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Synthesis of highly functionalized dihydrofurans via multicomponent reaction

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Abstract: An efficient synthesis of dihydrofurans via reaction between 1,3-dicarbonyl compounds with α-haloketones in H_2O is described.

Keywords: Dihydrofurans; Phenacyl bromide; *β*-Dicarbonyl; Multicomponent reaction

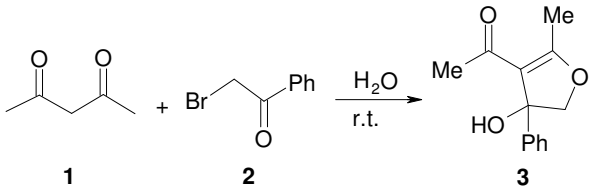
Introduction

The Feist-Benary reaction involves condensation of β-dicarbonyl compounds with α-haloketones to produce hydroxydihydrofurans, followed by elimination to form furans [1]. However, running the reaction under new conditions allowed the isolation of a dihydrofuran intermediate. Several groups studied the mechanism and scope of this "interrupted" Feist-Benary (IFB) reaction [2,3]. Dihydrofurans which are constituents of many natural products arising from plants and marine organisms with promising biological activities [4-7].
The use of water as a solvent for organic transformation offers several "green chemistry" benefits [8]. water is a "green solvent" with much to contribute to this steadily growing field. However, for organic synthetic chemist to put components in solution and frequently approach organic reaction like-needs-like perspective. It is less important because water is traditionally not a popular choice of solvent. As a part of our current studies on the development of new routes to heterocyclic systems in water [9], we wish to report an efficient synthesis of functionalized dihydrofuranes, employing readily available starting materials.

Results and Discussion

The reaction of 1,3-dicarbonyl **1** with Phenacyl bromide **2** in H_2O led to dihydrofurane **3** in good yields after purification (Scheme 1, Table 1). In this procedure, we have modified the "interrupted" Feist-Benary (IFB) reaction method for dihydrofurans synthesis via the reaction of β-dicarbonyl compounds with α-haloketones compounds. The structures of compounds **3a-3d** were deduced from their elemental analyses and their IR, 1H- and ^{13}C-NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at the appropriate m/z-values.

Scheme 1. Simple preparation of highly functionalized dihydrofuran (**3**) derivatives



1 **2** **3**

Table1. Synthesis of dihydrofuran derivative (**3**) in H_2O

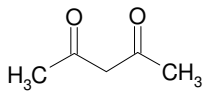
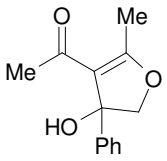
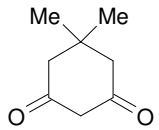
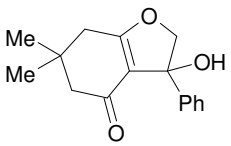
Entry	**1**	**3**	%Yield
a			85%
b			90%

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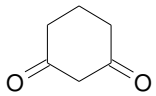
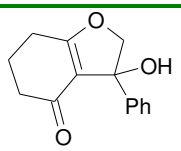
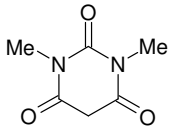
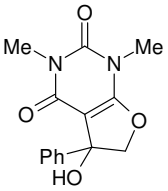
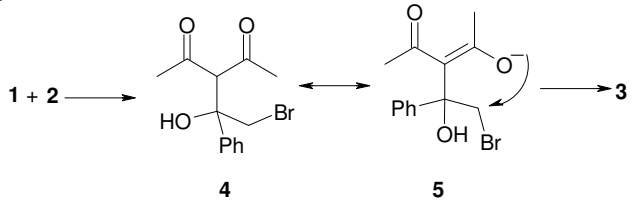
Table 1. Continued

c			85%
d			90%

Mechanistically, the reaction starts with the formation of a 1:1 adducts **4** between β-dicarbonyl **1** and **2**, which undergoes intramolecular substitution reaction to produce **3** (Scheme 2).

Scheme 2. Proposed mechanism for the one-pot dihydrofuran synthesis



In conclusion, we have described a convenient route to functionalized dihydrofurane from β-dicarbonyl and α-haloketone in water as a solvent. The advantage of the present procedure is that the reaction is performed in water by simple mixing the starting materials.

Experimental

All compounds in these reactions were obtained from Fluka and were used without further purification. Mp: Electrothermal-9100 apparatus. IR spectra: Shimadzu IR-460 spectrometer. 1H and 13C NMR spectra: Bruker DRX-500 Avance instrument; in (CD3)2CO at 500.1 and 125.7 MHz, respectively; δ in parts per million, J in hertz. EIMS (70 eV): Finnigan-MAT-8430 mass spectrometer, in m/z. Elemental analyses (C, H, N) were performed with a Heraeus CHN-O-Rapid analyzer.

Typical experimental procedure:

A mixture of Phenacyl bromide (2 mmol) and acetyleacetone (2 mmol) in H_2O (3 mL) was stirred at room temperature for about an hour. Upon completion, monitored by TLC, the solvent was removed under reduced pressure, and the residue was purified by CC (SiO_2; hexane/AcOEt 4:1) to afford pure dihydrofuran **3** in 85% yield.

4-Acetyl- 3-hydroxy–s- methyl -2,3- dihydrofuran -3-carboxylate (3a)

Yellow oil, (0.18 g, 85%). IR (KBr) (ν_{max}/cm^{-1}): 3432, 2923, 2856, 1736, 1609, 1460, 1097 cm^{-1}. ^{1}H NMR (500.1 MHz, $(CD_3)_2CO$): δ = 2.27 (3 H, *s*, CH_3), 2.34 (3 H, *s*, CH_3), 4.07 (1 H, *broad*, OH), 4.12 (1 H, d, ^2J = 11.0 Hz, CH), 4.52 (1 H, d, ^2J = 11.0 Hz, CH), 7.16 (2 H, d, ^3J = 7.6 Hz, 2 CH), 7.19 (1 H, t, ^3J = 7.4 Hz, CH), 7.33 (2 H, d, ^3J = 7.5 Hz, 2 CH) ppm. ^{13}C NMR (125.7 MHz, $(CD_3)_2CO$): δ 16.1 (CH_3), 29.2 (CH_3), 60.2 (CH_2), 80.8 (C), 119.2 (C), 120.7 (C), 125.6 (2 CH), 129.4 (2 CH), 133.8 (CH), 138.6 (C), 193.5 (C=O).

3-Hydroxyl-6,6-dimethyl-4-oxo–2,3,4,5,6,7-hexahydrobenzo furan-3-carboxylate (3b)

Yellow oil, (0.228g, 90%). IR (KBr) (ν_{max}/cm^{-1}): 3436, 2959, 2927, 1740, 1634, 1402 , 1078 cm^{-1}. ^{1}H NMR (500.1 MHz, $(CD_3)_2CO$): δ 1.11(3 H, s, CH_3), 1.16 (3 H, *s*, CH_3), 2.25 (2 H, d, ^2J=16.4, CH_2), 2.42 (2 H, d, ^2J=16.4 Hz, CH_2), 3.98 (1 H, *broad*, OH), 4.27 (1 H , d, ^2J = 10.5 Hz, CH), 4.65 (2 H , d, ^2J = 10.5 Hz, CH), 7.12 (2 H, d, ^3J = 7.4 Hz, 2 CH), 7.24 (1 H, t, ^3J = 7.8 Hz, CH), 7.35 (2 H, d, ^3J = 7.3 Hz, 2 CH) ppm. ^{13}C NMR (125.7 MHz, $(CD_3)_2CO$): δ 14.5 (CH_3), 28.3 (CH_3), 35.0 (C), 38.2 (CH_2), 51.3 (CH_2), 80.1 (CH_2), 83.6 (C), 116.0 (C), 121.5 (C), 126.0 (2 CH), 128.7 (2 CH), 132.8 (CH), 137.9 (C), 180.0 (C=O).

3-Hydroxyl-4-oxo-2,3,4,5,6,7-hexahdrobenzofuran-3-carboxylate (3c)

Yellow oil, (0.19 g, 85%). IR (KBr) (ν_{max}/cm^{-1}): 3422, 2923, 2856, 1737, 1623, 1091 cm^{-1}. ^{1}H NMR (500.1 MHz, $(CD_3)_2CO$): δ = 1.27 (2 H, m, CH_2), 2.37 (2 H, t, ^3J = 5.4 Hz , CH_2), 2.57 (2 H, *t*, ^3J = 5.7 Hz, CH_2), 4.04 (1 H, *broad*, OH), 4.27 (1 H , *d*, ^2J = 10.5 Hz ,CH), 4.64 (1H, d, ^2J = 10.5 Hz, CH), 7.10 (2 H, d, ^3J = 7.8 Hz, 2 CH), 7.28 (1 H, t, ^3J = 7.5 Hz, CH), 7.38 (2 H, d, ^3J = 7.6 Hz, 2 CH) ppm. ^{13}C NMR (125.7 MHz, $(CD_3)_2CO$): δ 21.8 (CH_2), 24.4 (CH_2), 36.8 (CH_2), 80.2 (CH_2), 83.5 (C), 117.5 (C), 122.0 (C), 126.4 (2 CH), 129.0 (2 CH), 133.7 (CH), 138.2 (C), 181.0 (C=O).

5-Hydroxy-1,3-dimethyl-2,4-dioxo-1,2,3,4,5,6-hexahydrofuro[2,3-d]pyrimidine-5-carboxylate(3d)

Yellow oil, (0.27g, 90%). IR (KBr) (ν_{max}/cm^{-1}): 3438, 2924, 2359, 1644, 1463, 1388, 1114 cm^{-1}. ^{1}H NMR (500.1 MHz, $(CD_3)_2CO$): δ 3.30 (3 H, *s*, CH_3), 3.40 (3 H, *s*, CH_3), 4.19 (1 H , *broad*, OH), 4.18 (1 H, *d*, ^2J = 11.0 Hz, CH), 4.84 (1 H, d, ^2J = 11.0 Hz, CH), 7.16 (2

H, d, ^3J = 7.4 Hz, 2 CH), 7.23 (1 H, t, ^3J = 7.5 Hz, CH), 7.42 (2 H, d, ^3J = 7.5 Hz, 2 CH) ppm. ^{13}C NMR (125.7 MHz, $(CD_3)_2CO$): δ 28.2 (CH_3), 29.8 (CH_3), 80.2 (CH_2), 84.4 (C), 113.4 (C), 123.4 (C), 127.5 (2 CH), 128.8 (2 CH), 134.0 (CH), 139.1 (C), 171.5 (C=O), 173.4 (C=O).

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