CESIUM CARBONATE CATALYZED EFFICIENT SYNTHESIS OF NAPHTHOCHROMENES UNDER MICROWAVE IRRADIATION

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Cesium carbonate catalyzed three-component condensation reaction of an aldehyde, malononitrile and α-naphthol or β-naphthol proceeded rapidly in ethanol to afford corresponding naphthochromenes in high yield under microwave irradiation.

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Introduction

Organic transformations involving benign reaction media are of considerable interest in synthesis; especially multicomponent condensation reactions (MCR) in which two or more steps are completed without isolation of any intermediate.[1] Microwaves have been emerged as extensively useful non-conventional energy source for performing organic synthesis. Microwave assisted reactions have received great importance due to their simplicity in operation, short reaction time, enhanced rate of reaction and better yields with high purity as compared to conventional heating[2] reactions.

Chromene is an important class of heterocyclic compounds as they are the main constituents of many natural products. Its derivatives are widely used as cosmetics, pigments[3] and potential biodegradable agrochemicals.[4] Fused chromenes are biologically active compounds showing a wide range of activities such as antimicrobial,[5] antiviral,[6] mutagenicitical,[7] sex pheromonal,[8] antitumoral[9] and CNS activities.[10] Compound EPC2407 (Fig-1) is currently inphase I/II clinical trials as vascular targeting anticancer agentand apoptosis inducer for the treatment of advanced solid tumors.[11] Some other chromene derivatives like etoposide, teniposide, andetopophos are currently in clinical use for the treatment of various malignancies.[12] Thus, the synthesis of 4H-chromene derivatives has recently attracted great interest. Various methods have been reported for synthesizing 4H-chromenes derivatives.

Chromenes are generally prepared by multicomponent condensation of aromatic aldehyde, active methylene derivatives and activated phenol or naphthol in presence of various base using acetonitrile or ethanol as a solvent under conventional heating.[13-16] Recently, we synthesized 4H-chromene derivatives by condensing barbituric acid, aldehyde and malononitrile using yttrium oxide in aqueous methanol as a catalyst system efficiently.[17]

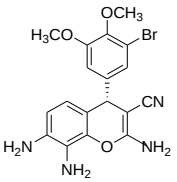


Figure 1. Structure of EPC2407

Cesium carbonate has been widely used as a strong base in organic synthesis due to its ease of handling, low hygroscopicity[18], and high solubility in organic solvents as compared to alkali metal hydroxides. In recent years, cesium carbonate has found extensive applications as an excellent base in variety of synthetic transformations[19-28] and has received even industrial acceptance. Its basic strength is shown by the fact that it is the base of choice for reactions that are too sensitive towards strong bases or reactions that require a "Balanced base," stronger than other carbonates and weaker than hydroxides and alkoxides[29]. It is compatible with a variety of functional groups.

Experimental

Materials and instruments

All starting materials and chemical reagents were purchased from SD Fine Chemical Company and used without further purification. Melting points were determined in open capillaries using Electrothermal Mk3 apparatus. Infrared (IR) spectra in KBr pellets were recorded using a Perkin-Elmer FT-IR spectrometer. ^{1}H NMR spectra were recorded on an 400 MHz FT-NMR spectrometer in $CDCl_3$ or DMSO-d6 as a solvent and chemical shift values were recorded in units δ (ppm) relative to tetramethylsilane (Me_4Si) as an internal standard.

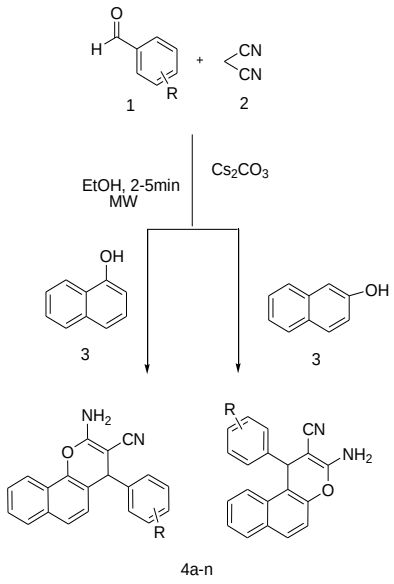
Table 1. Three-component condensation reaction

Entry	R	Naphthol	M.p., ^{0}C	Lit. M.p., ^{0}C	Time, min.	Yield, %
a	P-Cl	α - naphthol	234-237	231-232	2	92
b	P-NO_2	α - naphthol	242-245	239-241	1.5	94
c	m-NO_2	α - naphthol	209-211	210-212	2.5	93
d	H	α - naphthol	207-210	211-212	2.5	89
e	p-Br	α - naphthol	237-240	241-243	3	91
f	p-F	α - naphthol	225-228	230-232	2.5	92
g	p-OCH_3	α - naphthol	184-186	182-183	4	90
h	p-OH	α - naphthol	238-240	241-245	4.5	89
i	m-OH	α - naphthol	245-247	250-253	4.5	84
j	p-Cl	β - naphthol	210-211	206-208	4	90
k	p-NO_2	β - naphthol	182-184	185-186	4	91
l	p-Br	β - naphthol	244-246	242-244	4.5	88
m	p-F	β - naphthol	236-239	233-235	5	89
n	H	β - naphthol	281-283	280	4.5	90

The microwave irradiation was carried out in a scientific microwave oven (CATA-4R-Model No. QW-99, India makes), 2450 MHz Frequency, with power output of 140-700 W.

General procedure for the synthesis of naphthochromenes

A mixture of aromatic aldehyde (1 mmol), malononitrile (1 mmol), α-naphthol or β-naphthol (1 mmol) and cesium carbonate (10 mol %) in ethanol (5 mL) was mixed properly and irradiated under microwave oven at the power of 140W for a period 2-5 min (Table 1). The progress of reaction was monitored by thin layer chromatography (ethyl acetate: hexane 4:1). After completion of reaction (2-5 min), the reaction mass was cooled at room temperature and poured over cold water. The obtained solid was filtered, washed with water, and crude solid was recrystallized from hot ethanol to afford an analytically pure compound 4a–n. The products were confirmed by comparisons with authentic samples, IR, ^{1}H NMR and melting points.



Scheme 1.

Result and discussion

In this article, we described a simple and high yielding protocol for the synthesis of naphthochromenes involving three-component one-pot condensation of aldehyde1(1 mmol), malononitrile 2 (1 mmol) and α-naphthol or β-naphthol 3 (1 mmol) using cesium carbonate in ethanol (5 ml) under microwave condition (scheme 1). In order to determine the mole % of catalyst, we have carried out model reaction of p-NO_2 benzaldehyde, malononitrile and α-naphthol with different amount of catalyst and found the optimum catalyst loading of cesium carbonate to be 10 mol %. By decreasing the amount of catalyst to 5 mol % the yield of product 4a was reduced; however, by increasing the amount of catalyst from 10 to 15 mol %, no appreciable change in the yield of product was observed.

Next, in order to investigate the substrate scope of the reaction, a variety of substituted benzaldehydes were used employing the present optimized reaction conditions. The yield and reaction were found to be fairly equal and good (Table 1). Spectral data of some selected compounds shown below

4H-Naphtho[1,2-b]pyran-3-carbonitrile-2-amino-4-(4-chloro-phenyl) (Table 1, entry a):

IR (KBr): 3437, 3348, 3242, 2961, 2862, 2220, 1644, 1593, 1520, 1460, 1390, 1275, 1185, 1035, 881, 850, 764 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): 4.8 (1H, s) C-H, 6.89 (2H, s) N-H, 7.0 (1H,d) Ar-H, 7.2 (2H, d) Ar-H, 7.35 (2H, d) Ar-H, 7.50 (3H, m) Ar-H, 7.84 (1H, d) Ar-H, 8.1 (1H, d) Ar-H.

4H-Naphtho[1,2-b]pyran-3-carbonitrile-2-amino-4-(4-fluoro-phenyl) (Table 1, entry f):

IR (KBr): 3440, 3350, 3244, 2960, 2858, 2222, 1646, 1591, 1524, 1461, 1391, 1280, 1181, 1033, 883, 847, 763 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): 4.8 (1H, s) C-H, 6.9 (2H, s) N-H, 7.0 (1H,d) Ar-H, 7.1 (2H, d) Ar-H, 7.4 (2H, d) Ar-H, 7.5 (3H, m) Ar-H, 7.8 (1H, d) Ar-H, 8.2 (1H, d) Ar-H.

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Conclusion

In conclusion, naphthochromenes were successfully synthesized by using cesium carbonate catalyst under microwave radiation from aldehydes, malononitrile and a naphthol. The promising points for the present methodology are clean reaction procedure, short reaction times, simplicity in operation and catalyst with high catalytic activity.

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