A Simple Preparation of Ethyl 2,5-Dimethylfuran-3-Carboxylate and 2,5-Dimethylfuran-3,4-Dicarboxylic Acid from Diethyl 2,3-Diacetylsuccinate

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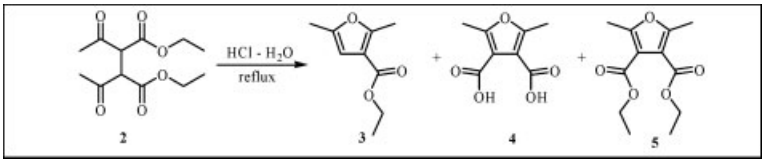

A simple preparation of ethyl 2,5-dimethylfuran-3-carboxylate (**3**), 2,5-dimethylfuran-3,4-dicarboxylic acid (**4**), and diethyl 2,5-dimethylfuran-3,4-dicarboxylate (**5**) by treatment of diethyl 2,3-diacetylsuccinate (**2**) with aqueous HCl is reported. The reaction is performed under organic solvent free conditions from a readily available cheap starting material.

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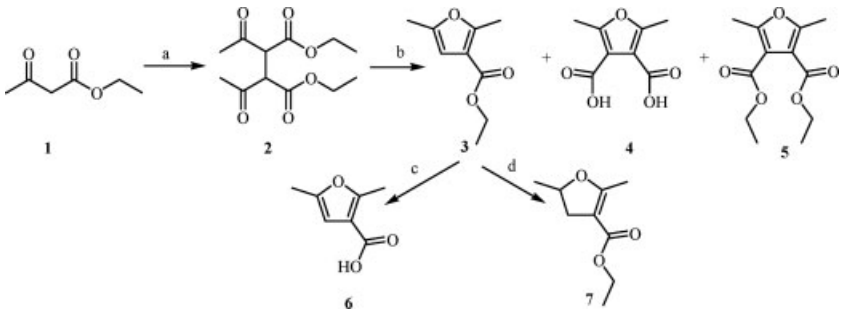
INTRODUCTION

Highly substituted furans play an important role as structural elements of many pharmaceutical and natural substances [1]. Moreover, they are useful building blocks in synthetic organic chemistry [2]. Especially, ethyl 2,5-dimethylfuran-3-carboxylate (**3**) (Scheme 1) is an important trisubstituted furan. Its derivatives have been used as wood preservatives [3], microbicides, insecticides [4], and fungicides [5]. 2,5-Dimethylfuran-3,4-dicarboxylic acid (**4**) and diethyl 2,5-dimethylfuran-3,4-dicarboxylate (**5**) are also useful intermediates in medicinal chemistry and organic synthesis [6–8]. Among the different approaches to multiply substituted furans [9–15], there are some methods for the preparation of **3**, such as gold(I) catalyzed cascade reaction of propargyl Claisen rearrangement and heterocyclization of propargyl vinyl ethers [1], polymer-supported selenium-induced electrophilic cyclization [16], I_2-induced cyclization of 2-alkenyl substituted 1,3-dicarbonyl compounds [17], treatment of α,β-unsaturated ketones with *N*-bromosuccinimide followed by cyclization [18], and treatment of ethyl 2-acetyl-4-oxopentanoate with montmorillonite clay in toluene at reflux with water removal [5]. Some methods require expensive reagents and some use unreadily accessed starting materials or hazardous organic solvents. Thus, the development of convenient strategies is still of considerable interest. We now wish to report a simple preparation of trisubstituted furan (**3**) starting from diethyl 2,3-diacetylsuccinate (**2**) by decarboxylation and subsequent Paal–Knorr cyclization [19–21] in aqueous HCl. Using this procedure, trisubstituted furan (**3**) and tetrasubstituted furan (**4**) or (**5**) can be easily prepared at will by adjusting the concentrations of aqueous HCl. The reaction is simple to perform, and the starting material is cheap and readily available.

RESULTS AND DISCUSSION

Diethyl 2,3-diacetylsuccinate (**2**) (Scheme 1) was prepared according to literature from ethyl acetoacetate (**1**) using sodium in diethyl ether followed by treatment with iodine at room temperature [22]. In our initial exploration, treatment of **2** with 0.4*N* aqueous HCl at reflux for 14–15 h in oil bath afforded trisubstituted furan monoester (**3**) and tetrasubstituted furan diacid (**4**), in 30–50% and 40–60% yields, respectively. Different aqueous HCl concentrations were further compared for the reaction under both oil bath heating and microwave irradiation (Table 1). When **2** was treated with 6*N* aqueous HCl or 3*N* aqueous HCl, tetrasubstituted furan diacid (**4**) was obtained as the only product in excellent to quantitative yields. Whereas using dilute aqueous HCl, trisubstituted furan monoester (**3**) was obtained. The highest yield of **3** was observed in 57% under oil bath heating in 0.3*N* aqueous HCl, and 50% under microwave irradiation in 0.2*N* aqueous HCl. Interestingly, tetrasubstituted furan ester (**5**) was obtained only under microwave irradiation possibly because of the shorter reaction time.

Scheme 1. Reaction conditions: (a) (i) Na, Et_2O, r.t., 12 h, (ii) I_2, Et_2O, r.t., 4 h, 66%; (b) HCl-H_2O, reflux under oil bath heating or under microwave irradiation; (c) 5% NaOH, reflux, 5 h, 96%; (d) H_2, 5% Pd/C, EtOH-H_2O, 4d, 90%.



A previous report by Fales *et al*. described the formation of diethyl 2,5-dimethylfuran-3,4-dicarboxylate (**5**) from diethyl 2,3-diacetylsuccinate (**2**) by using concentrated H_2SO_4 in CCl_4 [23]. In our procedure, tetra- or trisubstituted furans can be easily prepared by using different aqueous HCl concentrations. The product selectivity appears to be controlled by acid concentrations. More dilute aqueous HCl can provide trisubstituted furan monoester (**3**) probably through decarboxylation and subsequent Paal–Knorr dehydrative cyclization. Meanwhile, higher concentrations of aqueous HCl gave tetrasubstituted furan diacid (**4**) as main or even only product possibly through Paal–Knorr cyclization and subsequent hydrolysis. It is notable that no decarboxylation was observed under more acidic conditions. We think that it is possibly because the higher concentrations of aqueous HCl can accelerate dehydrative cyclization step to form furan ring before decarboxylation, and the resulting conjugated system between the furan ring and dicarbonyl groups is strong enough to prevent it from decarboxylation under employed reaction conditions. Actually, no decarboxylation of **4** was observed in our investigation. Therefore, compound **4** would be the major product if cyclization is faster than decarboxylation, otherwise **3** would be the major one.

To confirm the structure of **3**, the hydrolysis of **3** with 5% aqueous NaOH was performed to afford 2,5-dimethylfuran-3-carboxylic acid (**6**) as crystals (Scheme 1). The X-ray crystallographic analysis of **6** was shown in Figure 1 [24].

Moreover, we investigated the selective hydrogenation of **3**. Treatment of **3** with 5% Pd/C in EtOH-H_2O at H_2 atmosphere for 4 days yielded dihydrofuran **7** as the only product in excellent yield (Scheme 1). This selective hydrogenation is a useful approach for dihydrofurans which are also important structural elements of many pharmaceutical and natural products [16,25–27].

The procedure described earlier is a practical method for the preparation of trisubstituted furan **3**. Although **3** was obtained in medium yield, it is still a valuable approach because the starting material is a readily accessed symmetrically substituted 1,4-dicarbonyl compound. Moreover, using this procedure trisubstituted furan (**3**) and tetrasubstituted furan (**4** or **5**) can be easily prepared at will by adjusting the concentrations of

Table 1

Comparison of different HCl concentrations as reagents for diethyl 2,3-diacetylsuccinate (**2**) cyclization.

Entry	Concentration of HCl (*N*)	Reaction condition	Reaction time (h)	Yield (%)[a]		
				3	**4**	**5**
1	6	Oil bath	14		89	
2	3	Oil bath	14		91	
3	1	Oil bath	14	3	82	
4	0.5	Oil bath	14	8	86	
5	0.4	Oil bath	15	50	40	
6	0.3	Oil bath	15	57	38	
7	0.2	Oil bath	15	41	58	
8	0.1	Oil bath	15	44	52	
9	H_2O	Oil bath	15			
10	3	Microwave	1		100	
11	1	Microwave	1	20	24	52
12	0.4	Microwave	2	21		61
13	0.3	Microwave	2	39		52
14	0.2	Microwave	2.5	50		46
15	0.1	Microwave	2.5	38		56
16	H_2O	Microwave	3			

[a] Refers to yield of isolated product.

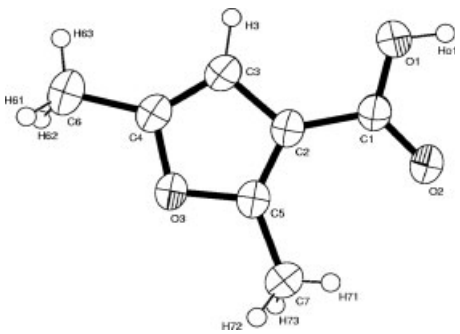


Figure 1. X-ray crystallographic analysis of **6**.

aqueous HCl under organic solvent free conditions. Both conventional and microwave heating were investigated for this method.

EXPERIMENTAL

General methods. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker AV-300 spectrometer with TMS as an internal standard. The chemical shifts (δ) are given in ppm, and the coupling constants (*J*) in hertz (Hz). X-ray diffraction analysis was performed on a Bruker P4 X-ray diffraction meter. Melting points were determined on an X-4 digital display micro melting point apparatus and were uncorrected. Unless otherwise noted, all reagents were obtained from commercial suppliers and were used without further purification. Organic solvents used were dried by standard methods when necessary. All reactions were monitored by TLC with Haiyang GF254 silica gel plates. Flash column chromatography was carried out using 200–300 mesh silica gel at increased pressure.

Ethyl 2,5-dimethylfuran-3-carboxylate (3) and 2,5-dimethylfuran-3,4-dicarboxylic acid (4). A solution of diethyl 2,3-diacetylsuccinate (**2**) (145 mg, 0.56 mmol) in aqueous HCl (0.4*N*, 1.8 mL) was refluxed for 15 h in oil bath. After cooling to r.t., the reaction mixture was extracted with diethyl ether thoroughly. The combined extracts were washed with water, brine, dried (Na_2SO_4), and filtered. The solvents were removed and the residue was purified by flash chromatography (petroleum ether/diethyl ether 5:1, then pure diethyl ether) to give compound **3** (47 mg, 50%) as colorless oil, and compound **4** (41 mg, 40%) as white crystals.

Compound 3. ^{1}H NMR ($CDCl_3$) δ 1.33 (t, 3H, $J = 7.1$ Hz), 2.36 (s, 3H), 2.52 (s, 3H), 4.26 (q, 2H, $J = 7.1$ Hz), 6.21 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.2, 13.7, 14.5, 60.0, 106.3, 114.2, 150.0, 157.6, 164.4. Identical to that previously reported [28].

Compound 4. Mp 214–216°; ^{1}H NMR (CD_3COCD_3) δ 2.60 (s, 2 × 3H); ^{13}C NMR (CD_3COCD_3) δ 14.5, 112.4, 161.5, 166.6. Spectroscopic data were in accordance with commercially available material.

Diethyl 2,5-dimethylfuran-3,4-dicarboxylate (5). A solution of **2** (243 mg, 0.94 mmol) in aqueous HCl (0.4*N*, 3.3 mL) was refluxed under atmospheric pressure for 2 h within a synthetic microwave reactor (Sineo microwave MAS-II), which was equipped with a condenser and set at 100°. After cooling to r.t., the reaction mixture was extracted with diethyl ether thoroughly. The combined extracts were washed with water, brine, dried (Na_2SO_4), and filtered. The solvents were removed and the residue was purified by flash chromatography (petroleum ether/diethyl ether 5:1) to give compound **5** (138 mg, 61%) as colorless oil, and compound **3** (51 mg, 21%) as colorless oil.

Compound 5. ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 2 × 3H, $J = 7.1$ Hz), 2.43 (s, 2 × 3H), 4.29 (q, 2 × 2H, $J = 7.1$ Hz); ^{13}C NMR ($CDCl_3$) δ 13.0, 13.8, 60.5, 113.6, 155.5, 163.5. Identical to that previously reported [14].

2,5-Dimethylfuran-3-carboxylic acid (6). A solution of **3** (76 mg, 0.41 mmol) in aqueous NaOH (5%, 3 mL) was refluxed for 5 h. After cooling to r.t., the solution was treated with aqueous HCl to make pH = 3. The reaction mixture was extracted with diethyl ether thoroughly. The combined extracts were washed with water, brine, dried (Na_2SO_4), and filtered. The solvents were removed to obtain compound **6** (61 mg, 96%) as white crystals, mp 131–132°; ^{1}H NMR ($CDCl_3$) δ 2.26 (s, 3H), 2.55 (s, 3H), 6.25 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.3, 14.0, 106.4, 113.5, 150.4, 159.5, 169.9. Identical to that previously reported [29].

Ethyl 2,5-dimethyl-4,5-dihydrofuran-3-carboxylate (7). A mixture of **3** (230 mg, 1.25 mmol) and 5% Pd/C (146 mg) in EtOH-H_2O (6:1, 3 mL) was vigorously stirred at r.t. at H_2 atmosphere under ordinary pressure for 4 days. The reaction mixture was extracted with diethyl ether. The combined extracts were washed with water, brine, dried (Na_2SO_4), and filtered. The solvents were removed and the residue was purified by flash chromatography (petroleum ether/diethyl ether 20:1) to get compound **7** (206 mg, 90%) as colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.26 (t, 3H, $J = 7.1$ Hz), 1.34 (d, 3H, $J = 6.2$ Hz), 2.16 (s, 3H), 2.47 (1H, dd, $J = 7.6$, 14.0 Hz), 2.98 (dd, 1H, $J = 11.0$, 14.0 Hz), 4.14 (q, 2H, $J = 7.1$ Hz), 4.76 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.3, 14.6, 22.0, 37.0, 59.5, 78.8, 101.6, 166.5, 167.7. Identical to that previously reported [30].

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