Article

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One-pot Synthesis of Benzamidonaphtho[2,1-*b*]furans and Benzamidobenzo[*b*]furans as Novel Polycyclic Heteroaromatic Compounds

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An operationally simple, green and efficient procedure for one-pot synthesis of novel polycyclic heteroaromatic compounds such as benzamidonaphtho[2,1-*b*]furans and benzamidobenzo[*b*]furans has been developed from the reaction of arylglyoxals, benzamide, and phenols. The reactions were mediated with low amounts of yttrium nitrate hexahydrate as a suitable Lewis acid catalyst without using solvent.

Keywords: Heteroaromatic; Benzamidobenzo[*b*]furans; Benzamidonaphtho[2,1-*b*]furans; Arylglyoxals; Yttrium nitrate hexahydrate.

INTRODUCTION

Among polycyclic heteroaromatic compounds, benzofurans have been known for organic chemists. They are usually important constituents of plant extracts used in traditional medicine.[1] They have also 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 benzo[*b*]furans would be of general interest. So far, several strategies for the synthesis of benzofurans have been reported in literature. Almost all of the reported methods can be classified into two categories including (A) the intramolecular cyclization of benzene derivatives and (B) the creation of an annulated carbocyclic ring.[7] However, the traditional methods for the synthesis of benzofuran derivatives are the preparation via O-alkylation of salicylaldehyde with chloroacetic acid followed by dehydration of the resulting ether (category A)[8] and via Perkin rearrangement in which a coumarin is reacted with a hydroxide (category B)[9-11] Recently, the new strategies have been also reported for the preparation of amino and amido-substituted benzo[*b*]furans.[12-14]

RESULTS AND DISCUSSION

In continuation of our studies on the synthesis of heterocyclic compounds[15-18] and catalyzed organic reactions,[19-21] we treated arylglyoxals **1** (which in turn are obtained by selenium dioxide oxidation of the corresponding phenyl ketones) and benzamide (**2**) in the presence of yttrium nitrate hexahydrate as an efficient catalyst under solvent-free conditions for *in situ* generation of imine **4** followed by reaction with phenolic substrate **5** to produce final benzofurans **6** in a regiospecific manner. However, after characterization by FT-IR and NMR spectroscopy, we found that only regioisomer **6** have been formed and no trace for oxazole **7** was observed during the control of the reaction progress by thin layer chromatography (TLC). The formation of benzofuran **6** showed that at the first reaction, the imine **3** cannot be formed. However, it is clear that the ketones are less active than aldehyde group under nucleophilic attack.

In order to find the optimal reaction conditions for the synthesis of compounds **6**, the reaction of phenylglyoxal (**1a**), benzamide (**2**) and β-naphthol **5a** was selected as a model (Scheme II). It was found that in the absence of catalyst, the reaction did not complete, even at long reaction times in high temperatures. Through screening, it was found that this reaction is completed with yttrium nitrate hexahydrate (10 mol%) under solvent-free conditions at 70 ºC for the first step and 110 ºC for the second step.

Avoidance of organic solvents during chemical reactions requires a fundamental understanding of green chemistry factors. These concepts provide direction for improvements in organic synthesis and finishing of environmental and economic concerns. 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.[22-24]

After optimization, the scope was explored for differ-

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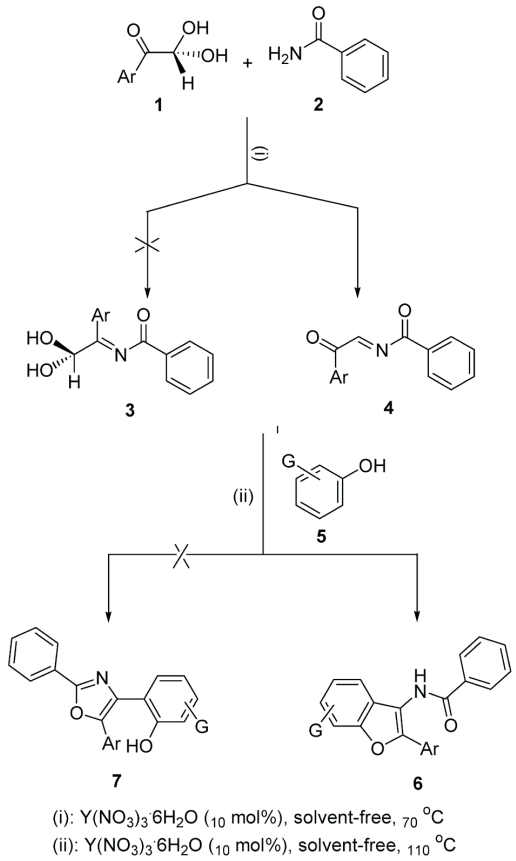
Scheme I Regiospecific reactions for preparation of novel benzofurans



Scheme II A model for the optimization of the reaction conditions

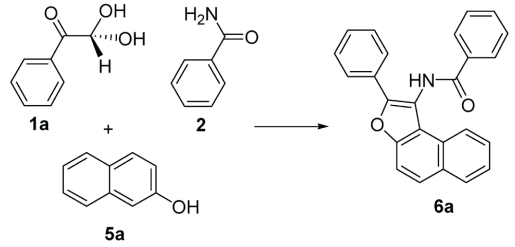
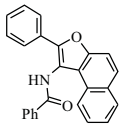
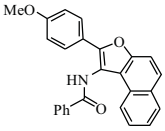
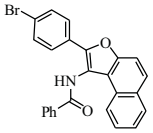
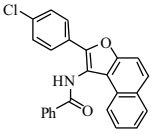
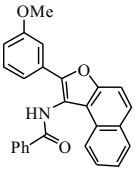
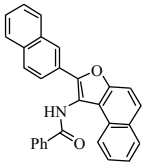
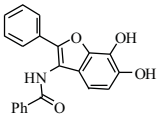
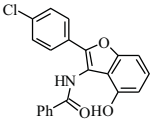


Table 1. Synthesis of benzofuran derivatives using yttrium nitrate hexahydrate under optimized reaction conditions

Entry	Product	Yielda (%)[a]	Mp (ºC)
6a		80	230-232
6b		75	239-241
6c		85	286-288
6d		80	270-272
6e		85	198-200
6f		75	220-222
6g		85	248-250
6h		75	225-227

[a] Refers to isolated yields.

ent arylglyoxals (Table 1, Entry **6a-6f**). Some hydroxylated benzofurans also play an important role in the natural defense mechanisms of their plants. For example, euparin[25] coumestrol,[26] dehydrotremetone,[27] and cicerfuran.[28] Due to this effect, a synthetic route leading to hydroxylated benzofurans would be of general interest. Another test of the efficiency of the developed procedure was our attempt to use pyrogallol and resorcinol as phenolic substrate in this research. Therefore, in this case, two novel hydroxylated benzo[b]furans such as 6,7-dihydroxy-2-phenyl-3-benzamidobenzofuran (**6g**) and 7-hydroxy-2-phenyl-3-benzamidobenzofuran (**6h**) were also obtained (Table 1, Entry **6h** and **6g**).

As a representative sample, the ^{1}H NMR (DMSO-d_6, 400 MHz) spectrum of **6d** exhibited a sharp singlet identified as amide (δ = 10.78) protons. The distinct signals (δ = 8.23-7.51) corresponded to the aromatic protons (Figure 1). The proton decoupled ^{13}C NMR spectrum of **6d** also showed 21 distinct resonances in agreement with the proposed structure. The appearance of the signal for carbonyl

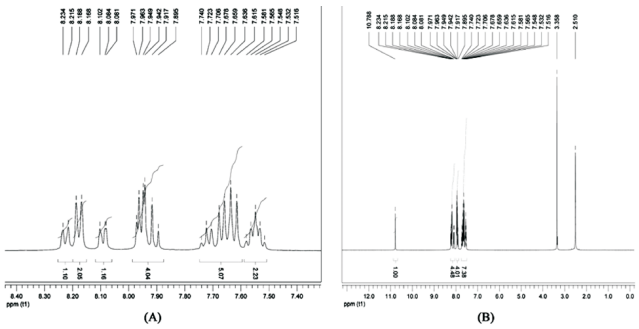
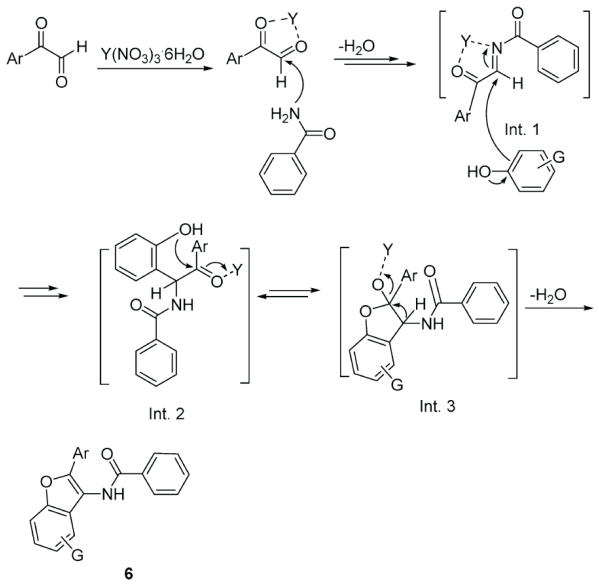


Fig. 1. Regular (A) and extended (B) ^{1}H NMR spectrums for compound **6d**.

of amide group at 166.63 ppm can prove that the compounds 6d have been formed as only isomer. Another evidence for the formation of regioisomer 6d is the appearance of one peak in the infrared for secondary amide at 3205 cm^{-1}.

On the basis of the general mechanistic pathway for the formation of compounds **6**, Scheme III 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, intramolecular cyclization of intermediate **2** gives intermediate **3** followed by dehydration to form corresponding product **6**.

Scheme III Suggested mechanism for the formation of benzofurans **6** using yttrium nitrate hexahydrate



We belive that one of the driving forces of this regiospecificity may be less reactivity of benzamido group than that of benzoyl group.

In summary, the reaction between benzamide, various arylglyoxals, and phenols in the presence of yttrium nitrate hexahydrate provides a simple one-pot entry for the synthesis of novel polycyclic heteroaromatic compounds of potential synthetic and pharmaceutical interest. This method has advantages such as high yields of products and a simple workup procedure.

EXPERIMENTAL

General. Arylgloxals were prepared by the appropriate reported procedure.[29,30] All other chemicals used in this study were commercially available and purchased from Merck and Aldrich. 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.

General procedure for the synthesis of benzofurans 6. A mixture of arylglyoxal (1 mmol), benzamide (1 mmol), and yttrium nitrate hexahydrate (0.1 mmol) was stirred and heated at 70 °C in a preheated oil bath for 30 min. Then the phenolic substrate was added and the mixture was stirred at 110 °C for an appropriate time (4-6 h). After completion of the reaction as indicated by TLC (EtOAc/hexane, 1:2), the reaction mixture was dissolved in hot EtOH and recrystallized to obtain pure products **6**.

1-Benzamido-2-phenylnaphtho[2,1-b]furan (6a). Mp 230-232 ºC; IR (KBr) *v*: 3160, 3110, 2089, 1640, 1485, 1260, 1040, 800, 700 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): 10.78 (s, 1H), 8.26 (d, 1H, J = 7.6 Hz), 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 (6b).** Mp 239-241 ºC; IR (KBr) *v*: 3165, 3110, 2950, 1640, 1510, 1475, 1260, 1040, 800, 700 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): 10.70 (s, 1H), 8.22 (d , 1H, J = 8.0 Hz), 8.24 (d , 2H, J = 6.8 Hz), 8.07 (d , 1H, J = 8.0 Hz), 7.89 (t , 4H, J = 8.4 Hz), 7.64-7.74 (m, 3H), 7.50-7.56 (m, 2H), 3.81 (s, 3H), 7.11 (d, 1H); ^{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 (6c).** 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 (6d).** 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 (6e).** 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 (d, 1H, *J* = 9.2 Hz), 7.91 (d, 1H, *J* = 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, 126.71, 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 (6f).** 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 (6g).** 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, 166.74, 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-benzamido-benzofuran (6h).** 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), 8.00-8.02 (m, 2H), 7.90-7.95 (m, 2H), 7.48-7.72 (m, 6H); ^{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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