Amidoalkyl Naphthols: Trifluoroacetic Acid (TFA) Catalyzed One-Pot, Multi-Component Synthesis

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Abstract: Trifluoroacetic acid (TFA) was found as an efficient catalyst for the synthesis of amidoalkyl naphthols from aromatic aldehydes, β-naphthol and acetamide/benzamide under solvent free condition at 80° C. All the synthesized compounds were characterized by IR, ^{1}H NMR and Mass spectra. The advantages of the new method were good yields, short reaction times, simple work-up, inexpensive and easily available catalyst and economical due to absence of solvent. Therefore, this method could be an attractive alternative to existing methods for the synthesis of biologically important amidoalkyl naphthols.

Keywords: Amidoalkyl naphthols, multicomponent reaction, solvent-free conditions, trifluoroacetic acid.

INTRODUCTION

In recent years, multicomponent reactions (MCRs) have gained much attention in organic synthesis as they furnish the desired products in a single operation without isolating the intermediates. Thus, reaction times are reduced and energy and raw materials saved [1]. Therefore, researchers have made great efforts to find and develop new MCRs. They have merits over two-component reactions in several aspects including the simplicity of a one-pot procedure, possible structural variations and building up complex molecules.

One of the MCRs is the synthesis of amidoalkyl naphthols, which are ubiquitous to variety of biological important natural product and potent drugs, including a number of nucleoside antibiotic and HIV protease inhibitor, such as ritonavir and lipinavir [2, 3]. Furthermore, amidoalkyl naphthols can be converted in to useful synthetic building block for drugs exhibiting depressor and bradycardiac activities [4, 5]. Amidoalkyl naphthol derivatives have attracted considerable interest because of their pharmaceutical and agricultural activities. For example, 1-aminomethyl-2-naphthols have been reported to show cardiovascular activity [4]. The hypotensive and bradycardiac effects of these compounds in normotensive rats as well as their *in vitro* inotropic and aortic contraction effects in the isolated left atria and aorta of rat have been evaluated. 1-Naphthaleneacetic acid and 2-naphthoxyacetic acid have been reported to act as plant-growth regulators [6, 7]. Looking at the importance of the amidoalkyl naphthols, clean methodologies for them have gained considerable attention.

The preparation of amidoalkyl naphthols can be carried out by multi-component condensation of aryl aldehydes, β-naphthol and acetonitrile or amide in the presence of Lewis or Bronsted acid catalysts such as Montmorillonite K10 clay [8], $HClO_4$-SiO_2 [9], Iodine [10], $K_5CoW_{12}O_{40}.3H_2O$ [11], *p*-TSA [12], Sulfamic acid [13], Cation-exchange resins [14], $Fe(HSO_4)$ [15], $Sr(OTf)_2$ [16], $Al(H_2PO_4)_3$ [17], $HClO_4$-Al_2O_3 [18], $NaHSO_4.H_2O$ [19], $In(III)Cl_3$ [20], Zinc benzenesulfonate [21], PPA-SiO_2 [22], $FeCl_3.SiO_2$ [23], $Ce(SO_4)_2$ [24] and Oxalic acid [25] have been reported. However, some of the reported methods suffer from disadvantages such as prolonged reaction time, higher reaction temperature (>100° C), low product yields, use of toxic and corrosive solvents, and unconventional methodologies such as microwave or ultrasonic irradiation. Therefore, it was of genuine interest to develop a more universal method for the synthesis of these products. There are several advantages of performing synthesis in solvent-free media such as simple workup, economical due to the absence of solvent and short reaction time.

RESULTS AND DISCUSSION

Herein, we are reporting a novel protocol for the rapid synthesis of a variety of amidoalkyl naphthols using a catalytic amount of trifluoroacetic acid (TFA) under solvent free condition (Scheme **1**).

To optimize the catalyst quantity, a reaction of p-nitrobenzaldehyde (1 mmol), β-naphthol (1mmol) and acetamide (1.3 mmol) was selected as a starting reaction. The effect of different amount of catalyst on

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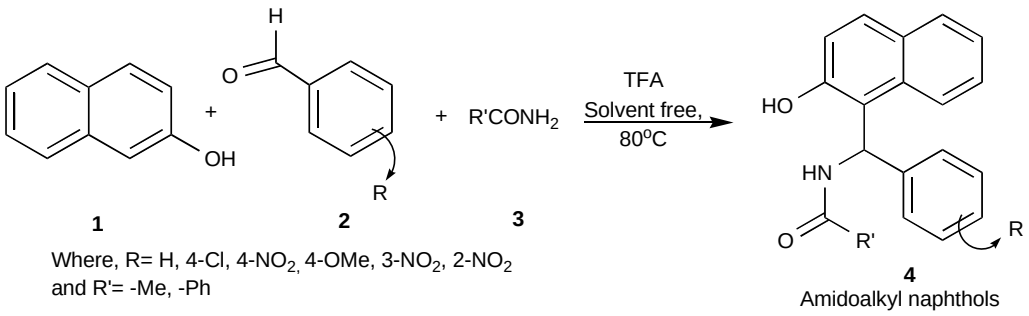


Scheme 1:

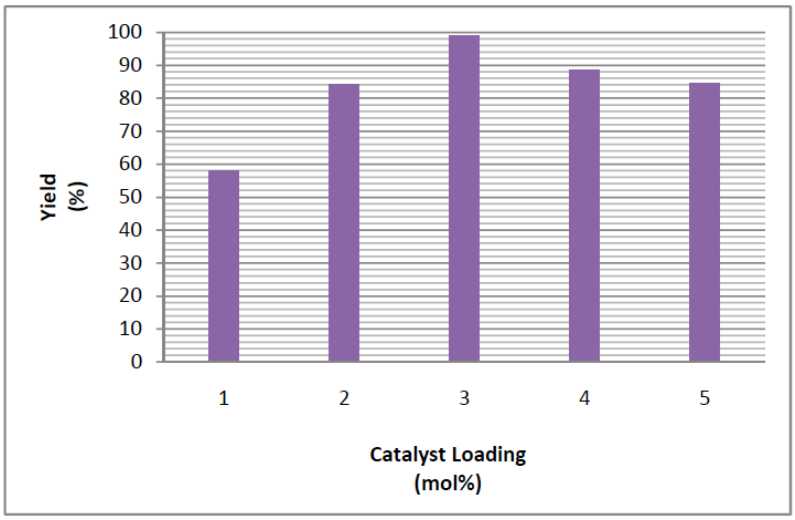


Figure 1: Optimization of Catalyst loading under solvent free condition (Equivalence ratio of Substrate to Catalyst).

the yield of the product has been shown in Figure **1**. The perusal of the data shows that 3 mol% of TFA gives maximum yield under solvent free condition. Therefore, 3 mol % of TFA was selected for further catalytic studies on various similar reactions.

To compare the methodology the same reaction was also carried out in 1,2-dichloroethane at room temperature as well as under reflux condition (15 hrs). The yield of amidoalkyl naphthol was found 5% and 38% in former and latter cases, respectively. Furthermore, to enhance the rate of the reaction, the same reaction was carried out under microwave irradiation. Upon irradiation in a microwave for 3 min., 5 min., 7 min., and 10 min., under solvent free condition above reaction gives desired product 22 %, 33 %, 45 % and 36 % yield, respectively. However, the yield was quite high (Table **1**) in solvent free condition with temperature at 80° C.

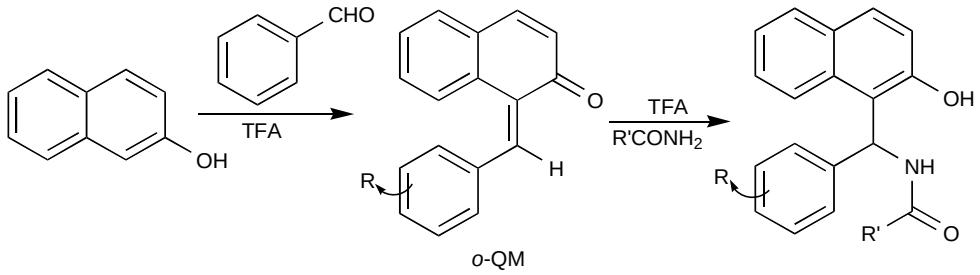
To test the general scope and versatility of this procedure in the synthesis of a variety of substituted amidoalkyl naphthols, we examined a number of substituted aromatic aldehydes, β-naphthol and acetamide/benzamide. The results are summarized in Table **1**. Due to the availability of a vast number of aromatic aldehydes this three component reaction can be very useful to synthesis the desired products. As Table **1** show that in the case of all aromatic aldehydes bearing electron-donating or electron-withdrawing substituent, gave desired amidoalkyl naphthols in good yields. As expected, the aldehydes with electron-withdrawing groups reacted faster than aldehydes having electron-donating groups. In all cases amidoalkyl naphthols were the sole product and no by-product was observed.

Reaction Mechanism

As reported in literature, following reaction mechanism was proposed (Scheme **2**). The reaction of β-naphthol with aromatic aldehyde in presence of acid catalyst is known to give an *ortho*-quinone methide (*o*-QM). The same *o*-QM, generated in-situ, have been reacted with acetamide via conjugate addition to form amidoalkyl naphthols. Electorn-withdrawing groups on the benzaldehyde in the *o*-QMs intermediates increase the rate of the 1,4-nucleophilic addition reaction

Table 1: TFA-Catalyzed One-Pot, Multi-Component Synthesis of β-Naphthol, Aldehydes and Acetamide/Benzamide

Entry	R	R'	Product	% Yield	m. p. °C	
					Observed	Reported
1	H	Me	4a	95	240-242	241-243 [11]
2	4-NO_2	Me	4b	98	246-248	245-247 [17]
3	4-Cl	Me	4c	72	235-237	236-238 [26]
4	4-MeO	Me	4d	73	184-186	185-187 [15]
5	3-NO_2	Me	4e	80	254-255	255-256 [16]
6	2-NO_2	Me	4f	98	217-220	218-220 [26]
7	H	Ph	4g	95	233-234	233-235 [18]
8	4-NO_2	Ph	4h	92	239-241	239-241 [25]
9	4-Cl	Ph	4i	68	186-188	187-188 [16]
10	4-MeO	Ph	4j	84	206-209	206-208 [26]
11	3-NO_2	Ph	4k	80	234-236	233-235 [27]
12	2-NO_2	Ph	4l	82	264-266	266-267 [26]



Scheme 2:

because the alkene lowest unoccupied molecular orbital (LUMO) is at lower energy in the presence of electron-withdrawing groups compared with electron-donating grops [9, 22, 23].

Comparison Results of TFA with other Catalysts Reported in the Literature

To show the merit of the present work in comparison with reported results in the literature, we compared reactions of TFA with other reported catalyst in the synthesis of N-((2-hydroxynaphthalen-1-yl) (phenyl)methyl)acetamide (4a) and N-((2-hydroxynaph-thalen-1-yl)(phenyl)methyl)benzamide (4g). The experimental data shown in Table **2** indicate that TFA can act as an effective catalyst with respect to yields of the products and reaction conditions.

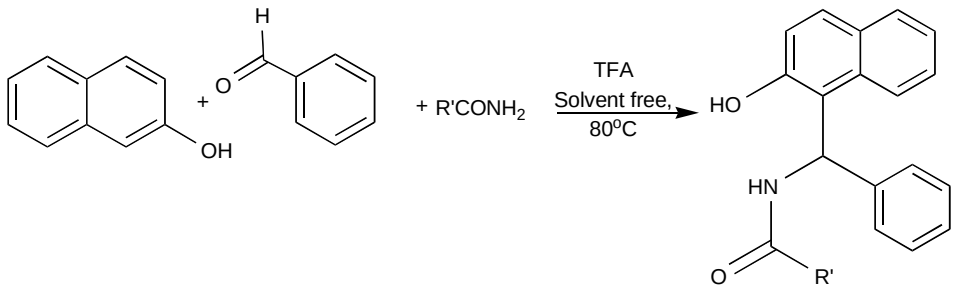
EXPERIMENTAL

Reagents were purchased from SD Fine, Sisco Research Laboratory (SRL), Qualigens Limited. TLC was performed on Merck 60 F_{254} aluminium coated plates and the spots were visualized under UV light. ^{1}H NMR spectra were recorded on Bruker Avance 400 spectrometer in dimethylsulfoxide (DMSO-d_6). Mass spectra were recorded on Thermo-Fischer DSQ II GCMS instrument. IR spectra were recorded on a Shimadzu Prestige 21 spectrometer. Melting points were recorded in a Thiele's tube using paraffin oil and are uncorrected.

General Procedure for the Synthesis of Amidoalkyl Naphthols

A mixture of aromatic aldehydes (1 mmol), β-naphthol (1 mmol), acetamide or benzamide (1.2 mmol) and trifluoro acetic acid (TFA) (3 mol %) was magnetically stirred on a preheated oil bath at 80˚C under solvent–free condition for one hour. The progress of the reaction was monitored by thin-layer chromatography (TLC). After completion of the reaction, the mixture was cooled to room temperature, washed with H_2O, and the residue was recrystallized from 20% ethanol. The products were characterized by their m.p. and spectral analysis (IR, ^{1}H NMR,

Table 2: Comparison Results of TFA with other Catalysts Reported in the Literature[a]



Entry	Amide	Catalyst	Catalyst amount, conditions	Time	%Yield
1	Acetamide	Montmorillonite K10 clay [8]	0.1 g, solvent free conditions, 125°C	1.5 h	89
		I_2 [10]	5 mol%, solvent free conditions, 125°C	5.5 h	85
		$K_5CoW_{12}O_{40}.3H_2O$ [11]	1 mol%; solvent free condition, 125 °C	2 h	90
		p-TSA [12]	10 mol%; solvent free condition, 125 °C	5 hrs	88
		Sulfamic acid [13]	2.5 mmol, solvent free conditions, irradiated in the ultrasonic cleaner at 30 °C	40 min	89
		$HClO_4$-Al_2O_3 [18]	0.1 g (0.2 mmol of H^+), solvent free conditions, 125 °C	30 min	90
		$NaHSO_4.H_2O$ [19]	45 mg, solvent free conditions, 120 °C	11 min	86
		Zincbenzenesulfonate [21]	0.2 mmol, solvent free conditions, 80 °C	6.5 h	51
		PPA-SiO_2 [22]	(0.03 g)1.5 mol%, solvent free conditions, 120 °C	7 min	86
		$FeCl_3.SiO_2$ [23]	25 mg, solvent free conditions, 120 °C	11 min	86
		TFA	3 mol%, solvent free conditions, 100 °C	1 h	95
2	Benzamide	$HClO_4$-SiO_2 [9]	1 mol%, solvent free conditions, 125 °C	10 min	90
		Sulfamic acid [13]	2.5 mmol, solvent free conditions, irradiated in the ultrasonic cleaner at 30 °C	24 min	92
		Zincbenzenesulfonate [21]	0.2 mmol, solvent free conditions, 80 °C	6.5 h	84
		PPA-SiO_2 [22]	(0.03 g)1.5 mol%, solvent free conditions, 120 °C	5 min	80
		TFA	3 mol%, solvent free conditions, 100 °C	1 h	95

[a]Based on a reaction of benzaldehyde, β-naphthol and amide.

Mass-spectra) and compared with those of the known compounds. Spectral data for some compounds are as follows.

Compound 4b: N-((4-nitrophenyl)(2-hydroxynaphthalen-1-yl)methyl)acetamide

Yield: 98 %, Yellow solid. m.p. 246-248^0 C, IR (KBr): *v* 3391, 3267, 2593, 1648, 1603, 1522, 1438, 1063, 825, 739, 447 cm^{-1}. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 2.02 (s, 3H, -CH_3), 7.16 (s, 1H, -CH), 7.18-8.15 (m,10H), 8.60-8.62 (d, 1H, -NH), 10.15 (s, 1H, Ar OH). EI-MS (*m/z*, %): M^+ 336 (37), 259.51 (83), 230.07 (100).

Compound 4c: N-((4-chlorophenyl)(2-hydroxynaphthalen-1-yl)methyl)acetamide

Yield: 72 %, White solid. m.p. 235-237^0 C, IR (KBr): *v* 3391, 2962, 2700, 2613, 1637, 1577, 2523, 1490, 1436, 1374, 1331, 1278, 1243, 1171, 1091, 819, 747, 588, 499 cm^{-1}. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 1.98 (s, 3H, -CH_3), 7.07 (s, 1H, - CH), 7.09-8.48 (m, 10H, ArH), 8.49 (d, 1H, -NH), 10.07 (s, 1H, Ar OH). EI-MS (*m/z*, %): M^+ 324.63 (56), 264.41 (67), 230.98 (100), 202.11 (12).

Compound 4i: N-((4-chlorophenyl)(2-hydroxynaphthalen-1-yl)methyl)benzamide

Yield: 68 %, White solid. m.p. 186-188^0 C, IR (KBr): *v* 3398, 3062, 2785, 2289, 2607, 1896, 1777, 1692, 1570, 1503, 1346, 1438, 1485, 1090, 1014, 813, 747, 584, 541, 526, 437 cm^{-1}. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 7.23 (s, 1H, -CH), 7.25-8.07 (m, 15H, ArOH), 9.05 (d, 1H, - NH), 10.40 (s, 1H, ArOH). EI-MS (*m/z*, %): M^+ 386.82 (25), 265.08 (100), 231.14 (73), 202.11 (22), 104.81 (12).

Compound 4k: N-((3-nitro phenyl)(2-hydroxy-naphthalen-1-yl)methyl)benzamide

Yield: 80 %, Pale yellow solid. m.p. 234-236^0 C, IR (KBr): *v* 3375, 3271, 3054, 2971, 2390, 1958, 1738, 1816, 1633, 1577, 1530, 1504, 1479, 1438, 1346, 1307, 1279, 1058, 927, 812, 733, 654, 591, 524, 447 cm^{-1}. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 7.24 (s, 1H, -CH), 7.26- 8.10 (m, 15H, ArH), 9.15-9.17 (d, 1H, -NH), 10.43 (s, 1H, ArOH). EI-MS (*m/z*, %): M$^+$ 397.6 (14), 230.58 (100), 260.09 (55), 275.41 (69), 380.41 (62), 202.10 (57), 105.14 (66), 115.42 (20), 144.51 (18).

CONCLUSION

In conclusion, a new protocol for a novel and highly efficient methodology for the synthesis of amidoalkyl naphthols by one-pot condensation reaction of aromatic aldehyde, β-naphthol and acetamide/benzamide catalysed by TFA has been established under ordinary laboratory conditions. This method offers several advantages such as high conversions, easy handling, clean reaction profile, simple work-up, and shorter reaction time, which makes it a useful and attractive process for the quick synthesis of amidoalkyl naphthols. In the present method, work-up procedure is very simple which includes washing of the reaction mixture with water and recrystallization from ethanol. Therefore, this method could be an attractive alternative to existing methods for the synthesis of biologically important amidoalkyl naphthols.

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