

Solvent-Free One-Pot Synthesis of Amidoalkyl Naphthols Catalyzed by Silica Sulfuric Acid¹⁾

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An efficient, inexpensive, and mild method for the synthesis of amidoalkyl naphthols, catalyzed by 'silica sulfuric acid' (SSA), was elaborated under solvent-free conditions at room temperature. Various amidoalkyl naphthols were synthesized in high yields from aromatic or aliphatic aldehydes, α - or β -naphthols, and amides or urea or thiourea.

Introduction. – There is current and general interest in heterogeneous systems because of their importance in industry and in the development of new technologies [1]. Heterogeneous-reagent systems have many advantages such as simple experimental procedures, mild reaction conditions, and minimum chemical wastes, when compared to analogous liquid-phase reactions [2]. Solid acid catalysts are easier to handle because they hold the acidity internally and are easily separated from products by simple filtration. Moreover, constraining a reaction to the surface of a solid habitually allows one to apply milder conditions.

Various methodologies based either on neat silica gel as catalyst [1] or on sulfuric acid (H₂SO₄)- and/or chlorosulfuric acid (ClSO₃H)-supported silica gel [3] have been developed. Chlorosulfuric acid reacts with silica gel (SiO₂) at ambient temperature to a material called 'silica sulfuric acid' (SSA): [SiO₂] + ClSO₃H → [SiO₂] – OSO₃H + HCl. In this solid material, the acidic SO₃H moiety is immobilized on the SiO₂ surface by covalent-bond formation.

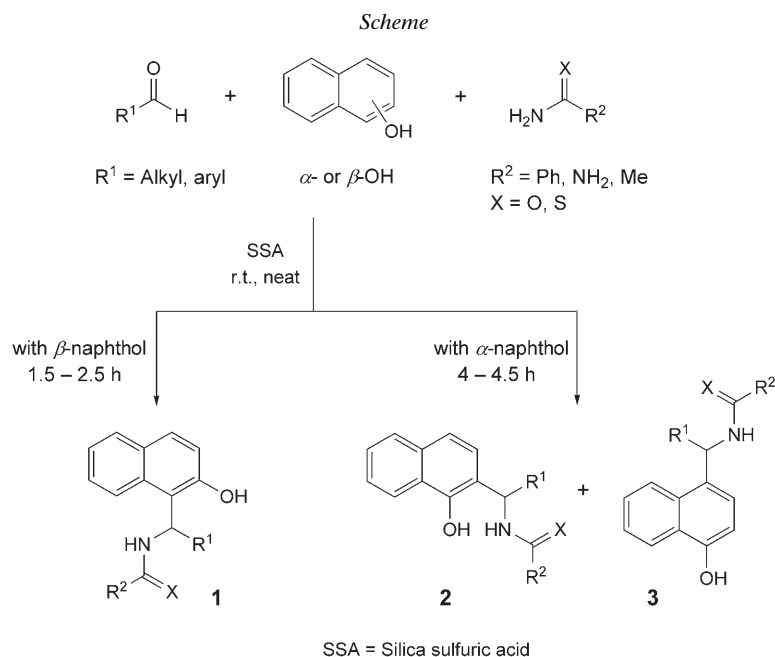
So far, a number of SSA-catalyzed reactions have been reported [4]. However, we wanted to find out if SSA is a suitable (or better) catalyst for one-pot multi-component reactions compared to other, homogeneous catalysts. Such reactions, including the *Biginelli* [5], *Passerini* [6], *Ugi* [7], or *Mannich* [8] transformations, have attracted considerable attention in recent years; and there is still a demand to develop new, elegant processes.

Our target compounds were amidoalkyl naphthols, which can be prepared from an aliphatic or aromatic aldehyde, a naphthol, and an amide, urea or thiourea. Amidoalkyl naphthols have been prepared with *para*-toluenesulfonic acid (TsOH), Bi(OTf)₃, Zn(OTf)₂, methanesulfonic acid (MsOH) [9], or iodine [10] as catalysts in organic solvents, elevated temperatures and prolonged reaction times often being required.

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Moreover, in all these reports, the reactions with aliphatic aldehydes were reported to suffer from low yields and harsh reaction conditions. Herein, we report a mild, simple, and efficient method for the one-pot three-component SSA-catalyzed synthesis of these compounds (see *Scheme* below).

Results and Discussion. – As shown in the *Scheme* and *Table*, the reaction was carried out by adding the three components, naphthol, alkyl or aryl aldehyde, and amide or (thio)urea to SSA. The mixture was stirred for 1.5–2.5 h (for β -naphthol) or for 4–4.5 h (for α -naphthol), which afforded the corresponding amidoalkyl naphthols of type **1** (79–92%) from β -naphthol, or a mixture of the regioisomers **2** (30–32%) and **3** (38–42%) from α -naphthol, respectively. In the reactions with α -naphthol, the isomers **2** and **3** were formed in similar proportions. The structures of all products were unequivocally confirmed spectroscopically (IR, ^1H - and ^{13}C -NMR) and by mass-spectrometric (MS) analysis (see *Exper. Part*).



Our procedure was found to be much more effective than those described in earlier reports [9][10]. In earlier reports, aliphatic aldehydes did not give satisfactory yields, and the corresponding products were not produced at all with thiourea. However, in the SSA-catalyzed reactions, the expected products were readily formed at room temperature under solvent-free conditions. All reactions proceed smoothly, without formation of by-products. No reactions were observed in the absence of the catalyst.

In conclusion, we have elaborated an efficient, simple, and mild procedure for the synthesis of a variety of different amidoalkyl naphthols. Since the SSA catalyst is

Table. *One-Pot Three-Component Reactions Catalyzed by Silica Sulfuric Acid (SSA). Without solvent, at room temperature.*

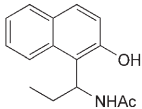
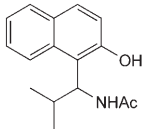
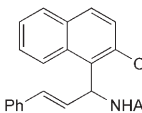
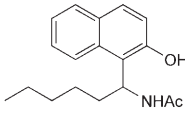
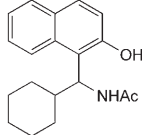
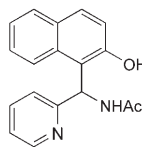
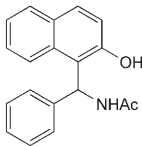
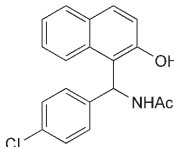
Series	Aldehyde	Amide or (thio)urea	Time [h]	Product(s)	Yield [%] ^a
For β -naphthol:					
a	Propanal	AcNH ₂	1.5		90
b	2-Methylpropanal	AcNH ₂	1.5		92
c	Cinnamaldehyde	AcNH ₂	1.7		90
d	Hexanal	AcNH ₂	1.9		85
e	Cyclohexanecarbaldehyde	AcNH ₂	2.0		90
f	Pyridine-2-carbaldehyde	AcNH ₂	2.0		84
g	Benzaldehyde	AcNH ₂	2.0		85
h	4-Chlorobenzaldehyde	AcNH ₂	1.6		89

Table (cont.)

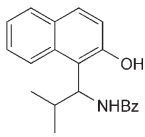
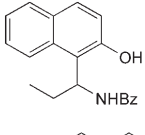
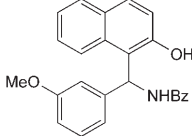
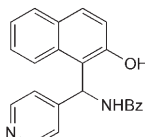
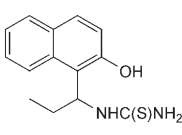
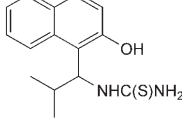
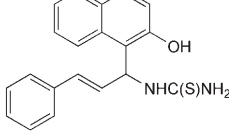
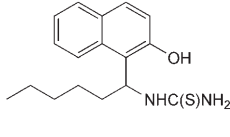
Series	Aldehyde	Amide or (thio)urea	Time [h]	Product(s)	Yield [%] ^{a)}
i	2-Methylpropanal	BzNH ₂	1.9		83
j	Propanal	BzNH ₂	2.0		85
k	3-Methoxybenzaldehyde	BzNH ₂	2.5		82
l	Pyridine-4-carbaldehyde	BzNH ₂	2.2		80
m	Propanal	Thiourea	1.8		83
n	2-Methylpropanal	Thiourea	1.5		82
o	Cinnamic aldehyde	Thiourea	1.8		80
p	Hexanal	Thiourea	1.8		81

Table (cont.)

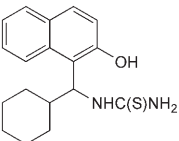
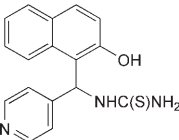
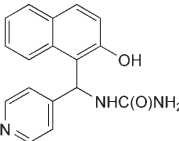
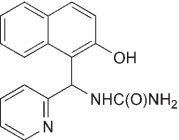
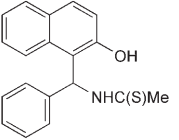
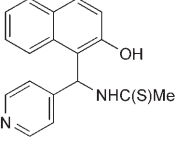
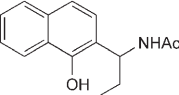
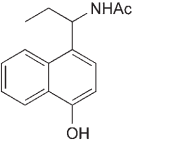
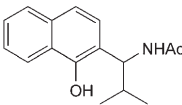
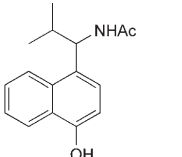
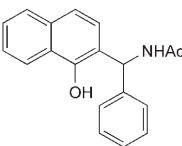
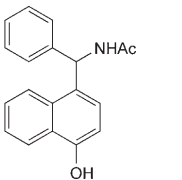
Series	Aldehyde	Amide or (thio)urea	Time [h]	Product(s)	Yield [%] ^a
q	Cyclohexanecarbaldehyde	Thiourea	2.0		84
r	Pyridine-4-carbaldehyde	Thiourea	2.0		80
s	Pyridine-4-carbaldehyde	Urea	2.5		85
t	Pyridine-2-carbaldehyde	Urea	2.3		82
u	Benzaldehyde	MeC(S)NH ₂	2.5		79
v	Pyridine-4-carbaldehyde	MeC(S)NH ₂	2.2		82
For α -naphthol:					
w	Propanal	AcNH ₂	4.0		32
					41

Table (cont.)

Series	Aldehyde	Amide or (thio)urea	Time [h]	Product(s)	Yield [%] ^{a)}
x	2-Methylpropanal	AcNH ₂	4.2		35
					42
y	Benzaldehyde	AcNH ₂	4.5		30
					38

^{a)} After chromatographic purification.

inexpensive, easy to prepare and handle, and readily removable, our method seems to be suited also for large-scale operations.

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Experimental Part

General. IR-Spectroscopic data are reported in cm⁻¹. NMR-Spectroscopic chemical shifts δ are reported in ppm rel. to Me₄Si (=0 ppm). Mass-spectrometric (MS) data are given in *m/z*.

General Synthetic Procedure. A mixture of an aliphatic or aromatic aldehyde (1 mmol), α - or β -naphthol (1 mmol), an amide or (thio)urea (1.1 mmol), and a cat. amount of silica sulfuric acid (SSA; 20 mg) [3] was stirred at r.t. for the appropriate time (see Table). The reaction was monitored by TLC. After completion of the reaction, the mixture was purified by column chromatography (SiO₂; hexane/AcOEt 4:1). The IR, ¹H- and ¹³C-NMR, and MS data of some representative compounds are given below.

N-[1-(2-Hydroxynaphthalen-1-yl)hexyl]acetamide (**1d**). IR (KBr): 3424, 1653, 1026, 1000, 826. ¹H-NMR (200 MHz, (D₆)DMSO): 9.85 (*s*, 1 H); 8.11 (*d*, *J* = 8.6, 1 H); 7.81–7.18 (*m*, 6 H); 5.80 (*q*, *J* = 7.8, 1 H); 2.02 (*m*, 2 H); 1.92 (*s*, 3 H); 1.40–1.21 (*m*, 6 H); 0.92–0.80 (*m*, 3 H). ¹³C-NMR (75 MHz,

(D₆)DMSO): 168.37; 152.90; 132.22; 128.17; 125.90; 122.41; 122.06; 119.73; 118.48; 45.81; 33.62; 31.04; 25.89; 22.63; 21.93; 13.73. EI-MS: 285 (*M*⁺), 215, 184, 173, 116, 44.

N-[2-Hydroxynaphthalen-1-yl](3-methoxyphenyl)methyl]benzamide (**1k**). IR (KBr): 3381, 1641, 1572, 1515, 1398, 1111, 693. ¹H-NMR (200 MHz, (D₆)DMSO): 9.87 (*s*, 1 H); 8.82 (*d*, *J* = 8.6, 1 H); 8.16 (*d*, *J* = 8.6, 1 H); 7.91–6.82 (*m*, 14 H); 6.65 (*d*, *J* = 7.8, 1 H); 3.71 (*s*, 3 H). ¹³C-NMR (75 MHz, (D₆)DMSO): 168.03; 165.79; 159.19; 153.14; 143.62; 134.28; 134.20; 132.28; 131.43; 131.20; 129.37; 129.28; 128.49; 128.35; 128.17; 127.42; 127.07; 126.77; 122.68; 118.81; 118.66; 118.25; 112.96; 54.86; 49.22. LC/MS: 406 ([*M* + Na]⁺), 383 (*M*⁺).

1-[1-(2-Hydroxynaphthalen-1-yl)propyl]thiourea (**1m**). IR (KBr): 3413, 1626, 1545, 1514, 1265, 811, 750. ¹H-NMR (200 MHz, (D₆)DMSO): 9.80 (*s*, 1 H); 8.35–7.10 (*m*, 8 H); 6.33 (*br.*, 2 H); 2.18–2.08 (*m*, 2 H); 0.83 (*t*, *J* = 7.3, 3 H). LC/MS: 283 ([*M* + Na]⁺).

1-[2-Hydroxynaphthalen-1-yl](pyridin-4-yl)methyl]urea (**1s**). IR (KBr): 3405, 1615, 1510, 1135, 784. ¹H-NMR (200 MHz, (D₆)DMSO): 9.70 (*s*, 1 H); 8.41 (*d*, *J* = 5.9, 2 H); 7.93–7.10 (*m*, 8 H); 6.70 (*s*, 1 H); 6.48 (*s*, 1 H). ¹³C-NMR (75 MHz, (D₆)DMSO): 154.44; 152.32; 149.12; 131.99; 129.31; 128.70; 128.15; 125.43; 124.85; 122.27; 120.64; 120.23; 117.99; 65.66. LC/MS: 316 ([*M* + Na]⁺).

N-[2-Hydroxynaphthalen-1-yl](phenyl)methyl]ethanethioamide (**1u**). IR (KBr): 3420, 1628, 1514, 1441, 1379, 1267, 1212, 1170, 811, 747. ¹H-NMR (200 MHz, (D₆)DMSO): 9.82 (*s*, 1 H); 8.19–7.11 (*m*, 13 H); 2.62 (*s*, 3 H). ¹³C-NMR (75 MHz, (D₆)DMSO): 199.51; 153.51; 140.25; 132.57; 129.57; 128.44; 128.17; 128.00; 126.51; 126.25; 122.70; 122.41; 118.43; 116.89; 55.33; 32.90. LC/MS: 330 ([*M* + Na]⁺).

N-[1-(1-Hydroxynaphthalen-2-yl)propyl]acetamide (**2w**). IR (KBr): 3390, 1617, 1575, 1540, 1460, 1377, 1079, 807. ¹H-NMR (300 MHz, CDCl₃): 9.95 (*s*, 1 H); 8.35 (*d*, *J* = 7.8, 1 H); 7.68 (*d*, *J* = 7.8, 1 H); 7.40 (*m*, 2 H); 7.28 (*d*, *J* = 8.5, 1 H); 7.12 (*d*, *J* = 8.5, 1 H); 6.08 (*d*, *J* = 8.6, 1 H); 5.08 (*q*, *J* = 7.7, 1 H); 2.01 (*m*, 2 H); 1.95 (*s*, 3 H); 0.98 (*t*, *J* = 7.4, 3 H). LC/MS: 266 ([*M* + Na]⁺).

N-[1-(4-Hydroxynaphthalen-1-yl)propyl]acetamide (**3w**). IR (KBr): 3401, 3275, 1644, 1583, 1542, 1384, 1276, 1054, 764. ¹H-NMR (200 MHz, (D₆)DMSO): 9.59 (*s*, 1 H); 8.22 (*d*, *J* = 7.8, 1 H); 8.05 (*d*, *J* = 7.8, 1 H); 7.72 (*d*, *J* = 8.6, 1 H); 7.52–7.20 (*m*, 3 H); 6.80 (*d*, *J* = 8.6, 1 H); 5.50 (*q*, *J* = 7.8, 1 H); 2.02–1.85 (*m*, 5 H); 0.95 (*t*, *J* = 7.8, 3 H). ¹³C-NMR (75 MHz, (D₆)DMSO): 169.25; 152.38; 132.10; 129.60; 126.49; 124.95; 124.45; 123.69; 123.14; 122.79; 107.55; 50.79; 49.65; 22.75; 11.15. LC/MS: 266 ([*M* + Na]⁺).

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