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RESEARCH ARTICLE

A Green Protocol for One-Pot Three-Component Synthesis of Amidoalkyl Naphthols Catalyzed by Succinic Acid

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Abstract: A green, genereal and efficient synthesis of amidoalkyl naphthols using succinic acid as a catalyst for the three-component condensation reaction of 2-naphthol, aldehydes and amides/urea under thermal solvent-free conditions is described. The advantages of this protocol are excellent yields, short reaction time, simple work-up, higher availability economical attraction, low cost catalyst, lack of toxicity and more environmentally friendly catalyst.

Keywords: Amidoalkyl naphthol, Three-component reaction, One-pot synthesis, Solvent-free

Introduction

One pot multicomponent reactions (MCRs) have attracted considerable interest owing to their exceptional synthetic efficiency. The structure of the reaction product can easily be diversified by the systematic variation of each input. Moreover, the starting materials are either commercially available or easy to prepare[1]. Some examples of MCRs are Biginelli[2], Ugi[3], Passerini[4] and Mannich[5]. Compounds bearing the 1,3-amino-oxygenated functional groups are ubiquitous to a variety of biologically important natural products and potent drugs including a number of nucleoside antibiotics and HIV protease inhibitors such as ritonavir, lipinavir and the hypotensive[6]. In addition, the bradycardiac effects of these compounds have been evaluated[7]. The importance of amidoalkyl naphthols for their synthesis has attracted renewed attention and various improved procedures have been reported. Amidoalkyl naphthols can be prepared by the condensation of aromatic aldehydes, 2-naphthol and amides, urea or acetonitrile in the presence of a Lewis or Brønsted acid catalysts. Several methods have been documented in the literature for synthesis of these compounds such as montmorillonite K10 clay[8], $Ce(SO_4)_2$,[9] $K_5CoW_{12}O_{40}.3H_2O$,[10] *p*-TSA[11], sulfamic acid/ultrasound[12], ionic liquids[13], Indion-130[14], $Al(H_2PO4)_3$,[15] $Fe(HSO_4)_3$,[16] $Yb(OTf)_3$,[17] wet cyanuric chloride,[18] Al_2O_3-$HClO_4$,[19] Silica chloride (SiO_2-Cl)/ultrasound[20], indium(III) chloride[21], $Sr(OTf)_2$,[22] P_2O_5,[23] $H_4SiW_{12}O_{40}$,[24] *N,N,N',N'*-Tetrabromobenzene-1,3-disulfonamide (TBBDA)[25], trityl chloride[26]and bismuth(III) nitrate pentahydrate[27].

However, most of these methods have drawbacks, such as highly toxic catalysts, environmental pollution caused by using an organic solvent, expensive catalysts or difficult preparation, unavailable reagents, prolonged reaction times and unsatisfactory yields. Therefore, it is necessary to further develop an efficient one-pot multicomponent synthesis of amidoalkyl naphthols without these problems. It is well known that homogeneous catalysts have gained attraction in recent years due to their operational simplicity, low cost, ease of preparation and handling, stability, lack of toxicity, economical and environmental consideration. One of these homogeneous catalysts is succinic acid (c_4-dicarboxylic acid). Succinic acid is a common metabolite in plants, animals and microorganisms and has been used widely in agricultural, food and pharmaceutical industries[28]. This acid has holds good industrial applications and is used in industries such as, resins, polymer, paints, cosmetics and inks, *etc.*[29]. To date, the economically renewable resources used in succinic acid production reported are cheese whey[30], cane molasses[31], Jerusalem artichoke[32], wheat flour[33], wood hydrolysate[34] and corn straw hydrolysate[35].

Experimental

Melting points and IR spectra were measured on a Electrothermal 9100 apparatus and a JASCO FT/ IR-460 plus spectrometer, respectively. The ^{1}HNMR spectra were obtained on Bruker DRX- 400 Avance instruments with DMSO as a solvent. All reagents and solvents obtained from Fluka and Merck were used without further purification.

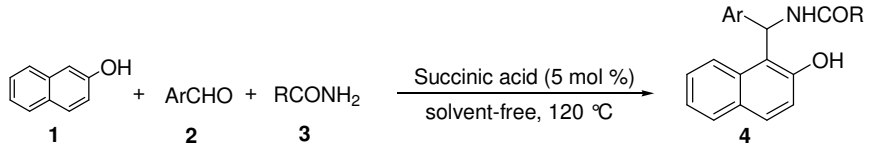
*General procedure for the synthesis of amidoalkyl naphthols **(4)***

A mixture of 2-naphthol (1 mmol), aromatic aldehyde (1 mmol), amide (1.3 mmol) and succinic acid (5 mol %) was stirred at 120 °C in an oil bath. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to r.t, and washed with H_2O (3 × 10 mL). The catalyst is solvable in water and was removed from the reaction mixture. Then the residue was recrystallized from EtOH.

Compound **4ac**: white solid, mp. 241-243 °C; IR (KBr): υ_{max} = 3390, 3247, 3062, 1640, 1582, 1515, 1436, 1372, 1276, 1208, 1165, 1060, 1028, 986, 932, 877, 808, 742 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.06 (brs, 1H, OH), 8.48 (d, 1H, *J* = 8.4 Hz, NH), 7.77-7.85 (m, 3H), 7.15-7.40 (m, 9H), 2.00 (s, 3H, CH_3).

Results and Discussion

In continuation of our work on MCRs[36-40], we report a general, efficient and green protocol for the synthesis of amidoalkyl naphthol derivatives from various aromatic aldehydes, 2-naphthol and amides/urea using catalytic amounts of succinic acid (5 mol %) as an effective and cost efficient catalyst under solvent-free conditions (Scheme 1).



Scheme 1. One-pot three-component synthesis of amidoalkyl naphthols **4**

Succinic acid is a readily available, low cost reagent; it can conveniently be handled, and removed from the reaction mixture. Thus, the remarkable catalytic activities together with its operational simplicity make it the most suitable catalyst for the synthesis of amidoalkyl naphthols.

In order to optimize the reaction conditions, various reaction media were screened using the model reaction of 2-naphthol, benzaldehyde and acetamide in the presence of succinic acid was performed under solvent-free conditions (Table 1). It was found that the best results were obtained with 5 mol % succinic acid under solvent-free conditions (Table 1, entry 8). The reaction was completed within 38 min and the expected product was obtained in a 92% yield, while diminishing the amount of catalyst would decrease the product yield (Table 1, entry 6, 7). It is noteworthy that the increasing the catalyst loading to 10, 15 and 20 mol% had no an improving effect on the yield of the product (Table 1, entry 5, 9, 10). In the absence of any catalyst, no desirable product could be detected (Table 1, entry 11).

Table 1. Optimization amount of succinic acid for the reaction of 2- naphthol, benzaldehyde, and acetamide under solvent-free conditions at different temperatures

Entry	Amount of Catalyst, mol%	T, °C	Time, min	Yield, %[a]
1	10	80	83	65
2	10	90	74	72
3	10	100	63	82
4	10	110	48	88
5	10	120	38	92
6	1	120	55	78
7	3	120	45	83
8	5	120	38	**92**
9	15	120	38	92
10	20	120	38	92
11	-	120	120	-

[a]*Isolated yields*

A variety of aromatic aldehydes, 2-naphthol and different amides, including acetamide, benzamide and urea, were submitted to these reaction conditions and the desired products were obtained in good to excellent yields (Table 2). In all cases, amidoalkyl naphthols were the sole products and no by-product was observed. Aromatic aldehydes carrying either electron-withdrawing or electron-donating groups reacted successfully and gave the desired products in high yields.

Table 2. Synthesis of amidoalkyl naphthols in the presence of succinic acid

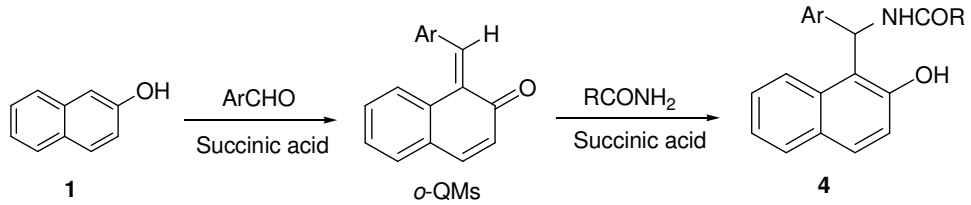
Entry	Ar	R	Time, min	Product	Yield, %[a]	mp, °C	Lit. mp , °C [Ref],[b]
1	C_6H_5	C_6H_5	7	**4a**	95	233-235	234-236[11]
2	4-Cl-C_6H_4	C_6H_5	3	**4b**	90	186-188	187-188[22]
3	4-MeO-C_6H_4	C_6H_5	30	**4c**	72	208-209	206-208[23]
4	4-Me-C_6H_4	C_6H_5	4	**4d**	88	193-195	192-193[12]
5	4-$(Me)_2$N-C_6H_4	C_6H_5	60	**4e**	65	220-222	220-221[23]
6	4-NO_2-C_6H_4	C_6H_5	8	**4f**	98	240-241	237-239[27]
7	2-NO_2-C_6H_4	C_6H_5	3	**4g**	92	270-272	266-267[23]
8	2-Cl-C_6H_4	C_6H_5	3	**4h**	98	272-274	265-267[27]
9	2,4-di-Cl-C_6H_3	C_6H_5	2	**4i**	98	243-244	238-239[27]
10	4-HO-3-MeO-C_6H_3	C_6H_5	15	**4j**	90	218-219	219[20]
11	3-MeO-C_6H_4	C_6H_5	7	**4k**	81	214-216	214-216[10]

Contd...

12	3-NO_2-C_6H_4	C_6H_5	6	**4l**	98	232-234	233-235[13a]
13	4-Me-C_6H_4	CH_3	50	**4m**	90	220-222	218-220[16]
14	4-NO_2-C_6H_4	CH_3	20	**4n**	85	252-254	248-250[16]
15	4-Cl-C_6H_4	CH_3	25	**4o**	95	237-238	237-238[23]
16	4-MeO-C_6H_4	CH_3	60	**4p**	90	184-186	184-186[9]
17	3-MeO-C_6H_4	CH_3	30	**4q**	92	204-206	203-205[8]
18	2-Cl-C_6H_4	CH_3	15	**4r**	96	210-212	206-207[23]
19	2-NO_2-C_6H_4	CH_3	60	**4s**	90	180-182	180-182[9]
20	3-NO_2-C_6H_4	CH_3	15	**4t**	85	263-265	255-256[22]
21	2,4-di-Cl-C_6H_3	CH_3	35	**4u**	80	226-228	228-230[8]
22	4-F-C_6H_4	CH_3	70	**4v**	91	213-215	209-210[9]
23	2,5-di-MeO-C_6H_3	CH_3	10	**4w**	98	253-255	251-253[16]
24	4-CN-C_6H_4	CH_3	14	**4x**	90	261-263	261-262[18]
25	3,4-di-MeO-C_6H_3	CH_3	23	**4y**	88	235-236	235-236[8]
26	2-Me-C_6H_4	CH_3	18	**4z**	97	200-203	200-202[14]
27	4-HO-C_6H_4	CH_3	45	**4aa**	70	205-207	206-208[13b]
28	3-Cl-C_6H_4	CH_3	14	**4ab**	98	237-239	237-238[13c]
29	C_6H_5	CH_3	38	**4ac**	92	241-243	241-243[9]
30	C_6H_5	NH_2	40	**4ad**	98	178-180	176-178[13a]
31	4-Me-C_6H_4	NH_2	40	**4ae**	94	115-117	117-118[22]
32	4-Cl-C_6H_4	NH_2	23	**4af**	87	169-171	168-169[12]
33	3-NO_2-C_6H_4	NH_2	10	**4ag**	93	190-192	191-193[14]
34	3-MeO-C_6H_4	NH_2	32	**4ah**	90	243-244	242-244[24]
35	4-NO_2-C_6H_4	NH_2	4	**4ai**	91	162-164	163-165[25]
36	4-HO-C_6H_4	NH_2	44	**4aj**	88	150-151	146-148[25]

[a]*Isolated yield.* [b]*All known products have been reported previously in the literature and were characterized by comparison of IR and NMR spectra with authentic samples*

A possible mechanism for this transformation is proposed in Scheme 2. As reported in the literature[11], reaction of 2-naphthol with aldehydes in the presence of an acid catalyst is known to give *ortho*-quinone methides (*o*-QMs). The same *o*-QMs, generated *in situ*, have been reacted with amides via conjugate addition to form 1-amidoalkyl-2-naphthol derivatives **4a-aj**.



Scheme 2. Proposed mechanism synthesis of amidoalkyl naphthols

In order to show the merit of the present work in comparison with reported results in the literature, we compared the reactions of succinic acid with Montmorillonite K10 clay[8], $K_5CoW_{12}O_{40}.3H_2O$[10], *p*-TSA[11] and sulfamic acid/ultrasound[12] in the synthesis of 1-amido-methyl-2-naphthol derivatives. As can be seen from Table 3, succinic acid is an efficient catalyst in the formation of 1-amidoalkyl-2-naphthol with high yields and shorter reaction times.

Table 3. Comparison of succinic acid with montmorillonite K10 clay[8], $K_5CoW_{12}O_{40}.3H_2O$[10], *p*-TSA[11] and sulfamic acid/ultrasound[12] in the synthesis of 1-amidoalkyl-2-naphthols (entries **4a** and **4o** from Table 1)

Entry	Catalyst	Aldehyde/2-naphthol/ (catalyst mol %); conditions	Time	Yield, %
4a	Montmorillonite K10 clay	1/1/(0.1 g); solvent-free, 125 °C	1.5 h	78
4a	$K_5CoW_{12}O_{40}.3H_2O$	1/1/(1 mol %); solvent-free, 125 °C	2 h	80
4a	*p*-TSA	1/1/(10 mol %); solvent-free, 125 °C	6 h	86
4a	sulfamic acid/ultrasound	1/1/(51.5 mol %); solvent-free, 28-30 °C	40 min	92
4a	Succinic acid	1/1/(5 mol %); solvent-free, 120 °C	7 min	95
4o	Montmorillonite K10 clay	1/1/(0.1 g); solvent-free, 125 °C	-	-
4o	$K_5CoW_{12}O_{40}.3H_2O$	1/1/(1 mol %); solvent-free, 125 °C	2 h	86
4o	*p*-TSA	1/1/(10 mol %); solvent-free, 125 °C	4 h	90
4o	sulfamic acid/ultrasound	1/1/(51.5 mol %); DCE, 28-30 °C	120 min	92
4o	Succinic acid	1/1/(5 mol %); solvent-free, 120 °C	25 min	95

Conclusion

we have developed a new, general and efficient procedure for the one-pot synthesis of amidoalkyl naphthols by coupling various aromatic aldehydes with amides or urea and 2-naphthol using succinic acid as a reaction mediator under solvent-free conditions. This protocol has the advantages of shorter reaction times, low costs, solvent-free condition, easy work-up, excellent yields, elimination of solvents, environmentally friendliness and it follows the principles of green chemistry. Along with the use of succinic acid as a highly efficient, low cost, non-toxic, environmentally friendly, readily available reagent which can be conveniently be handled and removed from the reaction mixture. We believe that this procedure is convenient, economical, and eco-friendly process for the synthesis of amidoalkyl naphthols of biological and medicinal importance.

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