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MILD, EFFICIENT SYNTHESIS OF 1-AMIDOALKYL 2-NAPHTHOL USING ETON'S REAGENT AT ROOM TEMPERATURE

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ABSTRACT
In present study, we have developed a mild, efficient protocol for the synthesis of 1-Aminoalkyl 2-Naphthol via a one pot three component reactions of aldehyde, β-Naphthol and acetamide by using Eton's reagent in ethanol as a solvent at room temperature. This procedure offers several advantages over reported protocol such as short reaction time, mild reaction condition, easy workup procedure and excellent yield.

Keywords: *multicomponent reactions, Amidoalkylnaphthols, acetamide, β-Naphthol.*

INTRODUCTION

Multicomponent reactions (MCRs) have gained much attention in organic synthesis, MCRshas several advantages over multistep synthesis, MCRs are one-pot processes in which three or more easily accessible components react to form a single product, which incorporates high atom economy[1].Multicomponent reactions (MCRs) have been an efficient and powerful tool in the modern synthetic chemistry. Isolation, purification and characterization steps for each intermediate will be removed under one-pot procedures.MCR has several advantages like, great efficiency and procedural convenience in the construction of complex structures from three or more reactants. In addition to this, MCRs are a promising and very important field in synthetic chemistry because synthesis of heterocycles can be achieved in anefficient,very fast,time and energy saving approachwithout the isolation of any intermediate.[2]

Amidoalkylnaphthols containing organic moiety exists in variety of effective drugs including a number of nucleosides, antibiotics and HIV protease inhibitors, such as lipinavir and ritonavir as well as in biologically important natural products. Amidoalkylnaphthols act as essential and important building blocks towards the synthesis of some organic compounds which possess excellent cardiovascular activity. Moreover this aminoalkylnaphthol containing metal complex has been used for asymmetric synthesis and also acts as a catalyst. In addition to this, these compounds exhibit antibacterial, hypotensive, and bradycardiac effects, etc. [3, 4].

Various method has been developed for the synthesis of amidoalkylnaphthols by three-component condensation of β-naphthol, aldehydes, and amides or different amine in the presence of Bronsted or Lewis acids such as p-TSA [5], $Fe(HSO_4)_3$ [6], H_2NSO_3H [7], $Sr(OTf)_2$ [8], $Al(H_2PO_4)_3$ [9],I_2 [10], $K_5CoW_{12}O_40\cdot3H_2O$ [11] and HPMo [12], Bronsted acidic ionic liquid [13], montmorillonite K_{10} [14], $HClO_4$–SiO_2 [15, 16] and cation-exchange resin catalysts like Indion-130 [17], Al_2O_3–$HClO_4$ [18]

Eaton's reagent is composed of 1:10 solution byweight of phosphorous pentoxide in methane sulfonic acid. It is an alternative to polyphosphoricacid because, it is easy to handle, and it has lower viscosity, inexpensive and simply removed from product by simply washing with aqueous sodium carbonate or water. A range of synthetic protocols were reported by using Eaton's reagent such as synthesis of Quinolone [19], synthesis of tetrahydro isoquinoline [20], chromenes and flavones [21], synthesis of mono and bis-chalcone derivatives [22],cationic arylation of aromatic carboxylic acids [23] andsynthesis of aryl mesylates [24]. Such successful catalytic activity of Eton's reagent has encouraged us to study its further application in organic synthesis. Herein, we desire to extend the synthetic applicability of such reagent for the synthesis of amidoalkylnaphthol.

EXPERIMENTAL

General Methods: All reagents, solvents and chemicals were purchased from SD fine chemicals used without further purification.All melting points are uncorrected and weredetermined on electrothermal Mk_3 melting point apparatus. Reaction progress was monitored by aluminum TLC plates. Infrared spectra were recorded (KBr pellets) on a Perkin-Elmer FTIR spectrophotometer 65, wave-numbers in the IR spectra are given in cm^{-1}.^1H NMR spectra were recorded on a 400 MHz FT-NMR spectrometer in DMSO-d_6 as a solventchemicalshifts had been expressed on the δ (ppm) scale downfield from TMSas an internal well-known reference.

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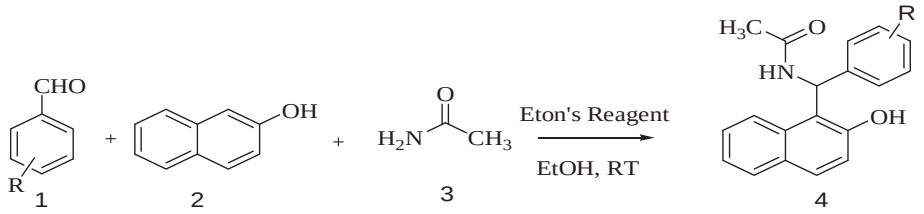
General procedure for the synthesis of Amidoalkylnaphthol

A mixture of aldehyde (1 mmol), β-naphthol (mmol) andacetamide (1.2 mmol) and Eton's reagent (20 mole %) in ethanol (2ml) was stirred at room temperature. The progress of reaction was monitored by TLC using ethyl acetate and pet ether as mobile phase. After completion, the reaction mixture was poured on crushed ice.The separated solid was filtered and washed with water several times. The residue was dried and recrystallized from ethanol to afford corresponding amidoalkylnaphthol.The products were confirmed by comparisons of melting points with authentic samples and spectral data such as IR, ^{1}H NMR.



Scheme 1

RESULT AND DISCUSSION

To promote environmentally friendly processes, first we choose β-naphthol (1), benzaldehyde (2) and Acetamide (3) as model reaction for the synthesis of amidoalkylnaphthol.Model reaction was carried out at room temperature in absence of catalyst and solvent; no desired product was obtained (Table 1, entry 1). Slight excess of the acetamidewas found to be advantageous and it gives desired product but in very less amount. Further model reaction was subjected to microwave heating; the desired product was formed in 10% yield (Table 1, entry 2).To increase the efficiency of reaction, the model reaction examined using 20 mol%Eton's reagent without solvent and the obtained desired product was 70% yield.No significant increase in yield was noted when the reaction was carried out with 25mol% catalyst.

Encouraged by these results, we further studied reaction in order to raise the yield of product.Model reaction was carried out using water, ethanol and methanol at room temperature and under microwave condition. It was observed that the uses of solvents in reaction media quicken the reaction rate and affords the preferred product in good yield than that for neat conditions. After screening a variety of reaction media, Eton's reagent in ethanol solvent were determined to be the best compared with reactions carried out in various polar solvent.

Table-1: Optimization of reaction conditions

Entry	Condition	Time	Yield %
1	Solvent and catalyst free, RT	3h	---
2	Solvent and catalyst free, MW	0.5h	10
3	Solvent free, Catalyst, RT	1h	70
4	Solvent free, Catalyst,MW	0.5h	60
5	H_2O, Catalyst, RT	1h	60
6	H_2O, Catalyst, MW	0.5h	55
7	EtOH, Catalyst, RT	1h	90
8	EtOH, Catalyst, MW	20 min	65
9	MeOH, Catalyst, RT	0.5h	82
10	MeOH, Catalyst, MW	0.5h	60

With the optimized condition in hand, we next explored the scope and generality of the model reaction. As shown in Scheme 1, a variety of substituted benzaldehyde was used for these protocol and we find that all benzaldehyde with electron donating and electron withdrawing groups were all suitable for the reactionsgivesmoderate to excellent yields.

Table-2: Preparation of 1-Amidoalkyl 2-Naphthol catalyzed by Eton's reagent

Entry	R	Time (min)	Yield (%)	M.P.(^{o}C)
1	H	60	90	240-241
2	p-CH_3	65	92	222-224
3	m-NO_2	55	96	255-257

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4	p-NO_2	45	97	244-246
5	p-Cl	55	94	230-232
6	m-Cl	60	92	236-238
7	p-Br	60	94	228-230
8	m-OH	70	90	203-205
9	p-OH	65	91	210-212
10	p-OCH_3	75	90	209-211

SPECTRAL DATA OF SOME REPRESENTATIVE COMPOUNDS

1)N-((2-hydroxynaphthalen-1-yl)(phenyl)methyl)acetamide:IR (KBr) (λmax): 3410, 3250, 2410, 1630, 1586, 1530, 1415, 1330, cm^{-1}. ^{1}HNMR (DMSO - d_6) 9.92 (s, 1H, OH), 8.25 (d, 1H, NH), 7.92-7.55 (m, 5H, Ar H), 7.50-7.24 (m, 6H, Ar H), 5.63 (d, 1H, NH), 2.10 (s, 3H, CH_3).

2)N-((2-hydroxynaphthalen-1-yl)(4-nitrophenyl)methyl)acetamide:IR (KBr) (λmax): 3415, 3235, 2420, 1645, 1565, 1522, 1430, 1310, cm^{-1}. ^{1}HNMR (DMSO - d_6) 10.05 (s, 1H, OH), 8.50 (d, 1H, NH), 8.10-7.68 (m, 4H, Ar H), 7.45-7.29 (m, 6H, Ar H), 5.78 (d, 1H, NH), 2.2(s, 3H, CH_3).

CONCLUSION

In summary, an efficient one-pot Eton's reagent mediated protocol for the synthesis of amidoalkylnaphthol skeleton from readily available substituted benzaldehyde, β-naphthol and acetamide has been developed.Clean and complete conversions leading to the corresponding amidoalkylnaphtholswere observed.

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