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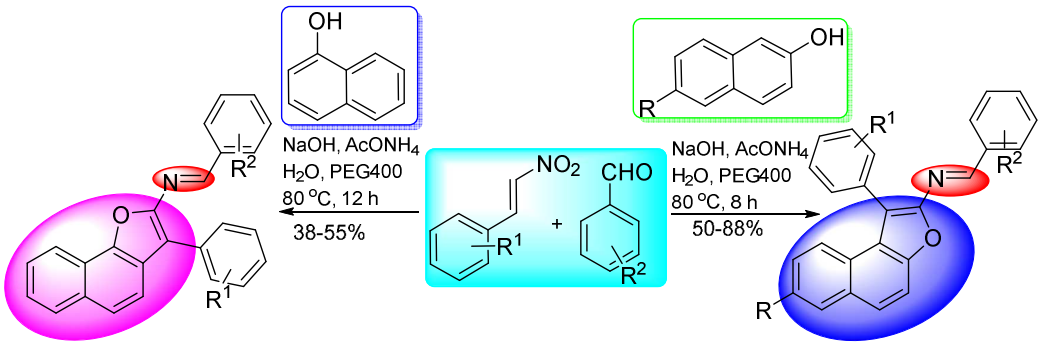

The diversity-oriented synthesis of naphtho[*b*]furans via four-component reaction between naphthanols, substituted *β*-nitrostyrenes, substituted benzaldehydes and ammonium acetate has been developed.

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ARTICLE TYPE

Four-component reaction between naphthols, substituted β-nitrostyrenes, substituted benzaldehydes and ammonium acetate in water-PEG 400: approach to construct polysubstituted naphthofuranamines

Jungui Zhang, Juan Yao, Jiaming Liu, Shuwen Xue, Yang Li and Cunde Wang*

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An eco-friendly straightforward and efficient one-pot four-component protocol has been developed for the synthesis of naphtho[*b*]furan scaffolds in water-PEG-400 (6:1, v/v) at 80 °C from naphthanols, substituted *β*-nitrostyrenes, substituted benzaldehydes and ammonium acetate. The new efficient domino reaction formed a furan ring and a Schiff base core by the concomitant formation of C–C, C–O, and C–N multiple bonds presumably involving a sequence of Michael reaction, aza-ene reaction, imine-enamine/keto-enol tautomerization, O-cyclization and aromatization as key steps.

Naphthofurans are ubiquitous structural subunits in natural products, synthetic pharmaceuticals, and a broad variety of bioactive molecules.[1] Recently, the naphthofurans have attracted more attention, numerous naphthofuran derivatives were investigated extensively as highly potent inhibitory kappa-*β* kinase inhibitors,[2] nicotinic acetylcholine receptor agonists,[3] hepatocyte nuclear factor 4 alpha inhibitors,[4] regulators of the nuclear receptor HNF4R,[5] imaging agents for *β*-amyloid plaques in the brain,[6] potential anticancer agents,[7,1a] antimicrobial agents,[8] anti-inflammatory agents,[9] anti-diabetic agents,[10] and analgesic active agents.[11] Due to the biological importance and synthetic utility, a lot of methods for the construction of naphthofurans have been developed. Traditionally, the classical preparation of the naphthofuran derivatives utilized the Williamson reaction/intramolecular Aldol reaction of 1-acyl naphthols or 2-acyl naphthols with *α*-halo ketones or esters, followed by dehydrative cyclization of the acyl ether intermediate.[12] The naphthofuran derivatives were also synthesized via the intramolecular Friedel-Crafts reaction of appropriate naphthoxy ketones prepared from *α*- or *β*-naphthols and α-halo ketone,[13] via the novel Friedel−Crafts alkylation/annulations cascade reaction from 2-naphthols and chalcone epoxides,[14] or Friedel-Crafts/oxa-Michael/aromatic annulation of naphthols with nitroallylic acetates.[15] Recently improved protocol involved the Michael addition of tertiary enaminoketones or *β*-ketoesters to naphthoquinones,[16] In addition to the conventional naphthofuran synthesis, there were also methods via transition metal-promoted reactions for the preparation of the naphthofuran derivatives, such as Pd(II)-catalyzed intramolecular addition of arylboronic acids to ketones,[17] Ru(III)-mediated C- and O-allyl isomerization followed by ring-closing metathesis from the substituted 1-allyl-2-allyloxybenzenes,[18] Pt(II)-catalyzed intramolecular coupling reaction of alkynes with furans,[19] In(III)-catalyzed Friedel-Crafts/ Williamson reaction of naphthols,[20] Cu(I) catalyzed intramolecular aldehyde/yne cyclization of 3-(1-alkenyl)-2-alkene-1-al,[21] Fe(III)-catalyzed intramolecular hydroaryloxylation of 2-propargyl naphthols,[22] $W(CO)_5$-catalyzed electrocyclization reaction of substituted aromatic enynes,[23] $TiCl_4$ assisted rearrangement of allyl naphthyl ethers.[24] Additionally, several other effective approachs have also been used for the synthesis of naphthofuran derivatives such as intramolecular cyclization of α-styrylnaphthols,[25] Michael addition/cyclization of phenolic Mannich bases and pyridinium ylides,[26] IBX assisted the oxidization of 2-(naphthalen-6-yloxy)ethanol followed intramolecular cyclization,[27] and via one-pot addition reaction of naphthols, aldehydes, and isocyanides under an argon atmosphere and solvent-free conditions.[28] However, most of these methods lacked generality and involved multistep reactions from commercially available starting materials. To address this problem, further development of novel and efficient methods for the preparation of naphthofurans with various structural features and substitution patterns, especially those containing nitrogen groups is highly desirable. During our studies on the Michael addition mediated transformations of *β*-nitrostyrenes,[29] we have demonstrated that *β*-nitrostyrenes is a highly efficient building block for the Michael addition/nitro-Mannich/lactamization cascade reactions between *β*-nitrostyrenes, aromatic aldehydes, dialkyl malonates or Meldrum's acid, and ammonium acetate or formamide to construct complex polysubstituted piperidines[29b,29c,29d] and for the novel Michael addition/aza-nucleophilic addition/annulations cascade reaction between substituted *β*-nitrostyrenes, aromatic aldehydes, ammonium acetate, and cyclohexane-1,3-diones or coumarins to construct polysubstituted benzo[*b*]furans and furo [3,2-c]chromens.[29e,29f]

Recent years more and more investigations found that water as a good reaction medium was used for various organic reactions.[30] In water as a solvent, the design of new MCRs has attracted numerous attention,[31] especially in the areas of drug discovery, and material science.[32] Additionally, because polyethylene glycol (PEG) possesses low toxicity and solubility in both aqueous and

non-aqueous media,[33] it is advantageous over toxic organic solvents, which is a greener alternative in various organic transformations. Several reports have used water as a solvent in the presence of PEG for organic reactions.[34] To the best of our knowledge, no example using one-pot multi-component reactions of substituted *β*-nitrostyrenes, naphthols, substituted benzaldehydes and ammonium acetate in water/PEG to construct the naphtho[*b*]furan core were reported. These products were described as potent anticancer agents, anti-inflammatory, antimalarial agents, and biologically active natural compound Furomollugin as shown in Figure 1.[35]

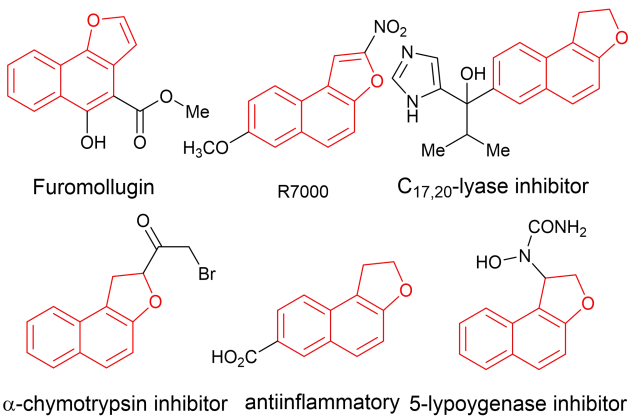
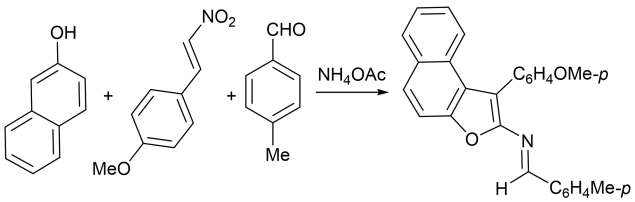


Fig. 1 Structure of bioactive naphthofurans.

Encouraged by the illustrated biological and synthetic interest in 1-arylnaphtho[*b*]furan-2-amines and prompted by the recent results for the combination of MCRs and water as a solvent, we envisaged a novel synthetic pathway to *N*-benzylidenearylnaphtho[*b*]furan-2-amines starting from naphthols (**1**), substituted nitrostyrenes (**2**), substituted benzaldehydes (**3**), and ammonium acetate. Herein we report a facile and straightforward method to synthesize polysubstituted naphtho[*b*]furan Schiff bases from substituted *β*-nitrostyrenes, naphthols, substituted benzaldehydes and ammonium acetate via one-pot four-component reactions in water-PEG-400.

Initially, based on our more recent results,[29a] we examined the reaction of *β*-naphthol (**1a**), 1-methoxy-4-(2-nitrovinyl)benzene (**2a**), *p*-methylbenzaldehyde (**3a**) with ammonium acetate in EtOH using piperidine as a promoter, but the desired product was not obtained (Table 1, entry 1). Next the replacement of piperidine and EtOH by trimethylamine and DMF also did not give the desired product (Table 1, entry 2).[29] Then the solvent DMF was replaced with EtOH or MeOH for the reaction under the same condition, no reaction still occurred (Table 1, entries 3 and 4). Considering the naphthalen-2-olate easily generated from *β*-naphthol with strong inorganic base such as NaOH for the electrophilic attack of *β*-nitrostyrene, the mixture of *β*-naphthol (**1a**), 1-methoxy-4-(2-nitrovinyl)benzene (**2a**), *p*-methylbenzaldehyde (**3a**), NH_4OAc with NaOH in EtOH was stirred at 8 h and refluxed at 16 h, pleasingly, the desired product **4a** was obtained in 17% yield (Table 1, entry 5). Next, switching the solvent to water, we performed the model reaction at 80 °C under similar conditions, which afforded the desired product **4a** in 32 % yield (Table 1, entry 6). Although the yield of **4a** was slightly improved, starting materials still encountered a solubility problem. Reconsidering that low molecule polyethylene glycol (PEG) could promote to solubilize organic components in water as a water soluble polyether, in order to make the reaction more efficient, we investigated the model reaction in various molecule PEG and water (1/6, v/v) at 80 °C, and to our delight the desired product was obtained in 35%, 65%, 64% yield within 10 h, respectively (Table 1, entries 7-9). Encouraged by the above result, we carried out the reaction by changing amount of NaOH in a mixture of PEG-400 and H_2O (1:6), using 2 equivalents NaOH afforded the desired product in 72% yield (Table 1, entry 10), and to our delight the yield of the desired product **4a** was obviously improved and the reaction time was shorted to 8 h. Further increase of the amount of NaOH had no significant beneficial effect on the reaction (Table 1, entry 11). The ratio 7:1 of water-PEG-400 was tested for the title reaction, the result showed that part of the starting materials did not dissolve in the mixture solvent, only afforded the desired product in 57% yield (Table 1, entry 12). Replacing NaOH with KOH led to similar yield of product **4a** (Table 1, entry 13).

Table 1 Optimisation of the reaction conditions[a]



1a **2a** **3a** **4a**

Entry	base	Solvent(V/V)	T (°C)	t (h)	Yield (%)[b]
1	Piperidine(1)	EtOH	reflux	24	0
2	Et_3N(1eq)	DMF	reflux	24	0
3	Et_3N(1eq)	EtOH	reflux	24	0
4	Et_3N(1eq)	MeOH	reflux	24	0
5	NaOH(1eq)	EtOH	reflux	24	17
6	NaOH(1eq)	H_2O	80	10	32
7	NaOH(1eq)	H_2O/PEG200(6/1)	80	10	35
8	NaOH(1eq)	H_2O/PEG400(6/1)	80	10	65
9	NaOH(1eq)	H_2O/PEG600(6/1)	80	10	64
10	NaOH(2eq)	H_2O/PEG400(6/1)	80	8	78
11	NaOH(3eq)	H_2O/PEG400(6/1)	80	8	73
12	NaOH(2eq)	H_2O/PEG400(7/1)	80	8	57
13	KOH(2eq)	H_2O/PEG400(6/1)	80	8	70
14	NaOH(2eq)	H_2O/PEG400(6/1)	80	8	80[c]
15	NaOH(2eq)	H_2O/PEG400(6/1)	80	8	79[d]
16	NaOH(2eq)	H_2O/PEG400(6/1)	80	8	86[c,e]

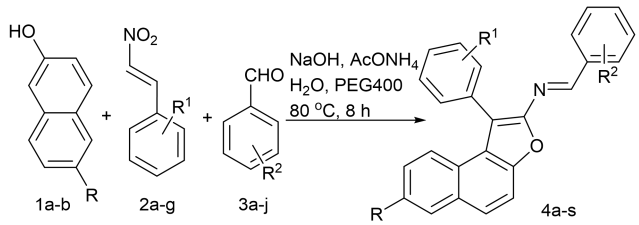
[a]Reaction conditions: 3 mmol **2a**, **1a**/**2a**/**3a**/NH_4OAc =1.5/1/1/1eq, 15 mL solvent, H_2O/PEG (6/1, V/V). [b]Yields were isolated.[c]**1a**/**2a**/**3a**/NH_4OAc =1.5/1/1/2eq; [d]**1a**/**2a**/**3a**/NH_4OAc =1.5/1/1/2.5eq;[e]The mixture of **3a**/NH_4OAc was stirred for 30 min firstly, then the reaction was carried out by above conditions.

Further experiments revealed that the ratio of starting materials as **1a**/**2a**/**3a**/NH_4OAc =1.5/1/1/2eq was confirmed to be the most effective ratio (Table 1, entries 14 and 15). When the mixture of **3a**/NH_4OAc was stirred for 30 min firstly, then the reaction was carried out by above conditions to give the best yield (Table 1, entry 16). A series of experiments revealed that the optimal results were obtained when the reaction of 1.5 equivalents *β*-naphthol (**1a**), 1 equivalent 1-methoxy-4-(2-nitrovinyl)benzene (**2a**), 1 equivalent *p*-methylbenzaldehyde (**3a**), 2 equivalent NH_4OAc together with 2 equivalent NaOH was carried out in a

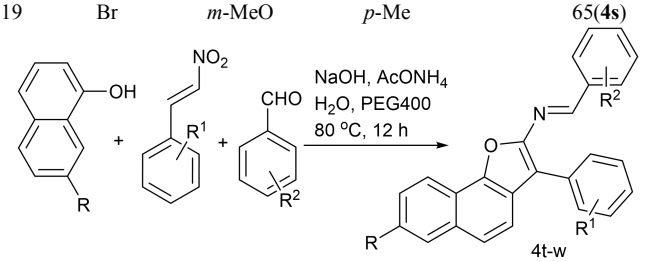
mixture of PEG-400 and H_2O (1:6, v/v), the resultant mixture was stirred for 8 h at 80 °C, whereby the yield of **4a** reached 86% (Table 1, entry 14).

Having established the optimal conditions for the synthesis of polysubstituted naphtho[2,1-*b*]furan **4a**, to determine the scope of the protocol, a number of available *β*-naphthols and substituted *β*-nitrostyrenes were condensed with substituted benzaldehydes and ammonium acetate under optimized reaction condition. The results were summarized in Table 2.

Table 2 Synthesis of polysubstituted naphthofuranamines via four-component reaction



Entry	R	R^1	R^2	Yield%[a]
1	H	*p*-MeO	*p*-Me	86(**4a**)
2	H	*m*-MeO	*p*-Cl	83(**4b**)
3	H	*p*-Br	*m*-Br	50(**4c**)
4	H	*p*-Br	*p*-Me	77(**4d**)
5	Br	*p*-Me	*o*-Cl	76(**4e**)
6	H	*p*-Br	*p*-MeO	80(**4f**)
7	Br	*p*-Me	*p*-Me	55(**4g**)
8	H	*p*-Cl	*o*-MeO	78(**4h**)
9	H	*p*-Cl	*p*-Me	82(**4i**)
10	H	*p*-NO_2	*p*-MeO	56(**4j**)
11	H	*p*-MeO	*o*-Cl	75(**4k**)
12	Br	*p*-Cl	3-phenoxy	83(**4l**)
13	H	*p*-MeO	*p*-MeO	88(**4m**)
14	H	*p*-MeO	3-thiophene[b]	76(**4n**)
15	H	*p*-Br	4-F-3-PhO	87(**4o**)
16	H	*p*-Cl	*m*-PhO	86(**4p**)
17	H	*p*-Cl	*m*-MeO	58(**4q**)
18	Br	*p*-Cl	*m*-Br	54(**4r**)
19	Br	*m*-MeO	*p*-Me	65(**4s**)



20	H	*p*-Br	*o*-MeO	38(**4t**)
21	H	*p*-Br	*p*-Me	45(**4u**)
22	H	*p*-Me	*p*-MeO	55(**4v**)
23	H	*p*-MeO	*p*-Br	50(**4w**)
24	H	*p*-Cl	*p*-Br	44(**4x**)

[a] isolated yield, [b]thiophene-3-carbaldehyde

The reaction tolerates different substituents on the aromatic ring of the naphthanols, substituted *β*-nitrostyrenes and substituted benzaldehydes, generally, *β*-nitrostyrenes and substituted benzaldehydes with a range of substitutents such as methyl, phenoxyl, methoxy, halo and nitro at *ortho*-, *meta*- or *para*-positions of phenyl groups all worked well to give polysubstituted naphtho[2,1-*b*]furan Schiff base derivatives. Various *β*-nitrostyrenes and substituted benzaldehydes possessing substituents of electron-donating groups afforded the corresponding naphtho[2,1-*b*]furan products in good to excellent yields. Substrates with *para*-position phenyl groups gave the products in higher yields than those with *ortho*-, or *meta*-position phenyl groups. The electronic properties of the substituents on the benzene ring of substituted benzaldehydes had a slight effect on the reaction. The introduction of an electron-withdrawing group such as NO_2 or Br speeded down the reaction and decreased the yield of product, thus various substituents should facilitate the synthesis of diversely polysubstituted naphtho[2,1-*b*]furan Schiff base derivatives. However, we found that the replacement of *β*-naphthalenol with *α*-naphthalenol gave the polysubstituted naphtho[1,2-*b*]furan Schiff base derivatives in slight lower yields, and a longer reaction time was required (Table 2, entries 20-24). In the presence of NaOH, β-naphthalenol was changed to β-naphthalenol anion, followed transferring to carbon anion by keto-enol tautomerism for attacking β-nitrostyrenes more easily than α-naphthalenol. All corresponding products were analyzed by their ^{1}H NMR, ^{13}C NMR and MS. Characteristic ^{1}H chemical shift of naphtho[*b*]furan Schiff base N=C*H*Ar at δ ca 9.00(s). Additionally, the structures of naphtho[2,1-*b*]furan Schiff base **4b** and **4f** were unambiguously solved by X-ray crystallography (Fig. 2).[36] X-ray crystallographic analysis determined that product **4b** and **4f** possess a naphtho[*b*]furan core, an aryl and an arylimine contiguous substituents at C(1) and C(2) of naphtho[2,1-*b*]furan. On the basis of spectroscopic evidence the structures of compound **4a-s** were identified as 1-aryl-2-arylideneamino naphtho[2,1-*b*]furan .

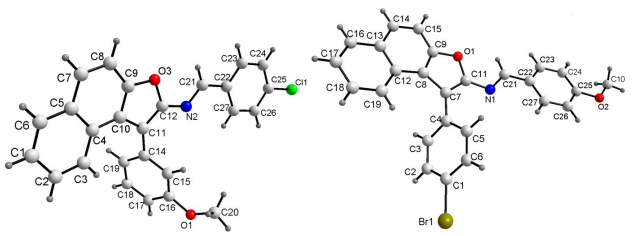
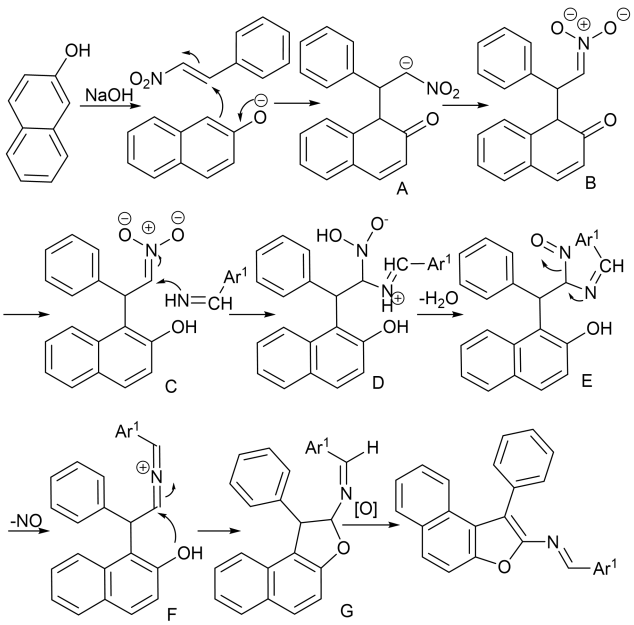


Fig. 2. Molecular structure of naphtho[2,1-*b*]furan derivatives **4b** and **4f**



Scheme 1 Tentative reaction mechanism.

The mechanism of this process can be rationalized as a sequence of reactions starting from the initial anion of the starting naphthalen-2-ol. The base-catalyzed Michael reaction between the naphthalen-2-olate anion and the *β*-nitrostyrene affords the corresponding intermediate carbanion [**A**]. Then, the carbanion [**A**] is transferred via the keto-enol tautomerism to an intermediate oxido oxime [**B**], the following forming an intermediate [**C**], which then reacts with arylimine generated from aromatic aldehyde and ammonium acetate to give intermediate [**D**]. Then dehydration of intermediate [**D**] gives a nitroso imine intermediate [**E**], Conversion of the intermediate [**E**] to an intermediate [**F**] takes place via removal of nitroso group, a final cyclocondensation affords intermediate [**G**].[37] Finally, aromatization of the intermediate [**G**] yields the corresponding polysubstituted naphtho[2,1-*b*]furan with a Schiff base (Scheme 1).

In summary, we have developed an eco-friendly straightforward and efficient one-pot four-component protocol for the synthesis of naphtho[2,1-b]furan and naphtho[1,2-*b*]furan scaffolds in water-PEG-400 (6:1; v/v) at 80 °C from naphthanols, substituted *β*-nitrostyrenes, substituted benzaldehydes and ammonium acetate. The new efficient domino protocol generated a furan ring and a Schiff base core by the concomitant formation of C–C, C–O, and C–N multiple bonds presumably involving a sequence of Michael reaction, aza-ene reaction, imine-enamine/keto-enol tautomerization, O-cyclization and aromatization as key steps. The merit of this method was highlighted by its broad substrate scope and excellent functionality tolerance, operational simplicity and simple workup procedure, which enabled the rapid assembly of diverse naphtho[*b*]furan frameworks utilizing all the four reactants efficiently for the generation of a wide range of structurally interesting and pharmacologically significant compounds. We expect that the resulting biologically intriguing structures will have broad applications in both synthetic and medicinal researches.

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Notes and references

School of Chemistry and Chemical Engineering, Yangzhou University,180 Siwangting Street, Yangzhou 225002, P. R. China. Fax: +86-514-8797-5244; Tel: +86-514-8797-5568; E-mail: wangcd@yzu.edu.cn; New division: School of Hydraulic, Energy and Power Engineering for Mr. Jungui Zhang

Electronic supplementary information (ESI) available: Reaction conditions and spectra. CCDC 1043771 and 1028400. For ESI and crystallographic data in CIF or other electronic format see DOI:

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