Polish J. Chem., **75**, 1943–1946 (2001) **COMMUNICATION**

Convenient Synthesis of Furan-2,5-dicarboxylic Acid and Its Derivatives

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(Received May 25th, 2001; revised manuscript July 26th, 2001)

Furan-2,5-dicarboxylic acid (**1**) is a well known starting material for the synthesis of polymers with interesting properties [1–4], widely used in pharmacology too. Its diethyl ester has strong anaesthetic action similar to cocaine [5], its calcium salt inhibits the growth of *Bacillum megatorrum* spora [6]. Variously substituted dianilides [7] are antibacterial agents. That is why studies on synthesis of 2,5-furandicarboxylic acid (**1**) have been largely performed, resulting in methods based on oxidative conversions of various furan derivatives [8–10] or the dehydration of mucic acids (**2**) with hydrobromic acid [11].

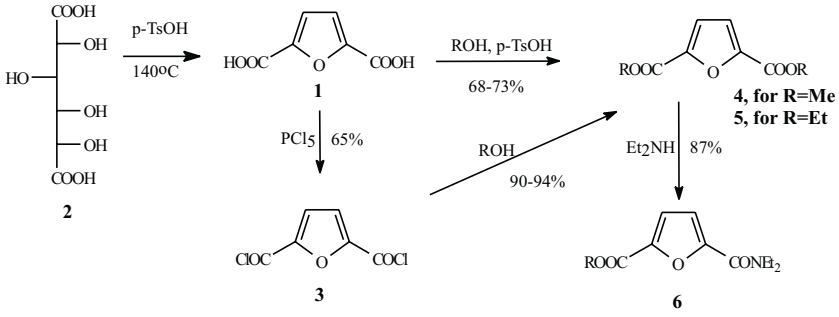
On the other hand, there are not many papers dealing with the preparation of its derivatives. Furan-2,5-dicarboxylic acid dichloride (**3**) was synthesized for the first time in 1882 by the action of acetyl chloride on diacid **1** [12], and till now, only two further methods, using thionyl chloride, have been published [9,13]. Dimethyl and diethyl esters (**4** and **5**) were synthesized directly from diacid (**1**) by the action of corresponding alcohols with strong mineral acids [14–17], or in the reaction of diacid (**1**) and diazomethane [18].

In this paper, convenient and easy methods of preparation of furan-2,5-dicarboxylic acid (**1**), its dichloride (**3**), dimethyl (**4**) and diethyl (**5**) furan-2,5-dicarboxylates are presented. The first preparation of 5-methoxycarbonyl-N,N-diethylfuramide (**6**) is also reported.

The diacid **1** was obtained in 53% yield by dehydration of mucic acid (**2**) by p-toluenesulfonic acid. The use of p-toluenesulfonic acid instead of mineral acids makes the reactions easier in manipulating. Dichloride (**3**) was prepared by treating furan-2,5-dicarboxylic acid (**1**) with phosphorus pentachloride in 65% yield. Its preparation was carried out without a solvent, which is advantageous in regard of the published method, where attempts to use phosphorus pentachloride in benzene were made [12].

Both esters **4** and **5** were synthesized in two different ways. One of them gave dimethyl and diethyl furan-2,5-dicarboxylate **4** and **5** by refluxing dichloride **3** in corresponding alcohol in 90 and 94% yields, respectively (Scheme 1). When furan-2,5-dicarboxylic acid (**1**) was refluxed in methanol and ethanol in the presence of p-toluenesulfonic acid, methyl and ethyl esters were obtained in 68 and 73% yields, respectively (Scheme 1).

Scheme 1



5-Methoxycarbonyl-N,N-dimethylfuramide (**6**) was obtained in 87% yield in the reaction of dimethyl furan-2,5-dicarboxylate (**4**) and diethylamine in methanol at room temperature. In such a type of the reaction one should rather expect the formation of diamide, but, surprisingly, the product of mono-substitution was obtained. The prolonged time of the reaction to 7 hours did not lead to the formation of the diamide. When the mixture was refluxed for 5 hours, *ca* 5% of the diamide was detected. Prolonged heating caused the decomposition of the furan reagent.

Such a result of the reaction is probably due to the counteraction between the ester and the amide groups in the molecule of 5-methoxycarbonyl-N,N-diethylfuramide (**6**). This is not a separate case, because the counteraction between two formyl groups in furan-2,5-dicarbaldehyde in various reactions was reported [19,20]. A significant resistance of 5-formyl-2-furancarboxylic acid towards the oxidation with nitric acid was observed [21] and the counteraction between the formyl and the carboxylic group was evident.

All solvents (PROLABO) were distilled and dried. Phosphorus pentachloride (MERCK), diethylamine, p-toluenesulfonic and mucic acids (FLUKA) were used as received. Spectra were recorded on a NICOLET 205 (FT-IR) and a BRUKER 200 MHz (^{1}H NMR) and 50 MHz (^{13}C NMR) spectrometers.

Synthesis of furan-2,5-dicarboxylic acid (2). Mucic acid (5 g, 0.0238 mol) and p-toluenesulfonic acid monohydrate (15.85 g, 0.0833 mol) were stirred at 140°C for 2 hrs. Then, after cooling, 4% aqueous calcium chloride (300 mL) was added and the formed solution was stirred at 100°C for 1 hour. Then, it was filtered and 100 mL of concentrated hydrochloric acid was added to yield 2 g (52%) of **2** as almost white crystals not melting below 320°C as it was reported [11]. IR (KBr): 3150 (OH), 1690 (C=O), 1590, 1560, 1410 (C_{furan}) cm^{-1}; ^{1}H NMR (CD_3SOCD_3): δ 12.10 (large s, COOH, 1H); 7.28 (s, =CH-CH=, 2H); ^{13}C NMR (CD_3SOCD_3): δ 118.36 (C_{furan}), 146.94 (C_{furan}), 158.61 (COOH).

Synthesis of furan-2,5-dicarboxylic acid dichloride (3). Furan-2,5-dicarboxylic acid (1.56 g, 0.01 mol) and phosphorus pentachloride (5.2 g, 0.025 mol) were stirred at 90°C for 2 hrs. Then, the resulting liquid was allowed to cool and 150 mL of petroleum ether was added to precipitate the solid, which was collected by filtration. Then

the solid was dissolved in 10 mL of chloroform, filtered and re-precipitated by adding 50 mL of petroleum ether to yield 6.27g (65%) of **3** as white crystals, m.p. 80–81°C, lit. [12] 80°C. IR (KBr): 1810 (C=O), 1550, 1500, 1380 (C_{furan}), 1200, 640 (C-Cl) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.52 (s, =CH-CH=).

Synthesis of 2,5-furandicarboxylates 4 and 5. Method A: Furan-2,5-dicarboxylic acid dichloride (1.93 g, 0.01 mol) was dissolved in 20 mL of alcohol and the mixture was refluxed for 2 hrs. Then the solvent was removed, the solid residue was recrystallized from methanol to yield 1.66 g (90%) of **4** as white crystals, or from petroleum ether to yield 2 g (94%) of **5** as almost white crystals. **Method B:** Furan-2,5-dicarboxylic acid (1.56 g, 0.01 mol) was suspended in 20 mL of alcohol, then p-toluenesulfonic acid monohydrate (4.75 g, 0.025 mol) was added. The mixture was refluxed for 3 hrs, then it was filtered, the solvent was removed and 20 mL of water was added, precipitate was collected and recrystallized as above to give 1.25 g (68%) of **4** or 1.55 g (73%) of **5** as white crystals identical to samples above.

Dimethyl furan-2,5-dicarboxylate (4): m.p. 110–111°C, lit. [16] 112°C; IR (KBr): 1717 (C=O), 1586, 1537, 1437 (C_{furan}), 1122 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.94 (s, CH_3, 3H), 7.22 (s, =CH-CH=, 2H).

Diethyl 2,5-furandicarboxylate (5): m.p. 46–48°C, lit. [17] 47°C; IR (KBr): 1740 (C=O), 1570, 1500, 1380 (C_{furan}), 1280, 1230, 1160 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.39 (t, J = 6.9 Hz, CH_3, 3H), 4.40 (q, J = 6.9 Hz, CH_2, 2H), 7.20 (s, =CH-CH=, 2H).

Synthesis of 5-methoxycarbonyl-N,N-diethylfuramide (6). Dimethyl furan-2,5-dicarboxylate (0.46 g, 0.025 mol) and diethylamine (0.6 mL, 0.05 mol) were dissolved in 15 mL of methanol. The mixture was stirred at room temperature for 3 hrs. Then the solvent was removed and the solid residue was dissolved in methanol. The formed solution was filtered and evaporated to give 0.47 g (87%) of **6** as white crystals, m.p. 52–53°C. IR (KBr): 1729 (C=Oester), 1601 (C=Oamide), 1500, 1455, 1380 (C_{furan}) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.33 (t, J = 7.2 Hz, $CH_2\underline{CH_3}$, 3H), 3.18 (q, J = 7.2 Hz,CH_2, 2H), 3.66 (s, CH_3, 3H), 7.01 (d, J = 3.7 Hz, =CH-CH=, 1H), 7.15 (d, J = 3.7 Hz, =CHCH=, 1H). Anal: Calcd for $C_{11}H_{15}NO_4$: C, 58.67; H, 6.67; N, 6.22. Found: C, 58.72; H, 6.71; N, 6.14.

Acknowledgment

I thank Prof. A. Gaset and Dr. L. Rigal for allowing to work in their laboratory.

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