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ZIRCONIUM CATALYZED CHEMOSELECTIVE SYNTHESIS OF NEW AMIDO-SUBSTITUTED BENZO[*b*]FURANS VIA A ONE-POT REACTION

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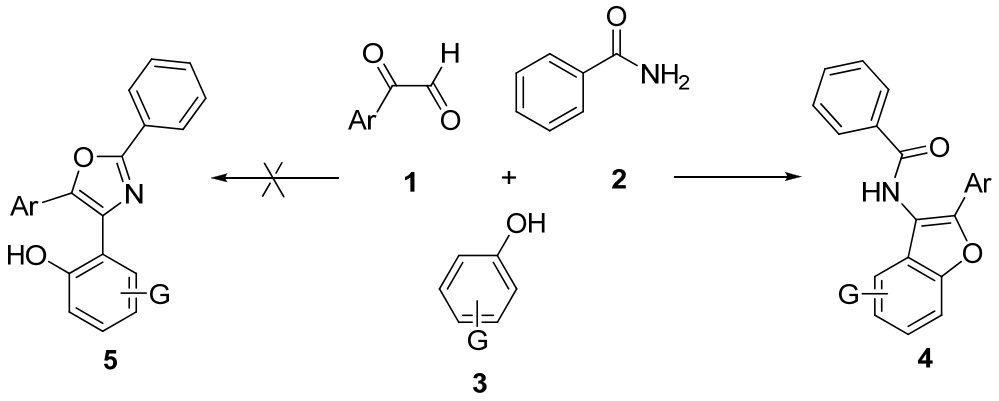
Abstract – A one-pot, three-component reaction of arylglyoxals, benzamide and phenols using catalytic amounts of zirconium oxychloride octahydrate under solvent-free conditions produce new amido-substituted benzo[*b*]furans. The reactions showed chemoselectivity towards benzofuran instead of oxazols which this claim has been confirmed by nuclear magnetic resonance (NMR) and infrared spectroscopy (IR).

Benzo[*b*]furan derivatives are important group among naturally occurring systems.[1] They have shown biological properties, such as anti-bacterial,[2] anti-fungal,[3] anti-inflammatory,[4] anti-depressant,[5] and anti-convulsant,[6] activities. Regarding to this background, a synthetic route leading to novel benzo[*b*]furans would be of general interest. So far, several strategies for the synthesis of benzofurans have been reported in literature.[7-10]

The traditional methods for the synthesis of benzofurans are the preparation via O-alkylation of salicylaldehyde with chloroacetic acid followed by dehydration of the resulting ether[11] and via Perkin rearrangement in which a coumarin is reacted with a hydroxide.[12] Also, the new strategies have been reported for the preparation of amino or amido-substituted benzo[*b*]furans.[13-15] The cysteinl leukotriene receptor 2 antagonist activity of some amido-substituted benzo[*b*]furans have been already known by Tsuji and co-workers.[14] The synthesis introduction of novel amido-substituted benzo[*b*]furan with unknown activity may be effective and useful in the field of biological researches.

Considering abovementioned background and our programmatic interest on the novel heterocyclic synthesis[16-18] and catalyzed organic reactions,[19-21] we found that arylglyoxals **1** can participate in a new one-pot, three-component reaction with benzamide (**2**) and phenols **3** in the presence of zirconium oxychloride octahydrate under solvent-free conditions yielding novel benzofurans **4** (Scheme 1). To the

best of our knowledge, there is no report on the synthesis of benzo[*b*]furans via the three-component reaction of these starting materials in literature. It is noteworthy that the reactions showed chemoselectivity toward benzofurans **4** as only isomer and the oxazoles **5** were not formed.

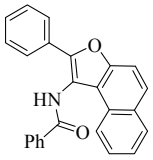
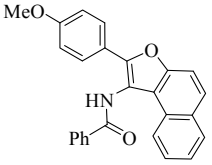
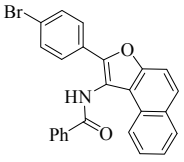


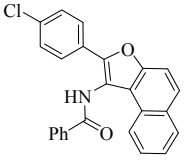
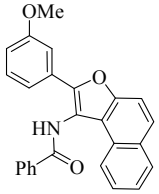
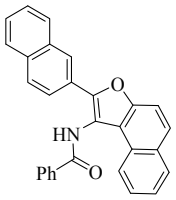
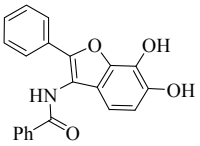
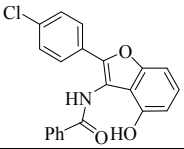
(i): $Zr(O)Cl_2 \cdot 8H_2O$, solvent-free, 100 °C

Scheme 1

In order to find the optimal reaction conditions for the synthesis of compounds **4**, the reaction of phenylglyoxal, benzamide and *β*-naphthol was selected as a model. It was found that in the absence of catalyst, the reaction would not be completed, even at long reaction times at high temperatures. Through screening, it was found that this reaction is completed with $Zr(O)Cl_2 \cdot 8H_2O$ (2 mol%) at 100 ºC under solvent-free conditions. To test the generality of the reaction, this thermal and solvent-free procedure was employed for similar substrates. The results have been shown in Table 1.

Table 1. Synthesis of benzofuran derivatives using $Zr(O)Cl_2 \cdot 8H_2O$ at 100 ºC under solvent-free conditions.

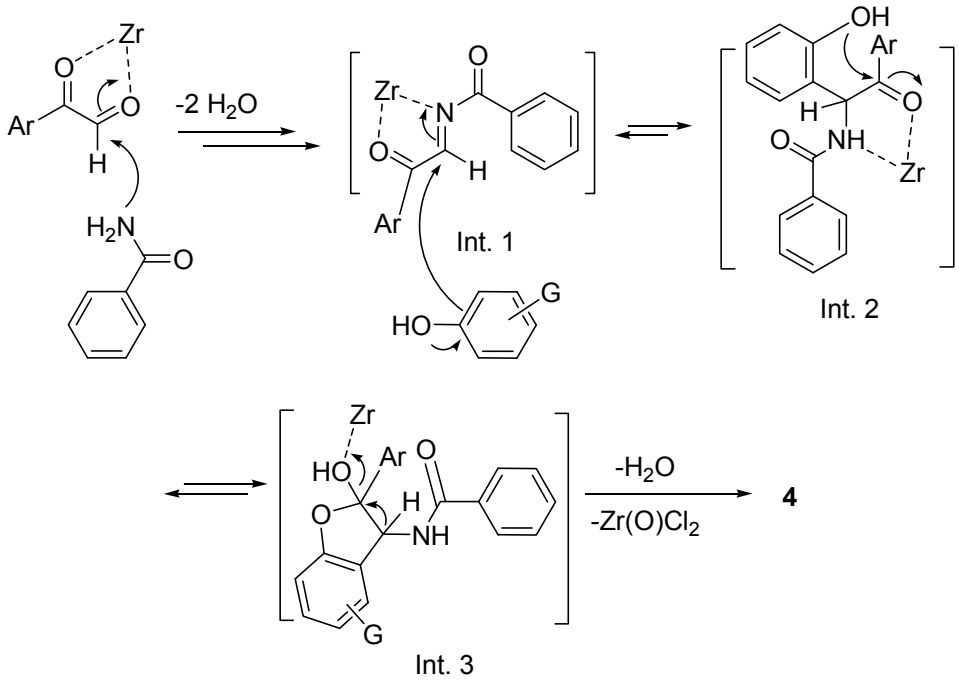
Entry	Ar	Phenol	Product	Yield[a] (%)	Time (h)
4a	C_6H_5	2-naphthol		80	6.0
4b	4-MeO-C_6H_4	2-naphthol		75	5.5
4c	4-Br-C_6H_4	2-naphthol		85	5.5

4d	4-Cl-C_6H_4	2-naphthol		80	6.0
4e	3-MeO-C_6H_4	2-naphthol		85	5.5
4f	2-naphthyl	2-naphthol		75	4.0
4g	C_6H_5	1,2,3-$(OH)_3 \cdot C_6H_3$		85	4.5
4h	4-Cl-C_6H_4	1,2-$(OH)_2 \cdot C_6H_4$		75	5.0

[a]Reffers to isolated yield.

The chemoselectivity of these reactions has been proved by NMR and IR spectroscopy. As a representative sample, the ^{1}H NMR (DMSO-d_6, 400 MHz) spectrum of **4e** exhibited a sharp singlet identified as a methyl (δ = 3.74) protons. The signals (δ= 8.25-6.99) corresponded to the aromatic protons. The protons of NH groups also appeared as a siglet at δ= 10.77. The proton decoupled ^{13}C NMR spectrum of **4e** also showed 24 distinct resonances in agreement with the proposed structure. The appearance of the signal for carbonyl of amide group at 166.63 ppm can prove the formation of compound **4e**. Other evidences for the formation of isomer **4e** are the disappearance of phenolic OH in H NMR spectrum and the appearance of one peak at 3200 cm^{-1} in the infrared spectrum as secondary amide. The nature of Ar groups showed no significant effect on the yield or reaction rate. The advantages of solvent-free procedures include cost savings, reduced energy consumption, decreased reaction times, and a considerable reduction in reactor size and, therefore, capital investment. These attributes have inspired a substantial research effort directed toward the development of solvent-free reactions.[22,23] Beside this, the zirconium (IV) oxychloride octahydrate has been considered as a safe potential catalyst in recent organic synthesis due to its low toxicity [LD50 ($ZrOCl_2 \cdot 8H_2O$) oral rate = 2950 mg/kg], low costs, ease of handling, and high activity.[24-26] On the basis of the general mechanistic pathway for the formation of compounds **4**, Scheme 2 shows a reasonable mechanism. The reaction is thought to take place in three

steps. It is reasonable to assume that the initial event involves the generation of intermediate **1** via condensation of the amide and arylglyoxal. In the next step, the intramolecular cyclization of intermediate **2** gives intermediate **3** followed by dehydration to form corresponding products **4**. Considering that the cyclization step can be the product-determining step, we guess that the role of Zr is important in the Int 2. For example, the formed chelation in **2** can reduce the nucleophilisity of carbonyl amide and promote the attack of the hydroxyl group to form isomer **4**.



Scheme 2

In conclusion, the reaction between arylglyoxals, benzamide, and phenol derivatives in the presence of catalytic amounts of zirconium oxychloride octahydrate provides a simple one-pot entry for the synthesis of new amido-substituted benzo[*b*]furans. This method has advantages such as the use of a safe and recyclable catalyst, avoidance of organic solvents, high yields of products, and a simple workup procedure.

EXPERIMENTAL

The reactions were monitored by TLC (silica gel 60 F_{254}, hexane/EtOAc). IR spectra were recorded on a FT-IR JASCO-680 and the NMR spectra were obtained on a Bruker-Instrument DPX-400 MHz Avance III model. The varioEl CHNS Isfahan Industrial University was used for elemental analysis.

Starting Materials. Arylgloxals were prepared by the appropriate reported procedure.[27] All other chemicals used in this study were commercially available and purchased from Merck and Aldrich.

General procedure for the synthesis of benzofurans 4. A mixture of arylglyoxal (1 mmol), benzamide (1 mmol), and $Zr(O)Cl_2 \cdot 8H_2O$ (0.02 mmol) was stirred and heated at 100 °C in a preheated oil bath for 30 min. Then the phenolic substrate was added and the mixture was stirred for an appropriate time (4-6 h). After completion of the reaction as indicated by TLC (EtOAc/hexan, 1:2), the reaction mixture was dissolved in hot EtOH and the catalyst was separated by filtration. The solvent was evaporated and the products **4** were purified by recrystallization in EtOH.

1-Benzamido-2-phenylnaphtho[2,1-*b*]furan (4a). mp 230-232 ºC; IR (KBr) *v*: 3160, 3110, 2089, 1640, 1485, 1260, 1040, 800, 700 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz,): 10.78 (s, 1H), 8.26 (d, 1H, *J* = 7.6), 8.21 (d, 2H, *J* = 7.2 Hz), 8.09 (d, 1H, *J* = 8.0 Hz), 7.90-8.04 (m, 4H), 7.74-7.65 (m, 3H), 7.53, 7.57 (2d, 4H, *J* = 8.0, 7.6 Hz), 7.43 (t, 1H, *J* = 7.6 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz): 167.21, 150.86, 149.10, 134.07, 132.72, 130.92, 129.83, 129.54, 129.47, 129.38, 129.25, 128.27, 127.66, 127.18, 126.87, 125.84, 125.41, 122.67, 121.40, 117.26, 113.05; Anal. Calcd for $C_{25}H_{17}NO_2$: C, 82.63; H, 4.72; N, 3.85. Found: C, 82.90; H, 4.65; N, 3.77.

1-Benzamido-2-(4-methoxyphenyl)naphtho[2,1-*b*]furan (4b). mp 239-241 ºC; IR (KBr) *v*: 3165, 3110, 2950, 1640, 1510, 1475, 1260, 1040, 800, 700 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): 10.70 (s, 1H), 8.22, 8.24 (2d, 3H, *J* = 8.0 , 6.8 Hz), 8.07 (d, 1H, *J* = 8.0 Hz), 7.89 (t, 4H, *J* = 8.4 Hz), 7.74-7.64 (m, 3H), 7.56-7.50 (m, 2H), 7.11 (d, 2H), 3.81 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): 167.20, 160.10, 150.46, 149.46, 134.11, 132.66, 130.89, 129.40, 129.35, 128.25, 127.58, 127.45, 126.99, 126.20, 125.28, 122.65, 122.36, 121.54, 115.61, 115.05, 112.95, 55.77; Anal. Calcd for $C_{26}H_{19}NO_3$: C, 79.37; H, 4.87; N, 3.56. Found: C, 79.51; H, 4.80; N, 3.45.

1-Benzamido-2-(4-bromophenyl)naphtho[2,1-*b*]furan (4c). mp 286-288 ºC; IR (KBr) *v*: 3200, 1650, 1490, 1395, 1270, 1090, 800, 690 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): 10.78 (s, 1H), 8.22 (d, 1H, *J* = 8.4 Hz), 8.17 (d, 2H, *J* = 7.6 Hz), 8.09 (d, 1H, *J* = 8.0 Hz), 7.96 (d, 1H, *J* = 8.8 Hz), 7.91-7.87 (m, 3H), 7.76 (dd, 2H, *J* = 6.8, 2.0 Hz), 7.72 (d, 1H, *J* = 7.1 Hz), 7.66 (t, 2H, *J* = 7.6 Hz), 7.57-7.53 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz): 167.10, 151.00, 148.13, 133.90, 132.79, 132.59, 130.93, 129.51, 129.39, 128.94, 128.28, 127.68, 127.58, 127.29, 127.25, 125.53, 122.65, 122.48, 121.24, 117.67, 113.03; Anal. Calcd for $C_{25}H_{16}BrNO_2$: C, 67.89; H, 3.65; N, 3.17. Found: C, 68.01; H, 3.48; N, 3.02.

1-Benzamido-2-(4-chlorophenyl)naphtho[2,1-*b*]furan (4d). mp 270-272 ºC; IR (KBr) *v*: 3205, 1640, 1485, 1395, 1280, 1090, 800, 710, 690 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): 10.78 (s, 1H), 8.22 (d, 1H, *J* = 7.6 Hz), 8.17 (d, 2H, *J* = 8.0 Hz), 8.09 (d, 1H, *J* = 7.8 Hz), 7.97-7.89 (m, 4H), 7.74-7.61 (m, 5H), 7.58-7.51 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz): 166.63, 150.47, 147.50, 133.43, 133.25, 132.26, 130.41, 129.19, 129.00, 128.87, 128.11, 127.78, 127.08, 126.94, 126.77, 126.70, 125.00, 122.13, 120.72, 117.25, 112.52; Anal. Calcd for $C_{25}H_{16}ClNO_2$: C, 75.47; H, 4.05; N, 3.52. Found: C, 75.55; H, 3.95; N, 3.31.

1-Benzamido-2-(3-methoxyphenyl)naphtho[2,1-*b*]furan (4e). mp 198-200 ºC; IR (KBr) *v*: 3200, 20100, 1650, 1509, 1390, 1250, 700 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): 10.77 (s, 1H), 8.24 (d, 1H, *J* = 8.0 Hz), 8.19 (d, 2H, *J* = 7.6 Hz), 8.09 (d, 1H, *J* = 7.6 Hz), 7.94, 7.91 (2d, 2H, *J* = 9.2, 8.8 Hz), 7.71-7.63 (m, 3H), 7.56-7.43 (m, 5H), 7.00 (dd, 1H, *J* = 8.2, 2.4 Hz), 3.74 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): 166.63, 159.43, 150.29, 148.35, 133.45, 132.25, 130.45, 130.39, 130.22, 128.96, 128.86, 127.71, 127.123, 126.711, 126.44, 124.93, 122.14, 120.86, 117.72, 116.95, 114.54, 112.54, 110.488, 55.043; Anal. Calcd for $C_{26}H_{19}NO_3$: C, 79.37; H, 4.87; N, 3.56. Found: C, 79.48; H, 4.70; N, 3.50.

1-Benzamido-2-(2-naphthyl)naphtho[2,1-*b*]furan (4f). mp 220-222 ºC; IR (KBr) *v*: 3190, 2200, 1650, 1500, 1395, 1010, 790; ^1H NMR (DMSO-d_6, 400 MHz): 10.86 (s, 1H), 8.28 (d, 1H, *J* = 7.6 Hz), 8.21 (d, 2H, *J* = 7.6 Hz), 8.11-7.93 (m, 8H), 7.75-7.68 (m, 3H), 7.59-7.52 (m, 4H); ^{13}C NMR (DMSO-d_6, 100 MHz): 166.84, 161.36, 150.54, 148.56, 133.64, 132.80, 132.55, 132.23, 130.43, 128.98, 128.90, 128.61, 128.28, 127.74, 127.66, 127.14, 126.98, 126.94, 126.740, 126.54, 124.97, 124.56, 122.67, 122.23, 120.97, 117.25, 112.53; Anal. Calcd for $C_{29}H_{19}NO_2$: C, 84.24; H, 4.63; N, 3.39. Found: C, 84.49; H, 4.48; N, 3.31.

6,7-Dihydroxy-2-phenyl-3-benzamidobenzofuran (4g). mp 248-250 ºC; ^1H NMR (DMSO-d_6, 400 MHz): 10.81 (s, 1H), 9.26 (s, 1H), 8.99 (s, 1H), 7.93, 7.98 (2d, 2H, *J* = 8, 7.6 Hz), 7.44-7.61 (m, 8H), 6.48 (d, 1H, *J* = 8.4 Hz), 6.28 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz): 166.82, 146.84, 144.76, 135.66, 134.31, 133.73, 133.62, 131.82, 129.15, 128.69, 128.61, 128.54, 128.19, 127.93, 119.57, 114.25, 107.35; IR (KBr) *v*: 3520-3100, 1620, 1521, 1470, 1285, 710, 690, 668; Anal. Calcd for $C_{21}H_{15}NO_4$: C, 73.03; H, 4.38; N, 4.06. Found: C, 73.15; H, 4.32; N, 3.95.

7-Hydroxy-2-phenyl-3-benzamidobenzofuran (4h). mp 225-227 ºC; IR (KBr) *v*: 3410-3200, 3050-3000, 1668-1615, 1540-1498, 1100-1098, 740-689; ^1H NMR (DMSO-d_6, 400 MHz): 10.74 (s, 1H), 9.31 (d, 1H, *J* = 8 Hz), 8.02-8.00 (m, 2H), 7.95-7.90 (m, 3H), 7.72-7.78 (m, 6H), 6.97 (d, 2H, *J* = 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): 166.56, 166.48, 138.78, 133.61, 132.81, 132.37, 131.32, 130.46, 130.03, 129.38, 128.89, 128.03, 126.03, 122.12, 120.01; Anal. Calcd for $C_{21}H_{14}ClNO_3$: C, 69.33; H, 3.88; N, 3.85. Found: C, 69.55; H, 3.71; N, 3.70.

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