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Formation of novel piperidinium salt during three components Condensation under Microwave Irradiation

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ABSTRACT

A novel synthesis of piperidinium salt by three-component reaction of 4- hydroxy coumarin, aldehydes and naphthol in the presence of piperidine as a catalyst under microwave irradiation is described.

Keywords: Multi component, microwave, 4-hydroxy coumarin, naphthol, piperidine

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INTRODUCTION

Multicomponent reactions have recently gained considerable economic and ecological interest as they address fundamental principles of synthetic efficiency and reaction design. Multicomponent reactions (MCRs) have been proven to be a very elegant and rapid way to access complex structures in a single synthetic operation from simple building blocks and show high atom economy and high selectivity [1]. Permitted rapid access to combinatorial libraries of organic molecules for efficient led structure identification and optimization in drug discovery [2]. These features are particularly important in the early steps of drug discovery, by either high-throughput screening or fragment-based design, as well as for hit-to-lead optimization [3]. Nevertheless, the development of new multi component reactions is still in demand. In this context, ortho-quinone methides (o-QMs) have been used in many tandem processes [4]. The condensation of phenols with aldehydes under acid or base catalysis is believed to proceed via ortho-quinone methide intermediates [5]. These intermediates mainly involve [4+2] cycloadditions with a wide range of dienophiles [6]. However, a limited work has appeared with carbon nucleophiles [7]. It is difficult to create proper reaction conditions compatible with the simultaneous generation of both the o-QM and the carbon nucleophile and this seems to hamper the proper exploitation of o-QMs in reactions with carbon nucleophiles in organic synthesis.

Coumarin derivatives have various biological activities such as anticoagulant, insecticidal, antihelminthic, hypnotic, antifungal, phytoalexin, and HIV protease inhibition [8–9]. It was found that the minimum active pharmacophore consisted of coumarin dimer containing an aryl substituent on the central linker methylene. Between the systems studied, the a,a-benzylidene bis(4-hydroxycoumarin-3-yl)toluene has been tested as HIV integrase inhibitor and has shown significant activity [10]. In this manuscript, we have reported simple, easy and highly efficient protocol for the formation of piperidinium salt by the Knoevenagel condensation of aromatic aldehydes, 4-hydroxy coumarin with naphthol in the presence of piperidine as catalyst.To the best of our knowledge, no reports on three-component coupling of 4-hydroxycoumarin, aldehydes and napthol to provide novel series of chromene derivatives.

Recently, tetrahydrobenzo[a]xanthene-11-one have been synthesized by one-pot three-component condensation of aldehydes, 2-naphthol and cyclic 1,3-dicarbonyl compound using $InCl_3$, P_2O_5 [11], $NaHSO_4.SiO_2$ [12], $Sr(OTf)_2$ [13], $Zr(HSO_4)_4$ [14], PEG-400 [15], and PWA [16]. This is a part of our research program on the development of new protocols in heterocyclic synthesis [17].

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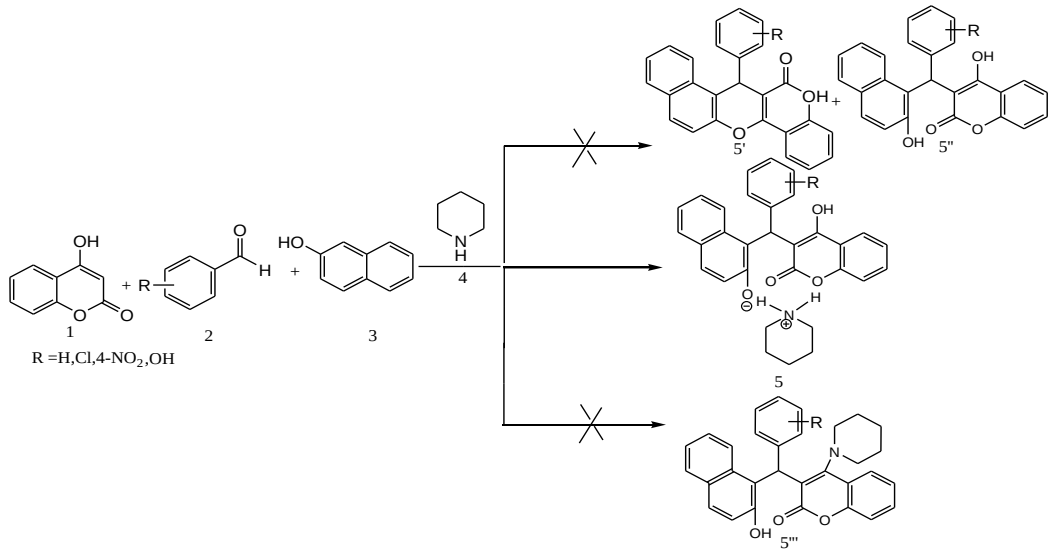
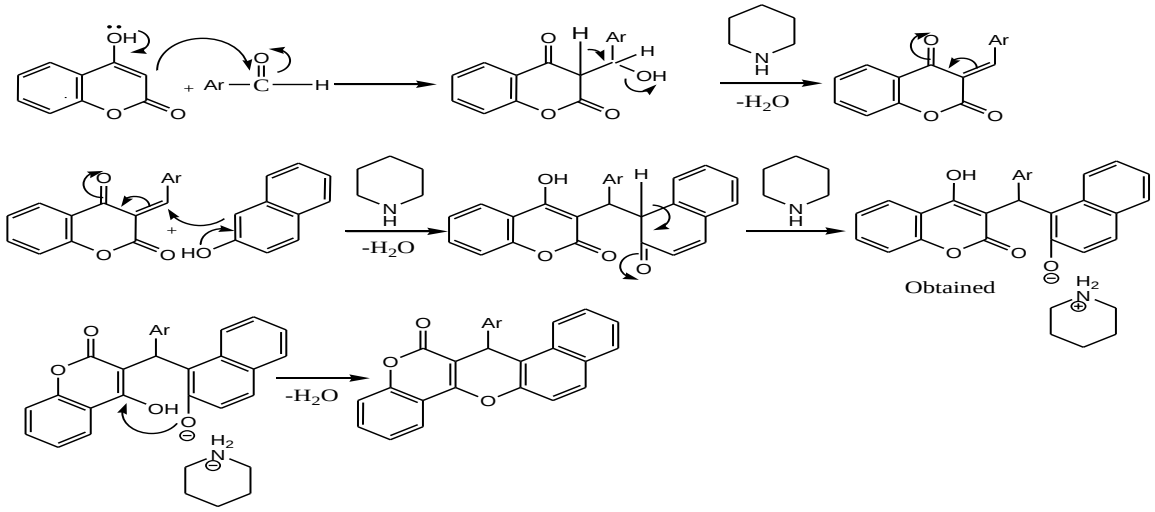


Scheme 1 Synthesis of piperidinium salt

Initially, we conducted the reaction of 2-naphthol, 2-chlorobenzaldehyde and 4-hydroxy coumarin in the presence of various heterogeneous solid acid, lewis acid, bases such as Amberlyst-15, Phospotungstic acid, para tolune sulfonic acid, $HBF_4.SiO_2$, Polyethylene glycol-6000, $ZnCl_2$, L-proline, potassium phosphate, and piperidine in thermal or microwave. The corresponding chromene derivative $5^{//}$ (Table 1) was formed in 5%, 24%, 17%, 20%, 30%, 7%, 37%, 32, 92% yield. Piperidine was thus selected as the most effective catalyst to carry out this reaction for corresponding chromene derivative **5**. The suggested mechanism of the reaction is shown in (Scheme 2**).** In this scheme it is assumed that first step involved reaction of aromatic aldehydes with 4-hydroxy coumarin follows by subsequent reaction with 2-naphthol. It is quite probable that the first step may involve condensation with 2-naphthol followed by subsequent condensation with 4-hydroxycoumarin.



Scheme 2 Suggested mechanisms for the synthesis of piperidinum salt

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Encouraged from the successful condensation of aldehydes, 2-naphthol and 4-hydroxy coumarin and piperidine under microwave irradiation condition to give piperidinium salt**,** unfortunately, the expected products may not be obtained. The results are shown in (Scheme 1).

Table 1 Catalyst effect on reaction using solvent free condition

Entry	Catalyst	Catalyst in(mol%)	Thermal / microwave	Time	Product	Yield (%)
1	Amberlyst-15	10	100 ^{0}C(T)	8 hr	5$^{//}$	5
2	Phospotungstic acid	10	90 ^{0}C(T)	8 hr	5$^{//}$	24
3	para tolune sulfonic acid	10	320 W (M)	9 min	5$^{//}$	17
4	$HBF_4.SiO_2$	10	100 ^{0}C(T)	10 hrs	5$^{//}$	20
5	Polyethylene glycol-6000	5	100 ^{0}C(T)	12 hrs	5$^{//}$	30
6	$ZnCl_2$	10	320 W (M)	10 min	5$^{//}$	7
7	L-proline	10	90^{0}C(T)	8 hrs	5$^{//}$	37
8	Piperidine	5	90^{0}C(T)	3 hrs	5	62
9	Potassium phosphate	10	90 ^{0}C(T)	6hrs	5$^{//}$	32
10	Piperidine	5	320 W (M)	3 min	5	79

Thermal =T, Microwave irradiation = M

The role of solvent was then examined (Table 2).As the highest yield was obtained in ethanol, this was selected as the ideal solvent.

Table 2 Optimization conditions of piperidinium salt at 5 mol% of catalyst.

Entry	Catalyst	Solvent	Time(min)	Yield (%)
1	Piperidine	Solvent free(M) 320W	3	79
2	Piperidine	Methanol (M) 320W	3	84
3	Piperidine	Ethanol (M) 320W	3	91
4	Piperidine	Ethanol:Water (50:50) 320W	4	30
5	Piperidine+TBABr	Ethanol+water(10:90)(M) 320W	8	60

The affect of catalyst concentration showed (Table 3) that best results are obtained with molar concentration of piperdine

Table 3 The effect of piperidine concentration at 320 W in solvent Ethanol

Entry	Catalyst	Molar percentage(mol%)	Time(min)	Yield (%)
1	Piperidine	2.5	4	55
2	Piperidine	5	3	91
3	Piperidine	5.5	3	92
4	Piperidine	7.5	2.5	87

The reaction under these conditions using 2-chlrorbenzaldehyde afforded white solid M.P.262-263^{0}C that showed IR bands at 3424, 3165, 1662, 1600, 1508 typical of NH/OH,

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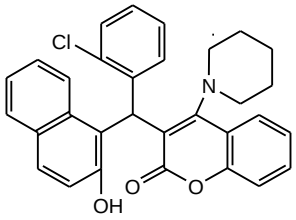
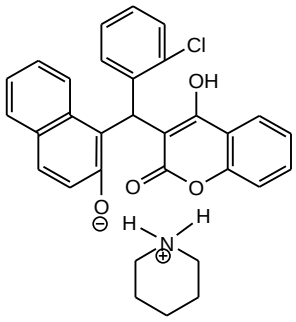
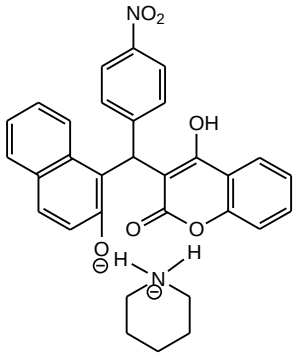
coumarin carbonyl and aromatic group. The ^{1}H NMR ($CDCl_3$) showed signals at 1.6(m,2H), 1.9(m,4H), 3.2(m,4H), 6.12(s,1H), 7.11 to 9.1 (m,16H) and 17.2 (s, OH) that suggested the incorporation of piperidine moiety along with naphthalene, coumarin and aromatic ring of the aldehyde. The CMR spectrum (DMSO d_6) with DEPT showed 3 CH_2 group at 22.07, 22.10, 43.73 and a CH at 36.01.The aromatic region showed eight CH signals and seven signals for fully substituted carbons at 102.68, 119.7, 132.60, 140.22, 152.3, 163.95, 167.73. These signals could suggest a structure similar to **5**$^{//}$. The elemental analysis was consistent with the formula $C_{13}H_{26}NO_4Cl$ suggesting the compound to be the salt **5.1.**



5$^{///}$



5.1



5.2

This structure was supported by the mass spectrum using matrix assisted laser desorption /ionization (MALDI) with a time of flight (TOF)mass spectrometer that gave a molecular weight 513 M^+, 515$(M+2)^+$.This techniques allows one to get the total weight of the salt [18].

These results were supported by carrying out the reaction using p-nitro benzaldehyde instead of 2-chlorbenzaldehyde. The IR, ^{1}H NMR, ^{13}C-NMR, elemental analysis coupled with the molecular weight of 524 was consistent with structure **5.4.**The reaction were then carried out on other aldehydes, the results are collected in table 4.In each the products were obtained in high yield (85-92%)

Table 4 Piperidine promoted condensation of aldehydes, 4-hydroxy coumarin with 2-napthol (1:1:1)

Product	R	Napthol	Time (min)	Yield (%)	Mp(^{0}C)
5.1	2-Cl C_6H_4	2-naphthol	3.0	92	262-263
5.2	C_6H_5	2-naphthol	4.0	90	254-256
5.3	4-Cl C_6H_4	2-naphthol	4.0	89	230-231
5.4	4-$NO_2C_6H_4$	2-naphthol	5.0	85	249-250
5.5	2-OMe C_6H_4	2-naphthol	4.0	87	235-236
5.6	4-OMe C_6H_4	2-naphthol	6.0	85	217-218
5.7	4-OH-3-OMe C_6H_3	2-naphthol	6.0	86	257-258
5.8	2-$NO_2C_6H_4$	2-naphthol	7.0	82	230-232
5.9	C_6H_5	1-naphthol	4.0	87	262-264
5.10	2-Cl C_6H_4	benzo[d][1,3]dioxol-5-ol	4.0	87	269-270

In conclusion, we have described a novel, efficient and one-pot synthesis of piperidinium salt in three-component reactions under microwave irradiation. This method gives an environmentally benign strategy for the synthesis of piperidinium salt and offers several advantages including high yield of products, short reaction time, and ease of work-up. Further, we are studying the scope of this salt in other multicomponent reactions.

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[19] General Procedure for the Synthesis of Piperidinum salt derivatives :The mixture of 2-naphthol (1 mmol), 2-chlorobenzaldehyde (1mmol),4-hydroxy coumarin (1mmol) and piperidine (5.5 mol %) were mixed thoroughly with ethanol (3 ml) in a round bottom flask and this reaction mixture was irradiated in microwave oven(320 W) The completion of the reaction was monitored by TLC. After completion of reaction the residue was filtered and recrystallized from ethanol to give piperidinium derivatives. Compounds were characterized by IR spectra, ^{1}H NMR, ^{13}C NMR, DEPT and Mass MALDI TOF and elemental analysis. IR spectra were recorded on Perkin–Elmer FT-IR-1710 instrument. NMR was recorded on BrukerAC-300 MHz, Bruker MSL-200 MHz instrument using TMS as an internal standard.
[20] Piperidinium 3-((2-Chlorophenyl)(2-hydroxynaphthalen-1-yl)methyl)-4-hydroxy-2H-chromen-2-one, 5.1: ^{1}H NMR($CDCl_3$, 300 MHz):1.6(m, 2H, CH_2),1.9 (m, 4H, CH_2),3.2(m, 4H, CH_2),6.12 (s, 1H, CH), 7.11-8.10(m, 16H,Ar-H,NH),17.2(brs, 1H,OH);^{13}C NMR (DMSO, 50 MHz): 22.07 22.10, 36.01,43.77, 102.68, 115.46,
119.77,122.99,124.03,125.94,127.10,129.94,130.02,130.86,132.60,140.22,152.30,
163.95,167.73,HRMS (ESI -TOF)-m/z Calcd.For $C_{31}H_{28}ClNO_4$ 513 M^+,Anal. Calcd C, 72.44; H, 5.49; N, 2.72; Found C, 72.50; H, 5.54; N, 2.77;
Piperidinium 4-Hydroxy-3-((2-hydroxynaphthalen-1-yl) (4-nitrophenyl)methyl)-2H-chromen-2-one, 5.4: ^{1}H NMR ($CDCl_3$, 300 MHz): 1.5(m, 2H, CH_2), 1.8 (m, 4H, CH_2),3.2(m,4H,CH_2), 6.17(s, 1H, CH), 7.24-7.99(m, 16H, Ar-H, NH),17.34 (brs,1H,OH);^{13}C NMR(DMSO, 50 MHz): 22.78,22.80, 37.13, 45.51,102.73, 115.73,119.87,123.36, 123.50,125.21,127.54, 131.72, 145.86, 149.19, 152.71, 167.73, 171.28. HRMS (ESI -TOF)-m/z Calcd. For $C_{31}H_{28}N_2O_6$ 524 M^+, Anal. Calcd C, 70.98; H, 5.38; N, 5.34; Found C, 70.96; H, 5.41; N, 5.39.