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Ultrasonochemical synthesis of 2,3-dihydrofuranediones in aqueous medium

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Abstract: 2,3-Dihydrofuranediones were prepared by an efficient one-pot multicomponent Knoevnagel-like condensation between pyrazolecarbaldehydes or indole-3-carbaldehyde, ethyl pyruvate and bromine, followed by an intramolecular cyclization in aqueous medium.

Keywords: 2,3-dihydrofuranedione; aqueous media; ethyl pyruvate; ultrasound irradiation; water.

Introduction

Furanones are constituents of many bioactive molecules [1–9]. Furan derivatives can be synthesized by the cyclization of γ-hydroxyalkynones [10], cycloisomerization of allenic hydroxyketones [11], domino reaction of α,β-acetylenic γ-hydroxy nitriles with arenecarboxylic acids [12], silver triflate-catalyzed intramolecular addition of a hydroxyl or carboxylic group to olefins [13], cyclization of alkynes bearing a carboxylic acid in the presence of commercially available Au_2O_3 [14], DBU-mediated tandem Michael addition/5-*exo*-*dig*-cycloisomerization of enynes and keto-methylenes [15], palladium-catalyzed isomerization of acetylenic aldehydes followed by base-promoted deacetylation [16] and copper-catalyzed oxidative [3+2] cycloaddition of alkenes with anhydrides in the presence of oxygen [17]. Furanediones can be prepared from alkyne precursors [18]. One of the most common preparative methods for the synthesis of furane-2,3-diones is the reaction of 1,3-dicarbonyl compounds with oxalyl chloride [19].

To the best of our knowledge, this paper is the first report of the multicomponent synthesis of pyrazolyl or indolyl-substituted 2,3-dihydrofuranediones using aryl aldehydes, ethyl pyruvate and bromine under ultrasonic irradiation in water. The importance of ultrasonic-assisted organic synthesis has been widely reported [20, 21] and reviewed [22]. Overall, ultrasonic irradiation conducted in water is both economical and environmentally friendly [23].

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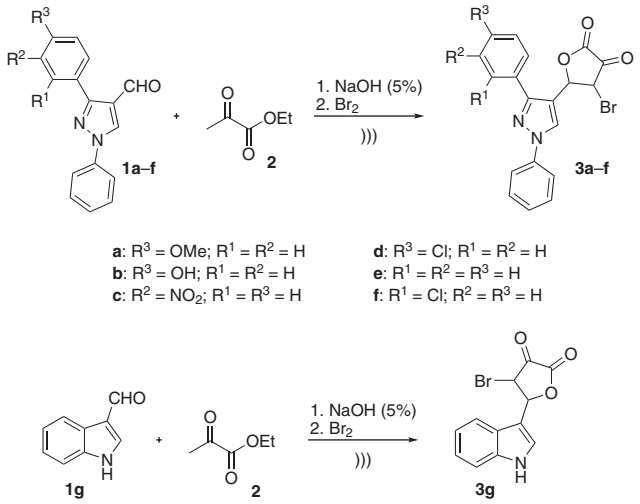
Results and discussion

In continuation of our efforts to develop pharmaceutical heterocyclic compounds [24–28], herewith we report a simple, one-pot multicomponent method for the construction of 2,3-dihydrofuranediones **3a–g** in water as a solvent starting from 4-pyrazolecarbaldehydes **1** or indole-3-carbaldehyde (**1g**), ethyl pyruvate (**2**) and bromine (Scheme 1). This reaction is enhanced by the use of microwave irradiation.

In order to optimize the preparation of products **3a–g**, several commonly available solvents including ethyl acetate, water, ethanol, hexanes, chloroform and *N,N*-dimethylformamide were studied for comparison. The effect of temperature, the use of ultrasonic heating and conventional heating were also studied. In the initial experiments, a mixture of pyrazolecarbaldehyde (**1a**, 1 mmol), ethyl pyruvate (**2**, 1 mmol), bromine (1 mmol) and NaOH (0.5 g) were allowed to react in various solvents (10 mL) under ultrasonic irradiation with a frequency of 45 kHz. Among the solvents indicated above, the reaction conducted in water furnished product **3a** in the highest yield of 92% after 30 min of irradiation. The use of other solvents provided compound **3a** in yields ranging from 53% (hexanes) to 78% (ethanol) after the irradiation time greater than 45 min. The reaction was best conducted at room temperature. The yield **3a** decreased to 56% at 0°C after the reaction time of 120 min, and the increase of the temperature to 60°C resulted in the yield of 91% after 30 min. Stirring of the mixture of substrates at room temperature for 120 min without microwave-assisted heating resulted in the yield of **3a** of 63%. Conducting the reaction under classical reflux conditions without assistance from ultrasound was also less efficient and furnished product **3a** in an 80% yield after 90 min. Under the optimized ultrasound-assisted reaction conducted in water at room temperature for 30 min, the remaining products **3b–g** were obtained in yields ranging from 83% to 90%.



Scheme 1 Synthesis of 2,3-dihydrofuranediones under ultrasonic irradiation.

We are currently studying the mechanism of this efficient reaction.

To the best of our knowledge, this one-pot multicomponent synthesis of 2,3-dihydrofuranediones is a novel methodology. The procedure presented here not only furnishes the desired products in good yields, but also problems associated with the use of conventional solvents such as cost, handling, safety and pollution are avoided. Aqueous medium for these reactions provides an environmentally safe protocol. Water is the cheapest, most abundant and non-toxic chemical in nature.

Conclusion

A one-pot three-component synthesis of 2,3-dihydrofuranediones from 4-pyrazolecarbaldehydes or indole-3-carbaldehyde, ethyl pyruvate and bromine under ultrasonic irradiation was developed for the first time. The simplicity of the process, easy workup, inexpensive materials and the use of aqueous medium are the notable features.

Experimental

Melting points were measured on an Electrothermal 9100 apparatus. Infrared spectra were recorded in KBr pellets on a Shimadzu Fourier transform infrared (FTIR) 8600 spectrophotometer. proton nuclear magnetic resonance (^{1}H NMR) (400 MHz) and carbon-13 nuclear magnetic resonance (^{13}C NMR) (100 MHz) spectra were taken in dimethyl sulfoxide-d_6 (DMSO-d_6) on a Bruker 400 DRX Avance instrument. Elemental analyses were done on a Carlo-Erba EA1110CNNO-S analyzer. An ultrasound apparatus Astra 3D operating at 45 KHz frequency, input power with heating, 305 W, from TECNO-GAZ was used.

General procedure for the preparation of 3a–g under ultrasonic irradiation

A mixture of aldehyde (**1a–g**, 1.0 mmol), ethyl pyruvate (**2**, 1.0 mmol) and aqueous NaOH (5%, 10 mL) were placed in a Pyrex-glass open vessel and microwave irradiated at room temperature for 10 min. Then, bromine (1.0 mmol) was added and the mixture was irradiated for an additional 20 min. The progress of the reaction was monitored by thin-layer chromatography (TLC) eluting with ethyl acetate/petroleum ether (1:2). After completion of the reaction, the mixture was filtered and the residue was subjected to silica gel chromatography eluting with ethyl acetate/petroleum ether (1:4).

4-Bromo-dihydro-5-(5-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-3-yl)furane-2,3-dione (3a) White solid; yield 92%; mp 283–285°C; IR: 1284, 1490, 1596, 1726, 2960 cm^{-1}; ^{1}H NMR: δ_H 3.94 (s, 3H, OCH_3), 4.08 (s, 1H, CHBr), 4.10 (s, 1H, CHO), 6.55 (dd, J = 6 Hz and 2 Hz, 2H), 7.51 (m, 2H), 7.59 (s, 2H), 7.71 (m, 2H), 7.92 (dd, J = 6 Hz and 2 Hz, 1H), 8.19 (d, J = 2 Hz, 1H); ^{13}C NMR: δ_C 62.4, 71.2, 95.8, 110.4, 118.4, 122.6, 124.7, 126.7, 128.9, 131.6, 132.5, 135.8, 138.9, 145.3, 164.8, 193.6. Anal. Calcd for $C_{20}H_{15}BrN_2O_4$: C, 56.22; H, 3.54; N, 6.56. Found: C, 56.24; H, 3.55; N, 6.54.

4-Bromo-dihydro-5-(5-(4-hydroxyphenyl)-1-phenyl-1*H*-pyrazol-3-yl)furane-2,3-dione (3b) White solid; yield 90%; mp 263–265°C; IR: 1282, 1465, 1600, 1728, 2960, 3068, 3419 cm^{-1}; ^{1}H NMR: δ_H 4.08 (s, 1H, CHBr), 4.09 (s, 1H, CHO), 7.53 (m, 5H), 7.71 (m, 4H), 8.26 (s, 1H); ^{13}C NMR: δ_C 71.8, 97.2, 110.6, 118.2, 125.8, 128.7, 128.8, 130.9, 132.4, 132.5, 135.1, 141.2, 148.3, 164.6, 199.8. Anal. Calcd for $C_{19}H_{13}BrN_2O_4$: C, 55.23; H, 3.17; N, 6.78. Found: C, 55.22; H, 3.17; N, 6.81.

4-Bromo-dihydro-5-(5-(3-nitrophenyl)-1-phenyl-1*H*-pyrazol-3-yl)furane-2,3-dione (3c) White solid; yield 85%; mp 274–276°C; IR: 1282, 1344, 1521, 1596, 1631, 2960 cm^{-1}; ^{1}H NMR: δ_H 4.09 (s, 1H, CHBr), 4.10 (s, 1H, CHO), 7.36 (m, 1H), 7.51 (m, 2H), 7.62 (m, 2H), 7.72 (m, 2H), 8.06 (s, 1H), 8.25 (s, 1H), 8.38 (s, 1H); ^{13}C NMR: δ_C 71.8, 94.9, 118.9, 120.2, 122.4, 123.1, 127.4, 128.8, 129.1, 129.3, 129.6, 130.9, 132.7, 133.2, 133.3, 163.4, 191.2. Anal. Calcd for $C_{19}H_{12}BrN_3O_5$: C, 51.60; H, 2.74; N, 9.50. Found: C, 51.62; H, 2.77; N, 9.49.

4-Bromo-5-(5-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-3-yl)dihydrofurane-2,3-dione (3d) White solid; yield 87%; mp 221–223°C, IR: 1282, 1492, 1595, 1726, 2923 cm^{-1}; ^{1}H NMR: δ_H 4.14 (s, 2H, CHBr and CHO), 7.42 (d, J = 6 Hz, 2H), 7.57 (m, 5H), 7.92 (d, J = 6 Hz, 2H), 7.98 (s, 1H); ^{13}C NMR: δ_C 71.9, 93.9, 119.4, 119.8, 127.8, 127.9, 128.6, 128.9, 129.2, 131.6, 133.7, 137.4, 148.3, 168.4, 197.8. Anal. Calcd for $C_{19}H_{12}BrClN_2O_3$: C, 52.87; H, 2.80; N, 6.49. Found: C, 52.86; H, 2.82; N, 6.46.

4-Bromo-dihydro-5-(1,5-diphenyl-1*H*-pyrazol-3-yl)furane-2,3-dione (3e) White solid; yield 90%; mp 124–126°C; IR: 1280, 1514, 1596, 1726, 2960, 3066 cm^{-1}; ^{1}H NMR: δ_H 4.09 (s, 1H, CHBr), 4.22 (s, 1H, CH-O), 7.44 (m, 3H), 7.54 (m, 2H), 7.60 (d, J = 7 Hz, 1H), 7.73 (m, 3H), 8.00 (m, 1H), 8.03 (s, 1H); ^{13}C NMR: δ_C 71.8, 94.4, 118.8, 126.9, 127.7, 128.3, 128.8, 129.5, 130.9, 131.7, 132.3, 139.5, 150, 165.3, 197.4. Anal. Calcd for $C_{19}H_{13}BrN_2O_3C$: C, 57.45; H, 3.30; N, 7.05. Found: C, 57.42; H, 3.32; N, 7.04.

4-Bromo-5-(5-(2-chlorophenyl)-1-phenyl-1*H*-pyrazol-3-yl)-dihydrofurane-2,3-dione (3f) White solid; yield 89%; mp 233–235°C; IR: 1099, 1237, 1593, 1670, 1726 cm^{-1}; ^{1}H NMR: δ_H 4.08 (s, 1H, CHBr), 4.10 (s, 1H, CHO), 7.25 (m, 2H), 7.51 (m, 4H), 7.67 (m, 1H), 7.73

(dd, J = 6 Hz and 3 Hz, 1H), 7.97 (m, 1H), 8.01 (s, 1H); ^{13}C NMR: δ_C 70.7, 93.6, 118.4, 123.4, 123.9, 128.0, 128.8, 128.9, 129.3, 129.8, 130.8, 133.6, 136.9, 139.0, 139.4, 151.7, 154.6, 197.2. Anal. Calcd for $C_{19}H_{12}BrClN_2O_3$: C, 52.87; H, 2.80; N, 6.49. Found: C, 52.89; H, 2.78; N, 6.48.

4-Bromo-dihydro-5-(1*H*-indol-3-yl)furane-2,3-dione (3g) White solid; yield 83%; mp 246–248°C, IR: 1095, 1234, 1435, 1589, 1733 cm^{-1}; ^{1}H NMR: δ_H 4.07 (s, 1H, CHBr), 4.09 (s, 1H, CHO), 7.45 (d, J = 3 Hz, 1H), 7.53 (dd, J = 7 Hz and 3 Hz, 1H), 7.59 (d, J = 7 Hz, 1H), 7.66 (d, J = 7 Hz, 1H), 7.73 (dd, J = 7 Hz and 3 Hz, 1H), 8.31 (s, 1H, NH); ^{13}C NMR: δ_C 71.0, 93.7, 118.9, 127.8, 129.9, 135.4, 136.8, 138.9, 142.3, 151.6, 153.7, 197.1. Anal. Calcd for $C_{12}H_8BrNO_3$: C, 49.01; H, 2.74; N, 4.76. Found: C, 49.02; H, 24.72; N, 4.78.

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