An Efficient and Direct Solvent-Free Synthesis of Naphtho[1,2-*b*]furans, Naphtho[2,1-*b*]furans, and Furo[3,2-*c*]chromenes

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Abstract: An efficient and direct synthesis of naphtho[1,2-*b*]furans, naphtho[2,1-*b*]furans, and furo[3,2-*c*]chromenes is described. Heating a mixture of a naphthol or 4-hydroxycoumarin, an isocyanide, and an aldehyde under an argon atmosphere and solvent-free conditions afforded the title compounds in excellent yields.

Key words: naphtho[1,2-*b*]furans, naphtho[2,1-*b*]furans, furo[3,2-*c*]chromenes, isocyanides, three-component reactions, solvent-free synthesis, cyclizations, heterocycles

Extended arenofurans have potential applications as fluorescent dyes, probes and photosensitizers, organic light-emitting diodes, two-photon absorption materials, second- and higher-order nonlinear optics, and supramolecular structures.[1–5]

The naphthofuran nucleus is a key structural motif found in some natural products such as (±)-laevigatin (**1**, Figure 1).[6] Several synthetic compounds containing a naphthofuran scaffold have been shown to possess diverse biological activities such as antifungal,[7] antibacterial,[8] antiviral,[9] β-adrenolytic,[10] antitumor,[11] and anthelmintic[12] activity. 7-Methoxy-2-nitronaphtho[2,1-*b*]furan (**2**) is one of the strongest mutagens described for mammalian cells.[13] The development of efficient syntheses of these bioactive heterocycles has thus attracted many organic and medicinal chemists for decades and continues to be an active research area.

In 2002, Nair et al. reported a three-component reaction between 4-hydroxycoumarin, 4-hydroxypyrone, or 4-hydroxyquinolinone, cyclohexyl isocyanide, and aldehydes in refluxing benzene to afford the corresponding annelated furans.[14] However, their procedure has some drawbacks such as long reaction times (12–24 h) and, in some cases, fairly low yields of the products (down to 34%). Furthermore, it cannot be extended to naphthols, which are unreactive under the same reaction conditions.

In 2006, an aminobenzofuran synthesis was reported from a three-component reaction between phenols, aldehydes, and isocyanides.[14] This procedure involved formation of Mannich adducts **3** from phenols or β-naphthol, an aldehyde, and *N*

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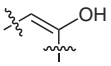
Table 1 Synthesis of 2-Aminoarenofurans **7a**–**p**

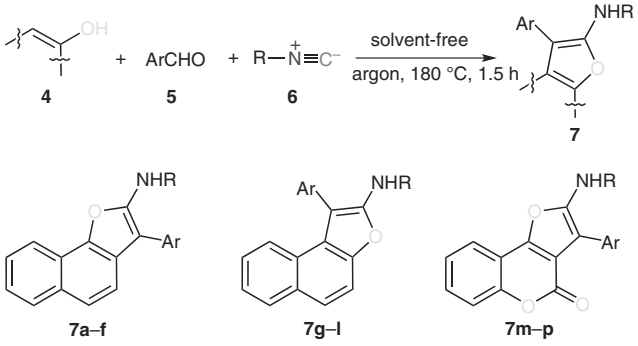
7		Ar	R	Yield (%)[a]
7a	α-naphthol	Ph	*c*-Hex	92
7b	α-naphthol	Ph	*t*-Bu	93
7c	α-naphthol	4-MeC_6H_4	*c*-Hex	90
7d	α-naphthol	4-MeC_6H_4	*t*-Bu	95
7e	α-naphthol	4-MeC_6H_4	1,1,3,3-tetramethylbutyl	90
7f	α-naphthol	4-MeC_6H_4	*c*-Hex	90
7g	β-naphthol	Ph	*c*-Hex	85
7h	β-naphthol	4-MeC_6H_4	*t*-Bu	88
7i	β-naphthol	3-MeC_6H_4	*c*-Hex	83
7j	β-naphthol	4-FC_6H_4	*t*-Bu	89
7k	β-naphthol	4-FC_6H_4	*c*-Hex	84
7l	β-naphthol	4-MeC_6H_4	*c*-Hex	89
7m	4-hydroxycoumarin	Ph	*c*-Hex	91
7n	4-hydroxycoumarin	Ph	*t*-Bu	95
7o	4-hydroxycoumarin	4-MeC_6H_4	*t*-Bu	95
7p	4-hydroxycoumarin	4-MeC_6H_4	1,1,3,3-tetramethylbutyl	93

[a] Isolated yields.

4 h to 1 d for the aminofuran formation), fairly low yields of the products (60–91% for the first step and 25–76% for the second, and lower yields in a one-pot procedure without isolation of the Mannich intermediate), and low atom-economy.

In recent times, the progress in the field of solvent-free reactions is gaining significance because of their high efficiency, operational simplicity, and environmentally benign processes.[15] As part of our continuing efforts on the development of new routes for the preparation of biologically active heterocyclic compounds,[16] we report herein an efficient and direct synthesis of these bioactive heterocycles via a one-pot and solvent-free reaction.

Thus a mixture of α-naphthol, β-naphthol, or 4-hydroxycoumarin **4**, an aldehyde **5**, and an isocyanide **6** underwent a one-pot addition reaction under an argon atmosphere and solvent-free conditions. The reaction proceeded at 180 °C and was complete within 1.5 hours to produce *N*-alkyl-3-arylnaphtho[1,2-*b*]furan-2-amines **7a**–**f** in 90–95% yields, *N*-alkyl-3-arylnaphtho[2,1-*b*]furan-2-amines **7g**–**l** in 83–89% yields, and *N*-alkyl-3-arylfuro[3,2-*c*]chromenes **7m**–**p** in 91–95% yields (Scheme 2, Table 1).[17] ^{1}H NMR analysis of the reaction mixtures clearly indicated formation of the corresponding 2-aminoarenofurans **7**.



Scheme 2

The structures of the isolated products **7** were deduced by means of ^{1}H NMR and ^{13}C NMR spectroscopy and elemental analysis.[17]

A mechanistic rationalization for this reaction is provided in Scheme 3. The first step may involve condensation of the enol **4** with the aldehyde and formation of enone intermediate **8**. Then [4+1] cycloaddition of this *ortho*-quinone methide and the isocyanide **6** gives an iminolactone intermediate **9**, which tautomerizes to 2-aminofuran **7** under the reaction conditions.

Scheme 3

In conclusion, we have developed an efficient and direct route for the preparation of naphtho[1,2-*b*]furans, naphtho[2,1-*b*]furans, and furo[3,2-*c*]chromenes of potential synthetic, chemical, and pharmacological interest. Readily available substrates, simple experimental procedure, excellent yields of the products, fairly short reaction times, and environmentally friendly reaction conditions characterize the present three-component reaction.

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