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A Highly Efficient Protocol for the Synthesis of 2-Amidoalkylphenols using SO_3H-Functionalized Phthalimide (SFP) under Solvent-free Conditions

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Abstract

A highly efficient and simple protocol for the synthesis of 2-amidoalkylphenols has been described. The one-pot multi-component condensation of phenols with aromatic aldehydes and amides in the presence of catalytic amount of SO3H-functionalized phthalimide (SFP) under solvent-free conditions afford the title compounds in high yields and relatively short reaction times. It is noteworthy that the reaction between phenols, arylaldehydes and amides has been scarcely studied in the literature (in spite of the condensation of 2-naphthol with arylaldehydes and amides, which has been extensively reported).

Keywords*: 2-Amidoalkylphenol, Phenol, Arylaldehyde, Amide, SO_3H-functionalized phthalimide (SFP), Solid acid.*

Introduction

The use of solid acid catalysts containing a SO_3H group has received considerable interest by chemists due to their unique advantages such as efficiency, high reactivity, operational simplicity, environmental compatibility, non-toxicity, low cost, ease of isolation, green nature, easy availability of their starting materials, and ability to promote a wide range of reactions [1-10]. One of the attractive SO_3H-contaning solid acids is SO_3H-functionalized phthalimide (SFP) (figure 1), which more recently we have used it as a highly efficient catalyst for preparation of 9-aryl-1,8-dioxo-octahydroxanthenes [10].

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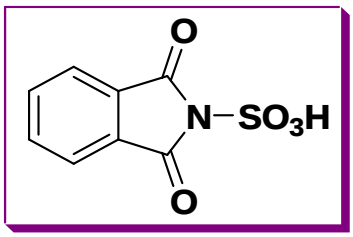


Figure 1. The structure of SFP.

1-Amidoalkyl-2-naphthol derivatives (figure 2a) are of significance as they can be easily converted to 1-aminoalkyl-2-naphthols (Fig. 2b) by hydrolysis. 1-Aminoalky-2-naphthols have been used as bradycardiac and hypotensive agents [11,12]. Moreover, 1-amidoalkyl-2-naphthols can be converted to 1,3-oxazine derivatives [13] (Figure 2c) with different pharmaceutical properties including analgesic [14], antitumor [15], antihypertensive [16], antimalarial [17], antibiotic [18], and antipsychotic [19] activities. Considering the above subjects, 2-amidoalkylphenols (Figure 2c) have been introduced as an important member of 1-amidoalkyl-2-naphthols [20-22]. Although the synthesis of 1-amidoalkyl-2-naphthols has been extensively studied [23-26]; there are a few reports on the preparation of 2-amidoalkylphenols [20-22]. In 2007, Das and et al. have reported synthesis of 2-amidoalkylphenols by the condensation of phenols with arylaldehydes and alkyl nitriles using triflic acid as catalyst [20]; in this method, 2-amidoalkylphenols have been produced in moderate yields and in relatively long reaction times. In 2013, Mulla and et al. have prepared these compounds by the reaction of phenols with arylaldehydes and amides/alkyl carbamates in the presence of ionic liquid ethylammonium nitrate [21]; in this work, only three 2-amidoalkylphenols have been synthesized, and large amount of catalyst has been applied. In 2014, Moosavi-Zare and et al. have achieved the reaction between phenols, arylaldehydes and amides using an ionic liquid namely 3-methyl-1-sulfonic acid imidazolium chloride to afford 2-amidoalkylphenol derivatives [22]; in this research, most of the products have been obtained in moderate yields, and the reaction has been performed at 110 °C.

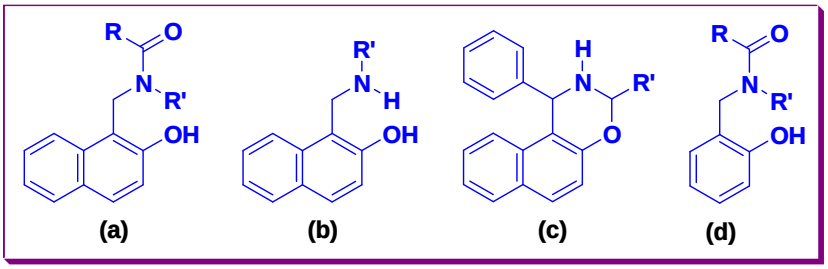
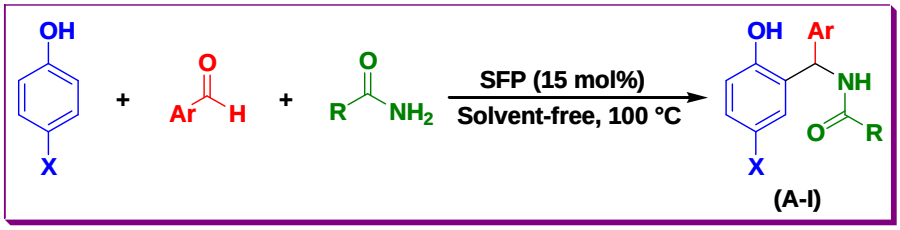


Figure 2. The structures of 1-amidoalkyl-2-naphthols (a), 1-aminoalkyl-2-naphthols (b), 1,3-oxazines (c), and 2-amidoalkylphenols (d).

Solvent-free technique is one of the green chemical protocols which has many advantages from economical and pollution aspects. Remarkable impact of solvent-free conditions is modernization of classical procedures making them to give products in shorter reaction times and higher yields, improves selectivity and facilitates purification of products [27-30].

Multi-component reactions (MCRs) have attracted much attention in modern organic synthesis and medicinal chemistry, because they are one-pot processes bringing together three or more components and show high atom economy and high selectivity. MCRs have great contributions in convergent synthesis of complex and important organic molecules from simple and readily available starting materials, and have emerged as powerful tools for drug discovery [31-34].

In this work, we report a highly efficient and simple procedure for the synthesis of 2-amidoalkylphenols via the one-pot multi-component condensation of phenols with arylaldehydes and amides using SO_3H-functionalized phthalimide (SFP) under solvent-free conditions (Scheme 1).



Scheme 1. The preparation of 2-amidoalkylphenols.

Experimental

All chemicals were purchased from Merck or Fluka Chemical Companies. All known compounds were identified by comparison of their melting points and spectral data with those reported in the literature. Progress of the reactions was monitored by TLC using silica gel SIL G/UV 254 plates. The ^1H NMR (250 or 400 MHz) and ^{13}C NMR (62.5 or 100 MHz) were run on a Bruker Avance DPX, FT-NMR spectrometer. Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes.

Procedure for the preparation of SO_3H-functionalized phthalimide (SFP)

To a round-bottomed flask (50 mL) containing phthalimide (0.736 g, 5 mmol), was added chlorosulfonic acid (0.594 g, 5.1 mmol) dropwise at 10 °C. After the addition was completed, the reaction mixture was stirred at room temperature for 5 h, and then at 70 °C for 3 h. At the end of the process, the residue was washed with CH_2Cl_2 (2×10 mL),

and dried to give SFP as a white solid in 98% yield. FT-IR (KBr): 3350-2950, 1718, 1305, 1287, 1182, 1088, 1070 cm-1; 1H NMR (250 MHz, DMSO-d_6, δ/ppm): 7.40-7.55 (m, 4H, aromatic hydrogens), 11.00 (s, 1H, OH of the SO_3H group). ^{13}C NMR (62.5 MHz, DMSO-d_6, δ/ppm): 122.6, 132.0, 134.0, 169.0. Mass (m/z): 227 (M^+), 228 (M^++1), 210 (M^+-OH), 146 (M^+-SO_3H), 132 (M^+-NSO_3H), 104 (M^+-$CONSO_3H$) and 76 (M+-$(CO)_2NSO_3H$) [10].

General procedure for the preparation of 2-amidoalkylphenols

A mixture of phenol (1 mmol), arylaldehyde (1 mmol), amide (1.2 mmol) and SFP (0.034 g, 0.15 mmol) in a test tube was magnetically stirred at 100 °C, and after solidification of the reaction mixture, it was stirred with a small rod at the same temperature. After the reaction was completed (as monitored by TLC), the mixture was cooled to room temperature, and the resulting precipitate was recrystallized from EtOH (95%) to give the pure product.

Selected spectral data of 2-amidoalkylphenols

*N-((5-benzyl-2-hydroxyphenyl)(phenyl) methyl)acetamide (***A***):*

^{1}H NMR (400 MHz, DMSO-d_6, δ/ppm): 1.96 (s, 3H), 3.85 (s, 2H), 6.48 (d, 1H, *J* = 8.4 Hz), 6.77 (d, 1H, *J* = 8 Hz), 6.99 (d, 1H, *J* = 8 Hz), 7.15-7.28 (m, 6H), 7.37-7.72 (m, 2H), 8.09 (d, 2H, *J* = 8 Hz), 8.76 (d, 1H, *J* = 8 Hz), 9.56 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6, δ/ppm): 23.1, 40.9, 50.6, 115.9, 121.8, 122.1, 126.3, 127.8, 128.8, 129.3, 130.2, 132.1, 134.4, 142.2, 145.2, 148.2, 153.1, 169.3.

*N-((5-benzyl-2-hydroxyphenyl)(p-tolyl) methyl)acetamide (***D***):*

^{1}H NMR (400 MHz, DMSO-d_6, δ/ppm): 1.91 (s, 3H), 2.23 (s, 3H), 3.83 (s, 2H), 6.30 (d, 1H, *J* = 6.0 Hz), 6.73 (d, 1H, *J* = 5.5 Hz), 6.88 (dd, 1H, *J* = 4.0, 1.4 Hz), 7.07-7.26 (m, 10H), 8.45 (d, 1H, *J* = 6.0 Hz), 9.56 (s, 1H). ^{13}CNMR (100 MHz, $CDCl_3$, δ/ppm): 21.0, 23.3, 41.0, 50.6, 115.5, 126.2, 127.6, 128.4, 128.6, 128.7, 128.9, 129.0, 129.2, 131.7, 136.0, 140.3, 142.3, 153.2, 168.9.

*N-((5-benzyl-2-hydroxyphenyl)(phenyl) methyl)benzamide (***E***):*

^{1}H NMR (400 MHz, DMSO-d_6, δ/ppm): 3.78 (s, 2H), 6.46 (d, 1H, *J* = 8.4 Hz), 6.67-6.92 (m, 11H), 7.13-7.27 (m, 7H), 8.23 (d, 1H, *J* = 8.4 Hz), 9.25 (s, 1H). ^{13}CNMR (100 MHz, DMSO-d_6): 41.0, 56.4, 111.9, 112.5, 115.4, 115.5, 126.2, 128.4, 128.6, 128.7, 128.9, 128.9, 131.1, 132.1, 142.4, 151.3, 153.5, 153.6, 168.6.

N-((5-bromo-2-hydroxyphenyl)(2,5-dimethoxyphenyl) methyl)acetamide (I):

^{1}H NMR (400 MHz, DMSO-d_6, δ/ppm): 1.82 (s, 3H), 3.31 (s, 3H), 3.76 (s, 3H), 6.30 (d, 1H, *J* = 6 Hz), 6.69 (d, 1H, *J* = 8.4 Hz), 6.87 (d, 1H, *J* = 6.4 Hz), 7.09-7.28 (m, 4H), 8.50 (d, 1H, *J*

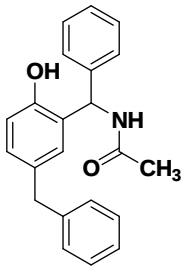
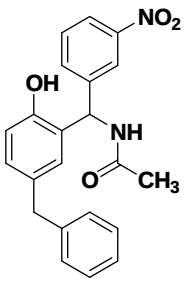
= 9.2 Hz), 9.35 (s, 1H). ^{13}CNMR (100 MHz, DMSO-d_6, δ/ppm): 23.1, 41.0, 50.5, 115.7, 126.3, 127.3, 128.3, 128.5, 128.8, 128.9, 129.0, 131.8, 141.5, 142.3, 152.9, 168.7.

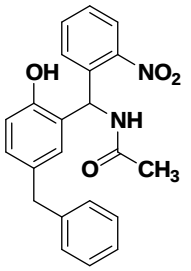
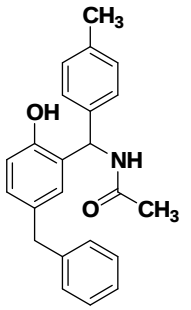
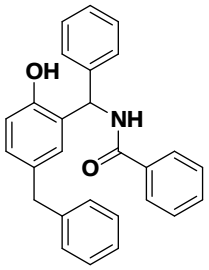
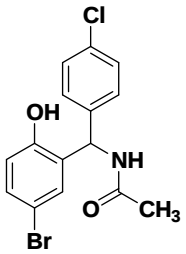
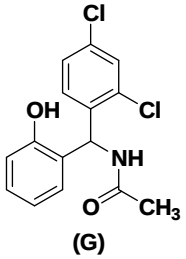
Results and discussion

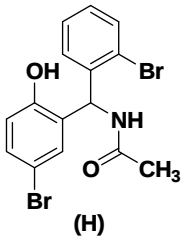
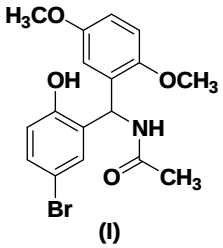
To optimize the reaction conditions, at first, the condensation of 4-benzylphenol (1 mmol) with 3-nitrobenzaldehyde (1 mmol) and acetamide (1.2 mmol) was chosen as a model reaction, and studied in the presence of different amounts of SFP at various temperatures. The best results were obtained when the reaction was carried out using 15 mol% of the catalyst at 100 °C; in these conditions, the desired product was obtained in 95% after 40 min.

After optimization of the reaction conditions, the efficacy and applicability of the method was assessed by examining the reaction using various phenols, arylaldehydes and amides. The results are summarized in Table 1. As this Table indicates, all reactions proceeded efficiently to give the desired products in high yields and in relatively short reaction times. Thus, the method was highly efficient and general.

Table 1. The preparation of 2-amidoalkylphenols using 15 mol% of SFP at 100 °C.

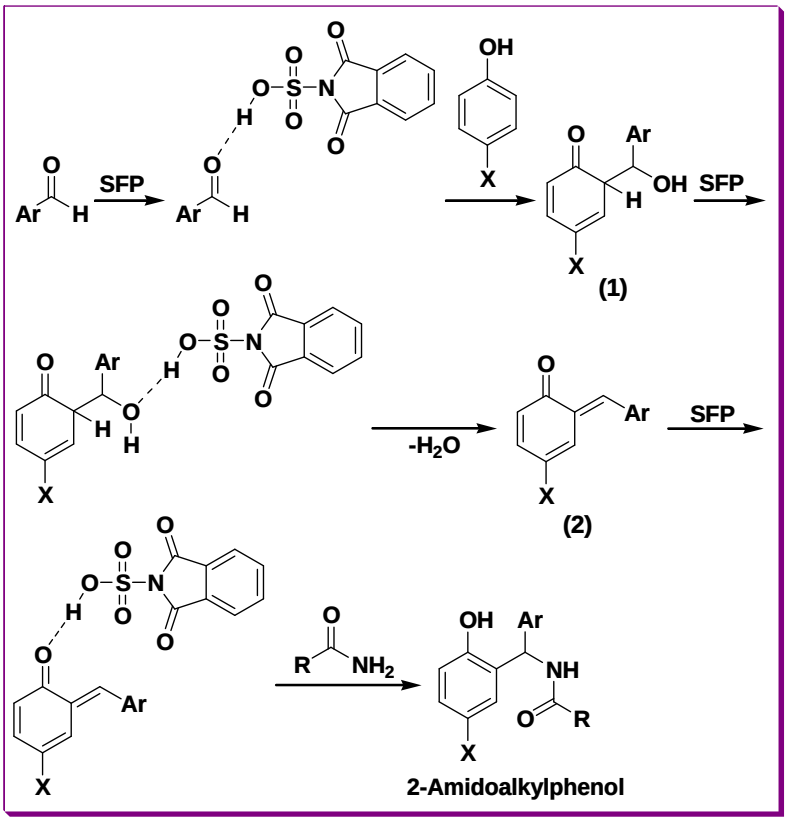
Product	Time (min)	Yield[a] (%)	Measured m.p. (°C)	Reported m.p. (°C)
 (A)	85	92	172-174	(174-176) [22]
 (B)	40	95	207-210	(210-215) [22]

 (C)	30	97	228-230	(226-228) [22]
 (D)	130	70	223-225	(183-184) [22]
 (E)	65	97	204-205	(204-206) [22]
 (F)	35	96	218-220	(220-225) [22]
 (G)	60	95	226-228	(228-230) [22]

 (H)	180	71	196-198	(197-200) [22]
 (I)	150	70	213-215	(215-217) [22]

[a]Isolated yield.

In a plausible mechanism that is supported by the literature [22] (Scheme 2); at first, the acidic hydrogen of SFP activates aldehyde. Then, ortho-carbon of phenol attacks to the activated aldehyde to give 1. Intermediate 2 is formed by removing one molecule of H2O from activated 1 by SFP. Michael acceptor 2 is activated by SFP, and amide attacks to the activated 2 to give the product.



Scheme 2. The proposed mechanism for the reaction.

Conclusion

In summary, we have developed a new protocol for the synthesis of 2-aminoalkylphenols as biologically interesting compounds via the one-pot multi-components condensation of phenols with arylaldehydes and amides using SFP under solvent-free conditions. The advantages of this method are generality, effectiveness, relatively short reaction times, high yields, cleaner reaction profile, simplicity, ease of preparation of the catalyst, ease of product isolation, and good compliance with the green chemistry protocols.

Acknowledgements

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