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

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A reported three-step procedure for Furan-2,5- and Thiophene-2,5-dicarboxaldehyde achieved using strongly basic reagents. Mono- and difunctionalization reactions have recently been achieved using strongly basic reagents. 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 reactions opened an attractive possibility for a one-pot conversion of furan into 2,5-diformylfurans (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'-tetramethylethlenediamine (TMEDA) reagent.14

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-dilithiophiene 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. 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-Furany1)-1,3-dioxolane (9) was metalated with lithium diisopropylamide at –70 °C; subsequent treatment with excess dimethylformamide afforded 2-(5-formyl-2-furany1)-1,3-dioxolane (11) in 85 % yield (Scheme B). It is essential to keep the reaction temperature below –70 °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 equilibriunm.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.1,6

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, for instance, in the synthesis of annulenes and polyenyl-substituted furans and thiophenes, in the preparation of macrocyclic ligands of bimetallic complexes for mimicking enzymes, and in crown ether chemistry. Important applications, for instance, in the synthesis of an-
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 N₂. Disopropylamine was dried with solid KOH and dry TMEDA was obtained by distillation from LiAlH₄ at –136 mbar. Furan, thiophene, and furfural were distilled prior to use. For further general remarks concerning procedures, see Ref. 7, pp. 3–23.

A solution of 2-(5-formyl-2-furanyl)-1,3-dioxolane (11) was prepared by the addition of butyllithium (0.13 mol in 87 mL hexane) to diisopropanolamine (0.075 mol) in hexane is added dropwise at –20°C to diisopropanolamine (0.080 mol) under N₂ and the mixture is stirred for 15 min. Then, THF (60 mL) is added, the solution is cooled to –80°C, 2-(5-furfuryl-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 is allowed to stand for 12 h during which period the temperature is allowed to gradually rise to 20°C.

Either (200 mL) is added, and the organic solution is washed with H₂O (3 × 150 mL), and dried (MgSO₄). 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 (C₁₄H₂₂O₄): calc. 248.158 found 248.158. IR (CCl₄): ν = 2950, 2870, 2800, 1675, 1340, 1100 cm⁻¹. ¹H-NMR (CDCl₃/TMS): δ = 3.90 (s, 1 H); 7.25 (d, 2 H, J = 8.0 Hz); 8.05 (d, 2 H, J = 8.0 Hz). The product is a mixture of 9:45% and 10:55%.

2-5-dicarbonylaldehydes (2,5-Diformylfuran, 6): This organic solution is washed with 15% aq K₂CO₃ (3 × 100 mL), H₂O (100 mL), and dried (MgSO₄; see previous remarks). The solvent is removed in vacuo, and the remaining solid is crystallized from cyclohexane/CHCl₃ to afford pure 6 as a yellow solid; yield: 1.56 g (90%); mp 100°C.

Alternatively, acetal 11 (0.014 mol) is dissolved in a mixture of acetone (150 mL) and 6 N HCl (10 mL) and this mixture 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 CH₂Cl₂ (150 mL). This organic solution is washed with 15% aq K₂CO₃ (3 × 100 mL), H₂O (100 mL), and dried (MgSO₄; see previous remarks). 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 Et₂O (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 (MgSO₄), and concentrated in vacuo. The residue is distilled; yield: 7.20 g (90%); bp 100°C/19 mbar. (see also, Ref. 7, p. 165.)


(9) Brandsma, L., unpublished results.