Tetrahedron Letters 52 (2011) 1213–1216

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A simple and efficient large-scale synthesis of 3-hydroxyphthalans via oxa-Pictet–Spengler reaction catalyzed by nanosilica sulfuric acid

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ARTICLE INFO

Article history:
Received 10 September 2010
Revised 27 November 2010
Accepted 10 January 2011
Available online 18 January 2011

Keywords:
Phthalans
3-Hydroxybenzyl alcohol
Aryl aldehyde
Oxa-Pictet–Spengler reaction
Nanosilica sulfuric acid
Microwave irradiation

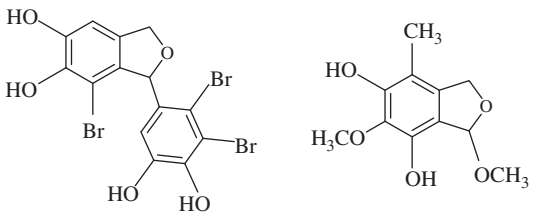
ABSTRACT

Nanosilica sulfuric acid is found to be a new, powerful and reusable heterogeneous catalyst for the rapid synthesis of 3-hydroxyphthalans via condensation of aromatic aldehydes and 3-hydroxybenzyl alcohols under conventional heating and microwave irradiation. Scale-up preparation of these heterocycles is also carried out.

Phthalans (1,3-dihydroisobenzofurans), especially their 3-hydroxy derivatives, constitute an important class of building block because such moieties are found in a wide range of biologically active compounds.[1] An example of such heterocycles is pestacin, which is isolated from the microorganism *Pestalotiopsis microspora* and exhibits a plethora of biological activities.[2] Compound **I** is another example and shows potential antitumor activity.[3] Kim and co-workers isolated hydroxylated 1,3-dihydroisobenzofuran **II**, from *Aspergillus flavipes* as an inhibitor of peptide deformylase (Fig. 1).[4] In addition, some of these derivatives have attracted attention due to their potential as anti-influenza agents.[5] Phthalans are utilized in the agricultural industry and other uses include perfumes and colorants.[6]

An important route to the synthesis of phthalans involves the Lewis acid assisted intramolecular cyclization, which is also known as the oxa-Pictet–Spengler reaction.[7] However, a large excess of a strong Brønsted acid is required and the number of reactants is limited. Recently, Marra and co-workers reported a modified procedure catalyzed by chloroacetic acid or *p*-toluenesulfonic acid in anhydrous methanol under an argon atmosphere,[8] but this method requires long reaction times (48 h) and the products were obtained in low to moderate yields. Therefore, to overcome these problems, more convenient methods for the synthesis of phthalans are required.

The utilization of silica as a solid catalyst has received considerable attention.[9] Modifications of its activity include immobilization of various Brønsted or Lewis acids on this solid support.[10] Silica sulfuric acid is a successful candidate for sulfuric acid replacement in organic synthesis and tolerates acid-sensitive functional groups.[11] Moreover, recent examination of functionalized nanosilica and its applications in organic synthesis has shown unusual behaviors.[12] To achieve an effective and new solid acid catalytic system for heterocyclic synthesis, we decided to concentrate our attention on nanosilica sulfuric acid (NSSA) as a solid Brønsted acid which was prepared easily by adding chlorosulfonic acid to nano-SiO_2 at room temperature. This procedure yielded a white solid which could be stored at room temperature for several months in a desiccator without loss of activity (Scheme 1).



I **II**

Figure 1. Examples of 3-hydroxyphthalans with antitumor **I** and peptide deformylase inhibition **II** activities.

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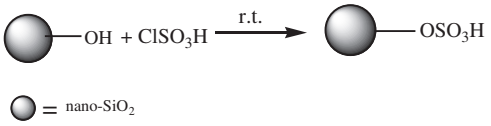
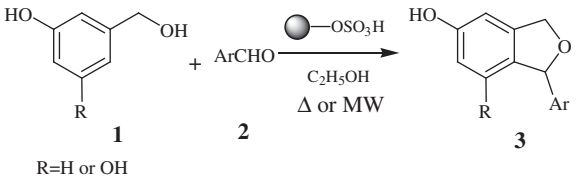
0040-4039/$ - see front matter © 2011 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2011.01.037

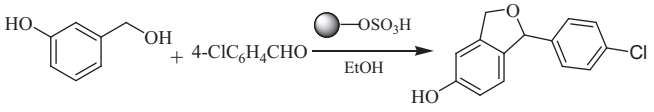


Scheme 1. Conversion of nano-SiO_2 into nanosilica sulfuric acid (NSSA).



Scheme 2. Synthesis of 3-hydroxyphthalans catalyzed by NSSA under conventional heating and microwave irradiation.

Table 1
Optimization of the oxa-Pictet–Spengler reaction catalyzed by NSSA under thermal conditions[a,b]



Entry	Catalyst (g)	EtOH (ml)	Yield[c] (%)
1	NSSA (0.08 g)	0.1	69[d]
2	NSSA (0.1 g)	0.1	81[d]
3	NSSA (0.15 g)	0.1	94
4	NSSA (0.2 g)	0.1	95
5	SSA[e] (0.15 g)	0.1	42
6	NS[f]	0.1	—
7	*p*-TSA (0.1)	0.1	28
8	NSSA (0.1 g)	0.2	92
9	NSSA (0.1 g)	0.5	83
10	NSSA (0.1 g)	1	77

[a] Synthesis of 1-(4‴chlorophenyl)-1,3-dihydroisobenzofuran-5-ol via reaction of 4-chlorobenzaldehyde (1 mmol) and 3-hydroxybenzyl alcohol (1 mmol) at 80 °C over 30 min.
[b] NSSA prepared from 0.2 mmol of chlorosulfonic acid and 60 mg of nano-SiO_2.
[c] Isolated yield.
[d] After 60 min.
[e] Silica sulfuric acid.
[f] Nano-SiO_2.

Herein we describe an efficient and facile synthesis of 3-hydroxyphthalans catalyzed by nanosilica sulfuric acid under thermal and microwave conditions (Scheme 2).[13]

The experimental procedure for the reaction is remarkably simple and does not require the use of toxic or expensive organic solvents or reagents. First, in order to optimize the conditions, the reaction of 3-hydroxybenzyl alcohol and 4-chlorobenzaldehyde was chosen as a model system under thermal conditions (Table 1).

The results listed in Table 1 showed that the conversions were sensitive to the catalyst. Nanosilica sulfuric acid proved to be the best catalyst affording the highest yield (Table 1, entry 4). In order to evaluate the effect of the catalyst particle size on the catalytic activity, the results were compared with those obtained using silica sulfuric acid (SSA). Utilizing NSSA increased the yield from 42% to 95% (Table 1, entries 4 and 5). One reason for this behavior may be related to the number of available active sites which in turn increases the catalytic activity. No activity was observed in the presence of pure nanosilica (NS) (Table 1, entry 6). The reaction was clean and fairly rapid. No side products were detected in these reactions. Only 0.15 g of NSSA was required to convert 1 mmol of the aldehyde into the corresponding product and higher amounts of the catalyst did not increase the yields significantly. Reaction with 0.1 g of the catalyst required a longer reaction time while the reaction with 0.08 g of NSSA produced only a 69% yield of the product after 60 min under thermal conditions (Table 1). Moreover, increasing the amount of ethanol led to lower yields (Table 1, entries 8–10).

Using microwave irradiation decreased remarkably the reaction times. So, to further optimize the reaction conditions, the temperature and the MW power were also optimized and the best results were obtained using 0.15 g of NSSA in 0.1 ml of EtOH at 400 W.[14] In both methods, 80 °C was the optimum temperature. No increase in yield was observed at higher temperatures, while lowering the temperature below 80 °C reduced the reaction rate.

Using the optimized reaction conditions, we explored the generality of this method with different aldehydes to prepare a series of 3-hydroxyphthalans (Table 2). In most cases, the reactions proceeded cleanly. The results obtained by the two different techniques: conventional heating (method A) and MW irradiation (method B), were compared. As shown in Table 2, the microwave-assisted NSSA-catalyzed reactions were superior to those using conventional heating. It was observed that under conventional heating (method A), sterically hindered or electron-deficient aryl aldehydes gave lower yields of products (Table 2, entries 4, 8

Table 2
Synthesis of 3-hydroxyphthalans catalyzed by nanosilica sulfuric acid

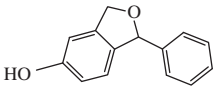
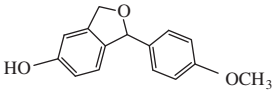
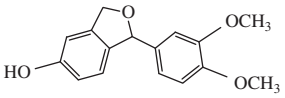
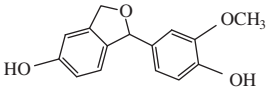
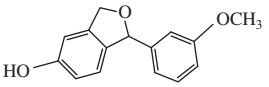
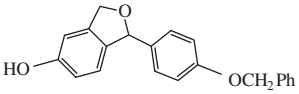
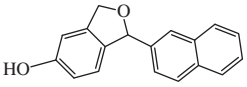
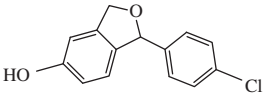
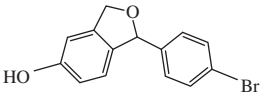
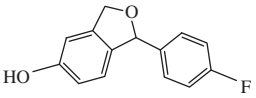
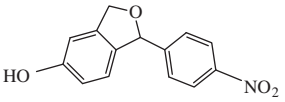
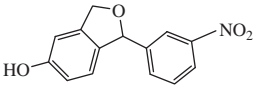
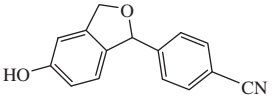
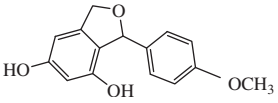
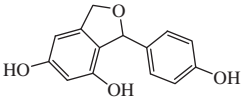
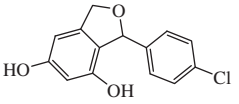
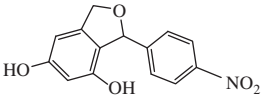
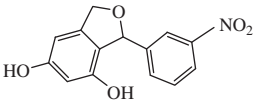
Entry	R	Ar	Product	Method A		Method B		Marra method[8]	
				Time (min)	Yield[a] (%)	Time (s)	Yield[a] (%)	Time (h)	Yield[a] (%)
1	H	C_6H_5		20	95	120	96	48	60
2	H	4-$CH_3OC_6H_4$		30	96	90	93	48	56
3	H	3,4-$(CH_3O)_2C_6H_3$		30	92	90	94	48	55
4	H	4-HO-3-$CH_3OC_6H_3$		20	95	90	97	48	55

Table 2 (*continued*)

Entry	R	Ar	Product	Method A		Method B		Marra method[8]	
				Time (min)	Yield[a] (%)	Time (s)	Yield[a] (%)	Time (h)	Yield[a] (%)
5	H	3-$CH_3OC_6H_4$		20	90	90	91	–	
6	H	4-$PhCH_2OC_6H_4$		90	55	120	82	–	
7	H	2-Naphthyl		90	65	300	84	–	
8	H	4-ClC_6H_4		30	92	120	97	48	56
9	H	4-BrC_6H_4		30	94	120	95	–	
10	H	4-FC_6H_4		30	68	180	90	–	
11	H	4-$O_2NC_6H_4$		40	60	90	85	48	61
12	H	3-$O_2NC_6H_4$		40	88	210	93	48	61
13	H	4-NCC6H_4		30	63	120	80	–	
14	HO	4-$CH_3OC_6H_4$		55	88	240	92	48	48
15	HO	4-HOC_6H_4		50	82	240	86	48	29
16	HO	4-ClC_6H_4		30	93	120	94	48	57
17	HO	4-$O_2NC_6H_4$		40	85	180	84	48	61
18	HO	3-$O_2NC_6H_4$		45	90	150	88	48	61

[a] Yields refer to isolated pure products characterized by ^1H NMR, ^{13}C NMR and IR spectroscopy and CHN analysis.

and 12). With method B, the type of substituent on the aryl aldehyde had little impact on the product yields.

For example, 4-nitrobenzaldehyde was converted into the corresponding product in 60% yield after 40 min under conventional conditions, while the yield was 85% in less than 90 s under MW irradiation (Table 2, entry 11). Also, surprising results were obtained when compared to those of Marra.[8] In the previous method,[8] reaction of 4-chlorobenzaldehyde with 3-hydroxybenzyl alcohol required more than 48 h to produce the phthalan in only 56% yield, but, with methods A and B, the corresponding product was obtained in 92% and 97% yields after 30 min and 120 s, respectively (Table 2, entry 8). Moreover, the use of 3,5-dihydroxybenzyl alcohol under the optimized conditions also afforded the corresponding products in very short reaction times (Table 2, entries 14–18). All the products were characterized by NMR, IR and mass spectroscopy, and also by comparison with authentic samples.

Table 3
Recyclability of NSSA

Run	Yield[a] (%)	
	Method A	Method B
1	92	97
2	90	96
3	90	95
4	90	93
5	88	91
6	72	85

[a] Isolated yield.

NSSA not only exhibits excellent activity in this condensation reaction, but also simplifies recycling and reuse of the catalyst. Recycling results are shown in Table 3.

The catalyst was separated by filtration and washed with ethanol. This catalytic system was easily recyclable after activation at 80 °C under reduced pressure. NSSA retained its activity over five consecutive runs.

Finally, the scale-up synthesis of phthalans was also investigated in the reaction of 3-chlorobenzaldehyde with 3-hydroxybenzyl alcohol. We increased the scale of the reaction to 10.0 mmol, keeping the reaction stoichiometry intact. The reaction was found to proceed successfully and the corresponding product was obtained in 91% and 94% yields via methods A and B, respectively.

In conclusion, we have demonstrated a convenient, simple, and efficient method for the synthesis of 3-hydroxyphthalans (3-hydroxydihydro-isobenzofurans) in the presence of NSSA under conventional heating and microwave irradiation. Moreover, this method represents the first application of nanosilica sulfuric acid as a powerful heterogeneous catalyst in heterocycle synthesis.

Acknowledgments

The authors are grateful to the Center of Excellence of Chemistry of University of Isfahan (CECUI) and the Research Council of the University of Isfahan for financial support of this work.

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13. *General procedure (Method A)*: Alcohol **1** (1 mmol) and aldehyde **2** (1.5 mmol) were taken in a mixture of NSSA (150 mg) and EtOH (0.1 ml) in a round-bottom flask. The reaction was stirred vigorously at 80 °C. After the reaction was complete (monitored by TLC) the mixture was filtered and concentrated under reduced pressure to leave a crude residue which was purified by silica gel column chromatography (EtOAc/hexane mixtures).
14. *General procedure (Method B)*: In a high pressure Teflon reactor equipped with a magnetic stir bar and an optical fiber (for controlling the reaction temperature), a mixture of alcohol **1** (1 mmol), aldehyde **2** (1.5 mmol), NSSA (150 mg) in EtOH (0.1 ml) was submitted to microwave irradiation at 80 °C (400 W) using a Micro-SYNTH lab station reactor for 1.5–5 min. The reaction mixture was cooled to room temperature, filtered and concentrated to give crude **3**, which was purified by silica gel column chromatography (EtOAc / hexane mixtures).
Data for 1,3-dihydro-1-(3,4-dimethoxyphenyl)isobenzofuran-5-ol (Table 2, entry 3): Red oily liquid, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.7–6.9 (6H, ArH), 6.09 (s, 1H), 5.89 (br s, 1H, OH), 5.25 (d, J = 12.3 Hz, 1H), 5.12 (d, J = 12.3 Hz, 1H), 3.85 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.4, 141.2, 139.1, 138.6, 134.6, 134.3, 123.2, 119.5, 114.8, 110.9, 110.2, 107.7, 85.8, 72.2, 56.0 and 55.9 ppm. IR ($CHCl_3$): ν = 3300, 2950, 1660, 1520, 1460, 1280, 1130, cm^{-1} MS: m/z = 271.3 [M−H]. Calcd for $C_{16}H_{16}O_4$ (272.30): C, 70.58; H, 5.92. Found: C, 70.22; H, 6.07.