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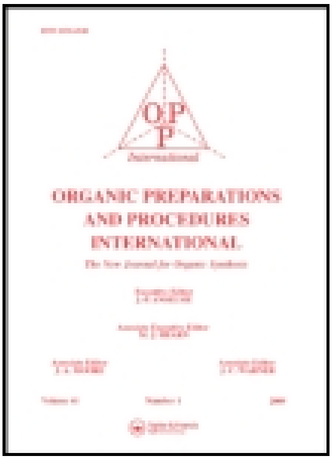

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Solvent-free Condensation of 2-Naphthol with Aromatic Aldehydes and Acetamide/Urea to 1-Amidoalkyl-2-naphthols

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Solvent-free Condensation of 2-Naphthol with Aromatic Aldehydes and Acetamide/Urea to 1-Amidoalkyl-2-naphthols

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In recent years, the use of solid-supported reagents has attained considerable attention both in industrial and academic research due to their unique properties such as enhanced reactivity as well as selectivity, efficiency, facile work-up, and eco-friendly reaction conditions.[1–18] Silica-supported phosphorus-containing reagents are a class of interesting solid-supported reagents which are inexpensive, safe and environmentally benign, and have been used in various organic transformations.[4–17] Nevertheless, most of the existing processes in organic synthesis involve toxic and volatile organic solvents as reaction media, and these are environmentally unacceptable from a green chemistry view point. One of the most effective techniques to solve this problem is solvent-free conditions which leads to remarkable decreases in reaction times, increased yields, easier workup,[3] and prevents waste, hazards, and toxicity due to solvents.[18] Consequently, it is noteworthy that the combination of safe reagents with the use of solvent-free reaction conditions represents a suitable way toward the so-called "ideal synthesis".[1–18]

1-Amidoalkyl-2-naphthol derivatives are of importance as they can be easily hydrolyzed to 1-aminoalkyl-2-naphthols. 1-Aminoalkyl-2-naphthols have been frequently applied as hypotensive and bradycardiac agents.[19–20] 1-Amidoalkyl-2-naphthols can also be converted to 1,3-oxazine derivatives.[21] 1,3-Oxazines have demonstrated a variety of biological activities including antibiotic,[22] antitumor,[23] antipsychotic,[24] and antianginal.[25] One-pot multi-component condensations of 2-naphthol with aromatic aldehydes and amide derivatives or acetonitrile has been used as a practical synthetic route toward 1-amidoalkyl-2-naphthols.[26–38] Several reagents including $Ce(SO_4)_2$,[26] $K_5CoW_{12}O_{40}.3H_2O$,[27] montmorillonite K-10,[28] iodine,[29] $FeCl_3/SiO_2$,[30] $Fe(HSO_4)_3$,[31] sulfamic acid/ultrasound,[32] *p*-toluenesulfonic acid,[33] *N*-(4-sulfonic acid)butyl triethylammonium bisulfate,[34] $H_3PW_{12}O_{40}$,[35] $Sr(OTf)_2$,[36] trityl chloride,[37] and 4-(1-imidazolium)butanesulfonate[38] have been used for this transformation. However, some of these reported methods suffer from one or more of the following drawbacks: (i) low product yield, (ii)

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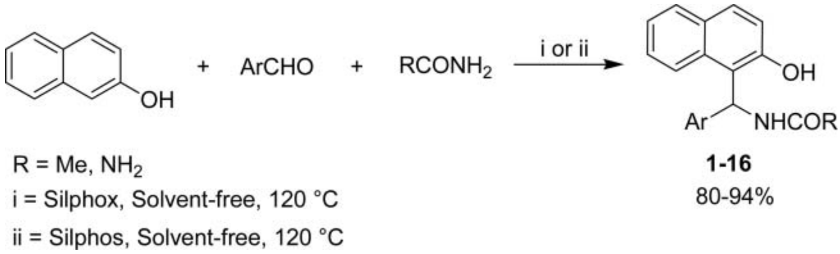
prolonged reaction time, (iii) the use of a large amount of reagent, (iv) the use of expensive, corrosive and toxic reagents, and (v) poor compliance with green chemistry protocols. Therefore, a search for finding a protocol for the synthesis of 1-aminoalkyl-2-naphthols which is not associated with the above disadvantages is still relevant. This paper reports a new, clean and efficient solvent-free method for the synthesis of 1-aminoalkyl-2-naphthols from 2-naphthol, aromatic aldehydes and acetamide/urea in the presence of a catalytic amount of silphox [$POCl_{3-n}(SiO_2)_n$] or silphos [$PCl_{3-n}(SiO_2)_n$] as inexpensive, green and heterogeneous silica-supported phosphorus-containing reagents (*Scheme* 1).



Scheme 1

As previously mentioned, silica-supported phosphorus-containing reagents are very important.[4-17] Silphox and silphos are two types of these reagents which have been successfully used to perform several organic reactions.[4–9] This precedent combined with the importance of 1-aminoalkyl-2-naphthols encouraged us to examine the preparation of these organic compounds using silphox and silphos. For this purpose, the condensation of 2-naphthol (2 mmol) with benzaldehyde (2 mmol) and acetamide (2.6 mmol) was chosen as a model reaction (*Scheme* 1), and its behavior was studied in the presence of different amounts of silphox as well as silphos under solvent-free conditions with a temperature range of 90-130°C. As indicated in Table 1, higher yields of the product were obtained when the reaction was carried out using 0.7 g of silphox or 0.6 g of silphos at 120°C. Increasing the reaction times or the temperature did not improve the yields.

The solvent-free reaction of 2-naphthol, benzaldehyde and acetamide was also checked in the presence of $POCl_3$, PCl_3 and SiO_2. $POCl_3$ and PCl_3 afforded the product in low yields, and SiO_2 gave only trace product. Moreover, $POCl_3$ and PCl_3 are very toxic and their use is very difficult especially at high temperatures because of their low boiling points and evolved HCl gas. It should be mentioned that silphox and silphos also generate HCl gas but much less than $POCl_3$ and PCl_3. In addition, the problem related to the low boiling point of $POCl_3$ and PCl_3 was solved by supporting them on silica gel, thus making use of of silphox and silphos in the reaction is easy.

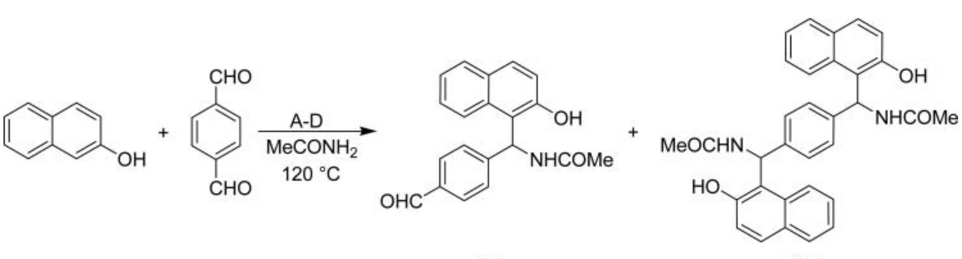
After optimization of the reaction conditions, 2-naphthol was condensed with different aromatic aldehydes bearing electron-releasing, electron-withdrawing, and halogens substituents with and acetamide or urea in the presence of the silica-supported phosphorus-containing reagents. The results are displayed in the Table 2. All reactions proceeded efficiently and the 1-amidoalkyl-2-naphthols were obtained in good to excellent yields (80–94%) within relatively short reaction times (20–55 min), thus making the method is general and efficient.

Table 1

Effect of Amount of the Reagents and Temperature on the Solvent-free Condensation of 2-Naphthol (2 mmol) with Benzaldehyde (2 mmol) and Acetamide (2.6 mmol)

Entry	Reagent (amount)	Temperature (°C)	Time (min)	Yield (%)
1	Silphox (0.7 g)	90	70	54
2	Silphox (0.7 g)	100	55	70
3	Silphox (0.7 g)	110	40	85
4	Silphox (0.7 g)	120	30	92
5	Silphox (0.7 g)	130	30	86
6	Silphox (0.6 g)	120	45	87
7	Silphox (0.8 g)	120	30	91
8	Silphos (0.6 g)	90	50	62
9	Silphos (0.6 g)	100	35	74
10	Silphos (0.6 g)	110	25	90
11	Silphos (0.6 g)	120	20	93
12	Silphos (0.6 g)	130	20	89
13	Silphos (0.5 g)	120	30	84
14	Silphos (0.7 g)	120	20	90

The condensation of 2-naphthol with *bis*-aldehydes (terephthaldehyde) and acetamide was also performed efficiently using silphox as well as silphos in the absence of solvent. The corresponding results are illustrated in *Scheme* 2 (*Table 3*). When one equivalent of 2-naphthol and one equivalent of the terephthaldehyde were reacted with 1.3 equivalents of acetamide in the presence of the reagents, 1-amidoalkyl-2-naphthol **17** and *bis*(1-amidoalkyl-2-naphthol) **18** were obtained in moderate yields. However, the reaction of two equivalents of 2-naphthol with one equivalent of the aldehyde and 2.6 equivalents of acetamide afforded compound **18** as a main product.

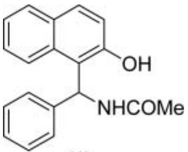
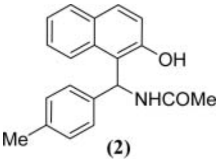
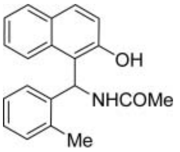
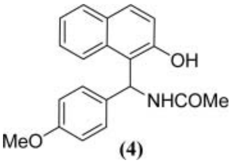
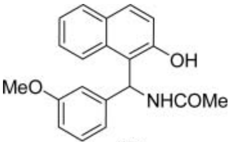
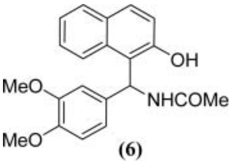
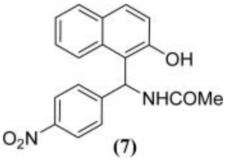
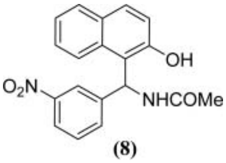


(17) (18)

Scheme 2

To compare the efficiency and the applicability of silphox and silphos with the reported reagents for the synthesis of 1-amidoalkyl-2-naphthols, the results of these reagents to effect the condensation of 2-naphthol with benzaldehyde and acetamide are reported in *Table 4*;

Table 2
The Solvent-free Synthesis of 1-Aminoalkyl-2-naphthols from 2-Naphthol, Aromatic Aldehydes and Amides using Silphox or Silphos at 120°C

Product	Silphox Time (min)/Yield (%)	Silphos Time (min)/Yield (%)	mp. °C (lit.)
 **(1)**	30/92	20/93	238-240 (241-243)[26]
 **(2)**	40/90	25/92	222-224 (220-230)[35]
 **(3)**	45/83	30/87	197-199 (200-202)[32]
 **(4)**	45/89	25/91	183-185 (183-185)[30]
 **(5)**	50/91	35/91	201-203 (203-205)[31]
 **(6)**	55/80	40/83	230-232 (235-236)[31]
 **(7)**	45/91	40/92	245-247 (248-250)[35]
 **(8)**	40/89	20/90	238-240 (236-237)[32]

(Continued on next page)

Table 2
The Solvent-free Synthesis of 1-Aminoalkyl-2-naphthols from 2-Naphthol, Aromatic Aldehydes and Amides using Silphox or Silphos at 120°C *(Continued)*

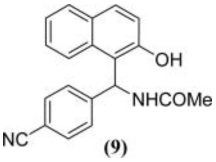
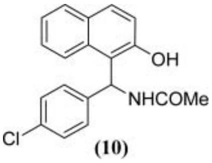
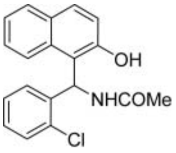
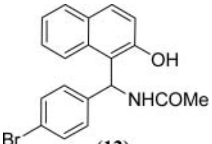
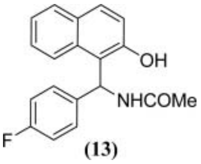
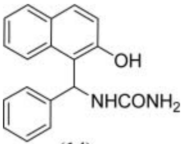
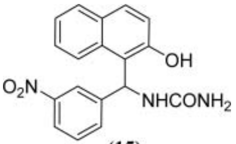
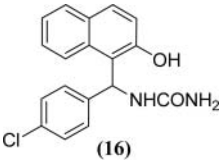
Product	Silphox Time (min)/Yield (%)	Silphos Time (min)/Yield (%)	mp. °C (lit.)
 **(9)**	40/82	25/89	229-231 (232-234)[34]
 **(10)**	45/93	40/94	220-222 (224-227)[26]
 **(11)**	40/86	40/92	196-198 (194-196)[32]
 **(12)**	45/88	25/91	226-228 (228-230)[31]
 **(13)**	35/91	25/93	205-207 (203-205)[32]
 **(14)**	50/89	30/90	174-176 (172-174)[32]
 **(15)**	50/81	35/86	183-185 184-186)[32]
 **(16)**	55/90	50/91	171-173(168-169)[32]

Table 3
Reaction of 2-Naphthol with Terephthaldehyde and Acetamide using Silphox or Silphos

Conditions	Reagent (amount)	2-Naphthol/aldehyde/ acetamide (molar ratio)	Time (min)	Yield (%)	
				17	**18**
A	Silphox (0.7 g)	2/2/2.6	50	33	14
B	Silphox (1 g)	4/2/5.2	70	16	59
C	Silphos (0.6 g)	2/2/2.6	40	38	21
D	Silphos (1 g)	4/2/5.2	60	13	65

evidentially, our reagents are superior to those previously reported in terms of yields and/or reaction times.

In summary, we have developed a new method for the one-pot three-component condensation of 2-naphthol with aromatioc aldehydes and acetamide or urea. The promising aspects of the present methodology are efficiency, generality, high yields, short reaction times, cleaner reaction profile, simplicity, ease of preparation of the reagents, and compliance with green chemistry protocols which, makes it an attractive procedure for the preparation of 1-amidoalkyl-2-naphthols as biologically interesting compounds.

Experimental Section

All chemicals were purchased from Merck or Fluka Chemical Companies. Silphox[4-6] and silphos[7] were prepared according to the reported methods. All products are known, and

Table 4
Comparison of the Results of the Reaction of 2-Naphthol with Benzaldehyde and Acetamide using Silphox and Silphos with those Obtained by Reported Reagents

Entry	Reagent, Temperature	(°C)Temp	Time (min)	Yield (%)	Ref.
1	Silphox	120	30	92	—[a]
2	Silphos	120	20	93	—[a]
3[b]	$Ce(SO_4)_2$, 85	85	2160	72	26
4	$K_5CoW_{12}O_{40}.3H_2O$	125	120	90	27
5	Montmorillonite K10 clay	125	90	89	28
6	I_2	125	330	85	29
7	$FeCl_3.SiO_2$	120	11	86	30
8	$Fe(HSO_4)_3$	85	65	83	31
9	Sulfamic acid (ultrasound)	28-30	15	89	32
10	$Sr(OTf)_2$ $CHCl_3$	Reflux	600	90	36
11[b]	Trityl chloride	RT	105	92	37
12	4-(1-Imidazolium)butanesulfonate	80	120	85	38

[a]Our reagents. [b]In this work, acetonitrile instead of acetamide has been used.

their structures were identified by comparison of their melting points and spectral data with those reported in the literature. The ^{1}H NMR (250 or 300 MHz) and ^{13}C NMR (62.5 or 75 MHz) were run on a Bruker Avance DPX-250 FT-NMR spectrometer. Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes.

General Procedure for the Synthesis of 1-Amidoalkyl-2-naphthol Derivatives (1–16)

A well-ground mixture of 2-naphthol (2 mmol, 0.288 g), aldehyde (2 mmol), amide (2.6 mmol) and silphox (0.7 g) or silphos (0.6 g) was added to a 10 mL round-bottomed flask fitted to a reflux condenser, and stirred in an oil-bath (120) °C for the times reported in *Table 2*. After the appropriate time, the reaction mixture was cooled to room temperature, and chromatographed on silica gel, and eluted with EtOAc/*n*-hexane (1/1) to give the pure products.

Note: When liquid aldehydes were utilized in the reaction, 2-naphthol, the amide derivative and the reagent were ground first vigorously, and then the aldehyde was subsequently added.

General Procedure for the Synthesis of 1-Amidoalkyl-2-naphthol (17) and bis(1-Amidoalkyl-2-naphthol) (18)

A mixture of compounds consisting of 2-naphthol (4 mmol, 0.576 g), acetamide (5.2 mmol, 0.307 g), terephthalaldehyde (2 mmol, 0.268 g) and silphox (1 g) or silphos (1 g) was ground vigorously, added to a 10 mL round-bottomed flask connected to a reflux condenser, and was stirred in an oil-bath (120 °C) for the times reported in Table 3. Afterward, the reaction mixture was cooled to room temperature, and warm aqueous ethanol (15%, 20 mL) was added to it, and the mixture was stirred for 5 min (1-amidoalkyl-2-naphthol is soluble in warm aqueous ethanol; however, *bis*(1-amidoalkyl-2-naphthol) is insoluble in this solvent). During this time, the crude 1-amidoalkyl-2-naphthol was dissolved in the ethanol, and pure *bis*(1-amidoalkyl-2-naphthol) remained undissolved; thus, two products were easily separated by filtration. Then, the crude 1-amidoalkyl-2-naphthol was purified by column chromatography on silica gel eluted with EtOAc/*n*-hexane (1/1), and the *bis*(1-amidoalkyl-2-naphthol) was separated from the reagent by short column chromatography on silica gel eluted with methanol.

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