Received: 16 February 2021 | Revised: 20 April 2021 | Accepted: 20 April 2021

DOI: 10.1002/jhet.4280

COMMUNICATIONS

JOURNAL OF HETEROCYCLIC CHEMISTRY WILEY

Silica sulfuric acid mediated synthesis of naphtho[2,1-*b*]furan derivatives and development of one-pot multicomponent synthesis of substituted pyrazole derivatives

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Abstract

Silica sulfuric acid (SSA) mediated synthesis of naphtho[2,1-b]furan derivatives starting from β-nitrostyrene derivatives and β-naphthol derivatives under solvent-free conditions have been developed. The scope of SSA as a heterogeneous catalyst is extended to one-pot multicomponent reaction for the synthesis of functionalized pyrazole derivatives under solvent-free conditions from readily available β-nitrostyrene derivatives, acetyl acetone, and hydrazine hydrate. The synthetic methods have significant advantages such as solvent-free conditions, simple operation, shorter reaction times, ease and clean isolation procedures, and very good yields of products.

KEYWORDS

Multicomponent, naphthofuran, nitrostyrene, Pyrazole, Silica sulfuric acid

1 | INTRODUCTION

In recent years, heterogeneous catalysts grabbed much attention toward synthetic organic chemistry due to environ-economic factors [1–3]. Among heterogeneous catalysts silica sulfuric acid (SSA) has demonstrated its potentiality as an efficient solid catalyst in various organic transformations under solvent-free conditions [4]. SSA, a product that is easily synthesized from silica gel and chlorosulfonic acid [5], was observed to improve the reactivity and selectivity in carbon–carbon bond formation reactions [6], in cycloaddition reactions [7], in protection–deprotection reactions of multistep syntheses [8], and in syntheses of heterocycles [9].

In the era of gradually increasing relevance of sustainability and environmental concern, the concept of multicomponent reactions (MCRs) is one of most efficient tools in synthetic organic chemistry since they have all features that contribute to ideal synthesis [10–12]. In synthetic methodology, MCRs never become old-fashioned because they always encourage creative spirits by following the basic quest: three or more compounds are combined to react in a one-pot fashion to form two or more bonds. Therefore, MCRs are regularly fascinating for industrial applications as thrilling and stimulating for academia [13].

Furan moieties are common substructures in numerous natural products [14]. Particularly, naphthofuran derivatives are known for several types of biological activities like antifertility, growth inhibitory, antitumor, mutagenic, and oestrogenic [15]. In recent years, a variety of efficient methods have been developed for the synthesis of naphtho[2,1-b]furan derivatives [16]. Recently, Tavakol and co-workers developed an efficient methodology from nitrostyrenes and naphthols in $ChCl/ZnCl_2$ DES as green reaction media [16d]. Hajra and co-workers used $In(OTf)_3$ as a catalyst for the reaction of nitroalkenes with naphthols that yielded naphthofuran derivatives in good yield [17]. Zheng and co-workers reported the synthesis of naphtho[2,1-b]furan derivatives under microwave irradiation [18]. Zhang et al. reported the synthesis of benzoindoles and naphthofuran

derivatives using carbonaceous materials [19]. However, most of the methods suffer from using metals as a catalyst, higher temperatures, and longer reaction times.

Heterocyclic compounds containing pyrazole nucleus is a recurring structural motif in a large number of drug molecules and pharmaceutically important naturally occurring molecules [20]. Importantly, bioactive natural products and synthetic analogs of pyrazole derivatives have demonstrated various biological profiles such as antibacterial, antihyperglycemic, antiviral, anti-inflammatory, pesticidal, and antitumor agents [20–28]. In general, the synthesis of pyrazoles can be achieved by reacting (substituted) hydrazines with β-functional (either 1,3-dicarbonyl compounds or α,β-unsaturated compounds) compounds, 1,3-dipolar cycloaddition with diazo compounds, degradation of fused pyrazole, and rearrangement of other monocyclic heterocycles under chemical, thermal, and photochemical conditions [29]. Due to the broad spectrum of applications of pyrazole moiety the synthesis of diversified pyrazole derivatives has been a continuously challenging task to synthetic organic chemist [30–33]. Shang and co-workers employed SSA as a heterogeneous catalyst for the synthesis of series of substituted pyrazole derivatives from the reaction of hydrazines with 1,3-dicarbonyl compounds [34]. Herein, we wish to report synthetic methodology for the construction of naphtho[2-1,b]furan derivatives and also functionalized pyrazole derivatives by one-pot multicomponent procedure using SSA as a catalyst.

From the literature survey, it was revealed that many synthetic procedures are reported for the preparation of benzofuran derivatives. However, the reports corresponding to the preparation of naphthofuran derivatives are scanty. We became interested to develop a facile and efficient methodology for the naphthofuran derivatives.

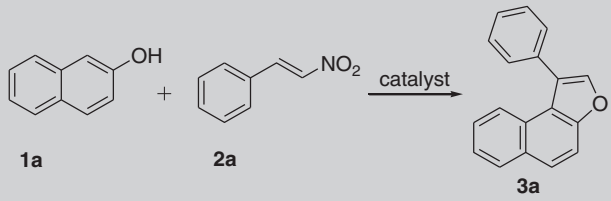


TABLE 1 Optimization of reaction conditions for the synthesis of naphthofuran derivative **3a**

Entry	Catalyst	Catalyst loading	Solvent	Time (h)	Yield[a] (%)
1	Silica gel	500 mg	Neat	2	60
2	Silica gel	600 mg	Neat	2	61
3	Silica gel	400 mg	Neat	2	52
4	Silica gel	500 mg	Neat	2	59[b]
5	Silica gel	500 mg	H_2O	4	17
6	Silica gel	500 mg	Acetic acid	6	29
7	Silica gel	500 mg	CH_2Cl_2	8	Trace[c]
8	Silica gel	500 mg	$CHCl_3$	8	Trace[c]
9	H_2SO_4	20 mol%	Neat	3	24
10	SSA	500 mg	Neat	0.5	94
11	**SSA**	**400 mg**	**Neat**	**0.5**	**96**
12	SSA	400 mg	H_2O	4	74
13	SSA	400 mg	CH_2Cl_2	8	11
14	SSA	400 mg	$CHCl_3$	8	Trace[c]
15	SSA	400 mg	Neat	0.5	92[b]
16	SSA	400 mg	Acetic acid	6	25

Note: All reactions were carried out with 1 equiv. of β-naphthol and 1 equiv. of β-nitrostyrene at room temperature unless otherwise mentioned. In case of water as solvent 5 ml and others 3 ml has been used. Bold value indicates that the reaction was stirred for 30 minutes underaerobic conditions using 400 mg of SSA.

[a]Yields of isolated products.

[b]Reaction carried out at 50°C.

[c]Isolated using preparative TLC.

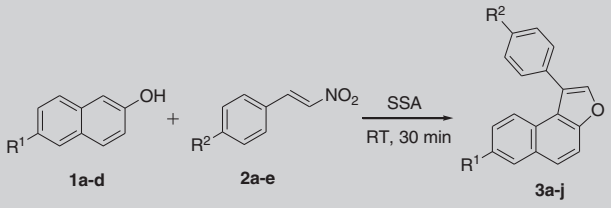
In our initial experiments, 1 mmol of β-naphthol **1a** is treated with 1 mmol of β-nitrostyrene **2a** in the presence of 500 mg of silica gel (100–200 mesh) at room temperature for 2 h. To our delight, we have obtained the product **3a** in 60% yield (Table 1 entry 1). To gauge the effect of catalyst loading, solvent and temperature we have performed series of reactions under different conditions and results of which are summarized in Table 1. Increasing the catalyst loading does not improve the yield of the product **3a** (Table 1, entry 2). However, decreasing the catalyst loading drops the yield of the product **3a** (Table 1, entry 3). No progress was observed when the reaction was carried out at 50°C (Table 1, entry 4) for 2 h and the product **3a** was isolated in 59% yield. Furthermore, the reaction was screened using different solvents (Table 1, entries 5, 6, 7, and 8) but yields of the product **3a** were not improved. We shifted our attention to SSA and carried out the reaction under solvent-free conditions. Intriguingly, the yield of the product **3a** was increased from 60% to 94% (Table 1, entry 10). Encouraged by these results we estimated the effect of solvents, temperature, and catalyst loading parameters. The yield of the product **3a** was slightly increased by decreasing catalyst loading from 500 to 400 mg (Table 1, entry 11). It was found that temperature was not showing any improvement of the yield of the product **3a** (Table 1, entry 15) and use of the solvents shows a negative effect on the yield of the product **3a** (Table 1, entries 12, 13, 14, and 16).

With a consistent set of conditions in hand, we have extended this synthetic procedure for the reactions of different β-nitrostyrenes **2a-e** with substituted β-naphthols **1a-d** (Table 2). The reactions proceeded smoothly at room temperature to furnish the naphtho[2,1-b]furan derivatives **3a-3i** in good to very good yield. When the reactions were performed with halogen-substituted β-naphthols the yield of naphthofuran derivatives **3b**, **3d**, **3f** and **3h** was dropped (Table 2, entries 2, 4, 6, and 8). This is perhaps due to the withdrawing nature of the halogen which reduces the nucleophilicity of β-naphthols. Accordingly, we carried out another reaction of β-naphthol bearing cyano group as a substituent (**1d**) with β-nitrostyrene under optimized conditions (Table 2, entry 10). No formation of the product **3j** even after 8 h shown by thin-layer chromatography (TLC) analysis and the reactants were recovered. The reactivity of β-nitrostyrene was not much affected by the electronic effects.

Apparently, the reaction involves Michael's addition of β-naphthol to β-nitrostyrene provides Michael adduct which simultaneously undergoes cyclization followed by loss of nitro group under the reaction produce naphtho[2,1-b]furan derivative (Scheme 1).

After successfully developing the synthesis of naphtho[2,1-b]furan derivatives by Michael addition of β-naphthols with β-nitrostyrenes followed by cyclization, it occurred to us that 1,3-diketones act as good nucleophiles via enol formation in the presence of acidic medium and then react with β-nitrostyrenes, transform into Michael adducts. The presence of functional group proximate in Michael adduct can be synthetically transformed into heterocyclic compounds with suitable substrates. Accordingly, we designed a one-pot

TABLE 2 Scope of the substrates

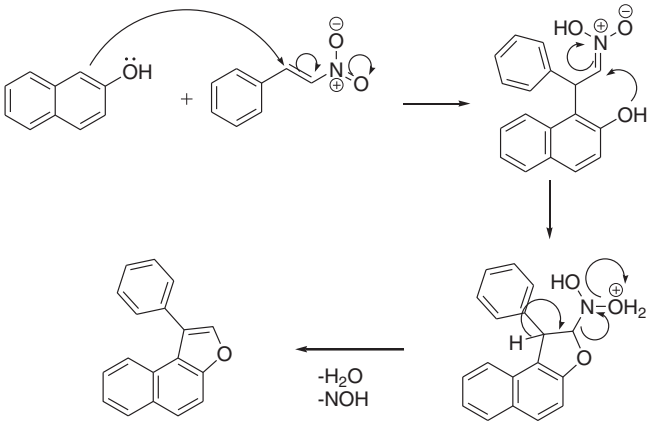


Entry	R^1	R^2	Product	Yield (%)[a]
1	H	H	**3a**	96
2	Br	H	**3b**	79
3	H	CH_3	**3c**	93
4	Br	CH_3	**3d**	78
5	H	OCH_3	**3e**	90
6	Br	OCH_3	**3f**	75
7	H	Br	**3g**	97
8	Cl	Cl	**3h**	75
9	Br	Br	**3i**	78
10	CN	H	**3j**	ND[b]

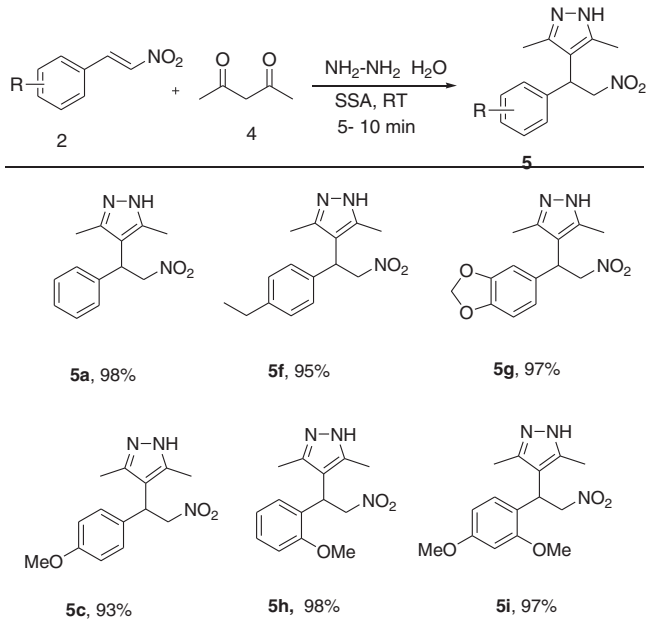
Note: All reactions were carried out with 1 equiv. of β-naphthol and 1 equiv. of β-nitrostyrene unless otherwise mentioned.

[a]Yields of isolated products.

[b]Not detected.



SCHEME 1 Plausible mechanism for the formation of naphthofuran derivatives



SCHEME 2 Synthesis of pyrazole derivatives. All reactions were carried out with 1 equiv. of β-nitrostyrene, 1 equiv. of acetylacetone, and 1 equiv. of hydrazine hydrate unless otherwise mentioned. Yields of isolated products

multicomponent synthetic strategy for the synthesis of pyrazole derivatives by employing β-nitrostyrenes, acetylacetone, and hydrazine hydrate in the presence of SSA. In our preliminary investigations, we allowed β-nitrostyrene, acetylacetone, and hydrazine hydrate to react in the presence of SSA at room temperature under solvent-free conditions. Surprisingly, the reaction was completed after 10 min and the corresponding pyrazole derivative **5a** was isolated in 98% yield (Scheme 2).

Encouraged by these results we proceeded further to extend this procedure to substituted β-nitrostyrenes. The reaction of masked β-nitrostyrene (**2g**) with acetylacetone and hydrazine hydrate provided the pyrazole derivative **5g** in very good yield without cleavage of acetal functional group. This observation reveals that the reaction conditions are very mild. The reactions of other β-nitrostyrenes with acetyl acetone and hydrazine hydrate went smoothly and furnished the corresponding pyrazole derivatives in excellent yield.

In summary, we have developed an efficient methodology for the synthesis of naphtho[2,1-b]furan derivatives from β-nitrostyrenes with β-naphthols in the presence of SSA at room temperature under solvent-free conditions. The method is operationally simple and high yielding at room temperature and circumvents purification problems. A variety of pyrazole derivatives was prepared from one-pot multicomponent procedure starting from readily available β-nitrostyrenes, acetylacetone, and hydrazine in the presence of SSA. The products are isolated in excellent yield. Nevertheless, the presented method provides a simple and short route for naphtho[2,1-b]furan and pyrazole derivatives.

2 | EXPERIMENTAL SECTION

2.1 | General procedure for the synthesis of (3a)

To a mixture of β-naphthol (1) (1.0 mmol) and β-nitrostyrene 2 (1.0 mmol) was added 400 mg of SSA and allowed to stir for 30 min at room temperature. The progress of the reaction was monitored by TLC, after completion of the reaction as shown by TLC. The product was extracted with ether and purified using silica gel column chromatography using 1:5 ethyl acetate and hexanes as eluent.

2.2 | General procedure for the synthesis of (5a)

To a mixture of β-nitrostyrene 2 (1.0 mmol), acetylacetone (1.0 mmol), and hydrazine hydrate (1.0 mmol) was added 400 mg of SSA and allowed to stir for 5–10 min. The progress of the reaction was monitored by TLC, after completion of the reaction as shown by TLC. The product was extracted with ethyl acetate and purified using silica gel column chromatography using 1:5 ethyl acetate and hexanes as eluent.

2.3 | 1-Phenylnaphtho[2,1-b]furan (3a)

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05 (d, J = 8.5 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.80 (d, J = 9.0 Hz, 1H), 7.73 (d, J = 12.5 Hz, 2H), 7.65 (d, J = 7.5 Hz, 2H), 7.57–7.51 (m, 3H), 7.47 (t, J = 7.5 Hz, 1H), 7.41–7.37 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.2, 141.7, 133.1, 130.8, 129.9, 128.9, 128.6, 128.3, 127.9, 126.0, 126.0, 124.5, 124.4, 123.4, 120.7, 112.6 ppm.

2.4 | 3,5-dimethyl-4-(2-nitro-1-phenylethyl)-1*H*-pyrazole (5a)

^{1}H NMR (500 MHz, $CDCl_3$): 7.35–7.29 (m, 2H), 7.28–7.22 (m, 1H), 7.18–7.13 (m, 2H), 5.09–4.99 (m, 1H), 4.93–4.83 (m, 2H), 2.18 (s, 6H).^{13}C NMR (100 MHz, $CDCl_3$): 11.61, 38.82, 78.11, 112.70, 127.09, 127.27,

128.86, 138.67, 142.56. See Appendix S1 for full experimental data.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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How to cite this article: D. S. Uppalapati, R. S. R. Dachuru, S. V. Sunkara, *J Heterocyclic Chem* **2021**, 1. https://doi.org/10.1002/jhet.4280