution is washed with 5 % aq K_2CO_3 (3 × 100 mL), H_2O (100 mL), and dried ($MgSO_4$). Further isolation as described.

2,5-Bis(methylthio)furan:

Following the procedure of Method A but adding a solution of dimethyl disulfide (0.15 mol) in Et_2O (100 mL) at – 60 °C instead of DMF. The temperature of the mixture may raise above 0 °C. Stirring is continued for 5 min, then ice water (150 mL) is added with vigorous stirring. The layers are separated, and the organic layer is washed with water (4 × 20 mL). The washings are combined with the first aq layer and extracted with hexane or light petroleum (2 × 30 mL). These extracts are washed with water (20 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The residue is distilled; yield: 7.20 g (90 %); bp 100 °C/19 mbar. (see also, Ref. 7, p. 165).

Thiophene-2,5-dicarboxaldehyde (7):

A suspension of 2,5-dilithiothiophene (**4**) is prepared by the addition of butyllithium (0.12 mol in 85 mL hexane) at room temperature to a mixture of TMEDA (13.9 g, 0.12 mol), thiophene (8.4 g, 0.10 mol), and hexane (30 mL) (cf. Ref. 14). The temperature of the white suspension is allowed to rise to 40 °C and the conversion is completed by refluxing the mixture for 30 min. Then, THF (120 mL) is added, the solution is cooled to – 40 °C, and excess DMF (0.27 mol) is added over a 10 min period. The temperature of the mixture is gradually raised to room temperature and stirring is continued for 30 min. The suspension is then poured into a mixture of 30 % HCl (200 g) and H_2O (1700 mL) at – 20 to – 5 °C under vigorous stirring. Part of the dialdehyde may separate during this hydrolysis. Saturated $NaHCO_3$ solution is slowly added until the aqueous layer has reached pH 6. The organic layer is separated and the aqueous layer extracted with Et_2O (7 × 50 mL). The organic solution is dried ($MgSO_4$), the solvent removed *in vacuo*, and the product crystallized from THF/Et_2O (4 : 1) to afford pure **7**; yield: 10.5 g (75 %); mp 109–112 °C (Lit.[12] mp 109–114 °C).

2,4-Bis-(Trimethylsilyl)thiophene:

The preparation of this compound is described in Ref. 7, p. 164.

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