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One-Pot Three-Component Synthesis of 3-(α-Aminobenzyl)-4-hydroxycoumarin Derivatives Using Nanocrystalline TiO_2 as Reusable Catalyst*

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Abstract—An efficient nanocrystalline TiO_2-catalyzed one-pot synthesis of 3-[(piperidin-1-yl)phenylmethyl]- and 3-[(morpholin-4-yl)phenylmethyl]-4-hydroxycoumarins has been developed via three-component Mannich type condensation of 4-hydroxycoumarin with aromatic aldehydes and secondary amines (piperidine or morpholine) in ethanol at room temperature. The catalyst can be easily recovered and reused with almost the same catalytic activity. The proposed method is advantageous due to its simplicity, short reaction time, catalyst reusability, good to excellent yield, and clean and easy work-up.

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Development of new multicomponent reactions (MCRs) and improvement of known MCRs constitute an area of considerable current interest. As opposed to the classical way of synthesizing complex molecules by sequential reactions, MCRs allow assembly of complex molecules from simple starting materials in one-pot mode and show a facile execution, high atom-economy, and high selectivity [1–5]. Therefore, the design of new protocol for MCRs has attracted great attention of research groups working in medicinal chemistry and drug discovery.

4-Hydroxycoumarin and its derivatives belong to an important class of heterocyclic compounds that have got tremendous application in various research fields, including biological science and medicinal chemistry. These compounds exhibit a broad spectrum of biological activity, in particular antiviral [6], anti-coagulant [7], anti-HIV [8], antioxidant [9], and anti-cancer [10]. Various compounds containing 4-hydroxycoumarin moiety like warfarin, acenocoumarol, dicoumarol, phenprocoumon, coumatetralyl, carbochromen, bromadialone, etc. are available clinically. Among various derivatives of 4-hydroxycoumarins, 3-benzyl-substituted ones have found important clinical applications [11].

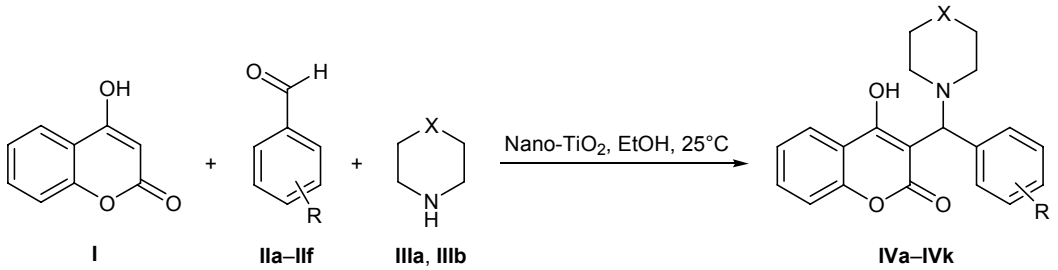
A number of synthetic protocols have been reported for the synthesis of α-aminobenzyl 4-hydroxycoumarin derivatives [12, 13]. The best way to synthesize such compounds is the condensation of 4-hydroxycoumarin with an aromatic aldehyde and a secondary amine, i.e., Mannich type reaction [14]. The known methods for the synthesis of such compounds suffer from severe disadvantages such as long reaction time, poor yield, laborious work-up, and the use of expensive non-recoverable catalysts [15–17]. Thus, the development of high-yielding, short-time, easy-work-up, and clean synthesis of α-aminobenzyl 4-hydroxycoumarin derivatives still remains a desired goal in organic chemistry.

In recent years, there has been a tremendous increase of interest in various chemical transformations performed under heterogeneous catalysis. Among heterogeneous catalysts, nanocrystalline metal oxides have attracted considerable interest in synthetic organic chemistry due to their high catalytic activity, reusability and benign character in the context of green chemistry. These materials possess numerous surface sites with enhanced surface reactivity such as crystal corners, edges, or ion vacancies [18–23].

Nanocrystalline titanium dioxide has attracted considerable interest of synthetic and medicinal chemists as an efficient, versatile, and reusable catalyst, but there are still a few reports available in the literature on the use of nanocrystalline TiO_2 in MCRs [24–26]. Nanocrystalline TiO_2 has been used as a solid acid catalyst in organic reactions like chemoselective trimethylsilylation of alcohols and phenols [27],

* The text was submitted by the authors in English.

Scheme 1.



I **IIa–IIf** **IIIa**, **IIIb** **IVa–IVk**

II, R = H (**a**), 4-MeO (**b**), 4-O_2N (**c**), 4-Me (**d**), 3,4-$(MeO)_2$ (**e**), 4-Cl (**f**); **III**, X = CH_2 (**a**), O (**b**); **IV**, R = H (**a**, **g**), 4-MeO (**b**, **h**), 4-O_2N (**c**, **i**), 4-Me (**d**, **j**), 3,4-$(MeO)_2$ (**e**, **k**), 4-Cl (**f**).

deprotection of silyl ethers [28], Friedel–Crafts alkylation of indoles with epoxides [29], synthesis of bis(indolyl)methanes [30], Mannich synthesis of β-amino carbonyl compounds, and esterification of free fatty acids [31]. In view of the above stated in continuation of our ongoing work on multicomponent reactions [32, 33], we have developed a new protocol for the efficient synthesis of α-aminobenzyl 4-hydroxycoumarin derivatives via one-pot three-component Mannich type reaction. Herein we report significant catalytic activity of nanocrystalline TiO_2 in the one-pot three-component condensation of 4-hydroxycoumarin with an aromatic aldehyde and a secondary amine (piperidine or morpholine) in ethanol at room temperature (Scheme 1).

Table 1. Three-component condensation of 4-hydroxycoumarin with benzaldehyde and piperidine in the presence of different catalysts (30 mol %; EtOH, 25°C)

Catalyst	Time, min	Yield of **IVa**,[a] %
Boric acid	300	56
Oxalic acid	240	63
Sulfamic acid	180	72
p-Toluenesulfonic acid	240	53
$AlCl_3$	300	48
$FeCl_3$	360	45
$ZnCl_2$	270	64
ZnO	150	70
TiO_2	120	82
Nanocrystalline TiO_2	15	97

[a] Hereinafter, isolated yield of pure product.

Table 2. Three-component condensation of 4-hydroxycoumarin with benzaldehyde and piperidine in the presence of nanocrystalline titanium dioxide (30 mol %) in different solvents at 25°C

Solvent	Time, min	Yield of **IVa**, %
Toluene	180	45
Dimethyl sulfoxide	120	68
Methanol	100	85
Ethanol	15	97
Tetrahydrofuran	150	58
Methylene chloride	100	79
Acetonitrile	100	74

Initially, 4-hydroxycoumarin (1.0 mmol), benzaldehyde (1.0 mmol), and piperidine (1.0 mmol) were used as reactants for the model reaction to synthesize 4-hydroxycoumarin derivative **IVa**. For optimization of the reaction conditions, we evaluated the effect of different catalysts using ethanol as solvent at room temperature (25°C). A wide variety of catalysts including boric acid, oxalic acid, sulfamic acid, *p*-toluenesulfonic acid, $AlCl_3$, $FeCl_3$, $ZnCl_2$, ZnO, TiO_2, and nanocrystalline TiO_2 were tested in an amount of 30 mol % (Table 1). The best yield of **IVa** (97%) was obtained in the presence of nanocrystalline TiO_2 in a shorter time (15 min) than with other catalysts.

The effect of solvent was studied using nanocrystalline TiO_2 (30 mol %) at room temperature (25°C). Among a variety of solvents tested (toluene, dimethyl sulfoxide, methanol, ethanol, tetrahydrofuran, methylene chloride, acetonitrile), ethanol emerged as a solvent of choice in terms of reaction rate (15 min) and product yield (97%) (Table 2). Also, the use of ethanol as solvent did not require any special efforts for the isolation of products in good yield. The amount of nanocrystalline TiO_2 was optimized in the model reaction in ethanol at room temperature. The catalyst was added in amounts of 0, 5, 10, 15, 20, and 30 mol %. The results shown in Table 3 indicate that increase in the catalyst load from 0 to 15 mol % increases the yield of **IVa** from 12 to 97%. However, further

increase of the amount of nanocrystalline TiO_2 to 20 and 30 mol % has almost no effect on the yield (97%). Therefore, 15 mol % of the catalyst was assumed to ensure the best yield.

Our results make the process under study more attractive and interesting from the viewpoint of economy and simplicity. Under the optimized conditions, we extended the aromatic aldehyde and secondary amine series and obtained 4-hydroxycoumarin derivatives **IVa**–**IVk**. The reaction proceeded smoothly under mild conditions with a wide range of aromatic aldehydes bearing both electron-donating and electron-withdrawing substituent along with piperidine and morpholine (secondary amine). As shown in Table 4, the isolated yield of **IVa**–**IVk** ranged from 92 to 97%, and the time necessary for the reaction completion was 15–20 min. The work-up of these reactions was very clean and required only filtration, and the desired products were thus isolated with high purity. To the best of our knowledge, the synthesis of 3-(α-aminobenzyl)-4-hydroxycoumarin derivatives using nanocrystalline TiO_2 as catalyst has not been reported previously. The catalyst is not only efficient but also mild and easy to handle.

Reusability of catalyst is very important from the industrial and economic points of view. The reusability of nanocrystalline TiO_2 was studied for the model reaction in ethanol at room temperature. When the reaction was complete, the catalyst was separated, repeatedly washed with acetone to remove organic substances, and dried at room temperature. The recycled catalyst showed no appreciable loss in activity even after the fifth cycle. Listed below are the cycle number and yield of **IVa** (%): 1, 97; 2, 97; 3, 95; 4, 93; 5, 92.

Scheme 2 illustrates a probable mechanism of formation of 3-(α-aminobenzyl)-4-hydroxycoumarins from 4-hydroxycoumarin, aromatic aldehyde, and secondary amine in the presence of nanocrystalline titanium dioxide.

In conclusion, we have developed a highly efficient one-pot three-component method for the synthesis of biologically significant α-aminobenzyl 4-hydroxycoumarin derivatives **IVa**–**IVk** from 4-hydroxycoumarin, aromatic aldehyde, and secondary amine (piperidine or morpholine) in ethanol at room temperature using nanocrystalline TiO_2 as catalyst. Advantages of the proposed procedure include mild reaction conditions, simplicity, short reaction time, easy work-up, high yield, and reusability of the catalyst. The method overcomes the earlier disadvantages and therefore will be of general use and interest to synthetic chemists.

Table 3. Three-component condensation of 4-hydroxycoumarin with benzaldehyde and piperidine in the presence of different amounts of nanocrystalline TiO_2 in ethanol at 25°C

Amount of nano-TiO_2, mol %	Yield of **IVa**, %
0	12
5	45
10	86
15	97
20	97
30	97

EXPERIMENTAL

Commercial 4-hydroxycoumarin, substituted aromatic aldehydes, and secondary amines (piperidine and morpholine) were used without further purification. The melting points were determined in open capillaries and are uncorrected. The purity of the isolated compounds was monitored by ascending TLC on aluminum plates coated with silica gel-G (Merck); spots were visualized by treatment with iodine vapor. The IR spectra (400–4000 cm^{-1}) were recorded in KBr on a JASCO FTIR (PS4000) instrument. The ^1H NMR spectra were recorded on a Varian Gemini spectrometer at 400 MHz using TMS as internal standard. The mass spectra were taken on a Waters Micromass-QUATTRO-II mass spectrometer.

General procedure for the synthesis of 3-(α-aminobenzyl)-4-hydroxycoumarin derivatives IVa–IVk. A mixture of 4-hydroxycoumarin (1.0 mmol), aromatic aldehyde (1.0 mmol), piperidine

Scheme 2.

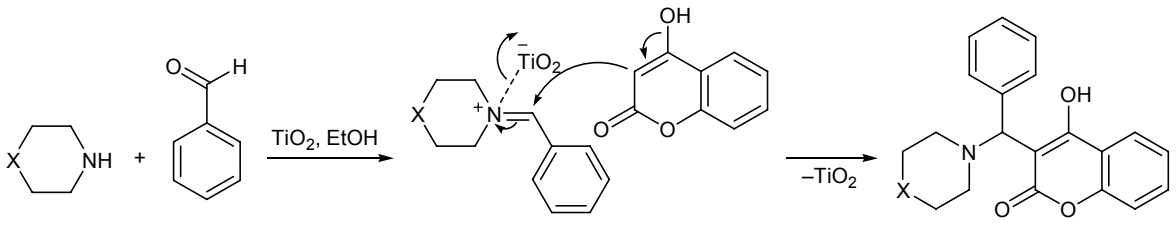


Table 4. α-Aminobenzyl 4-hydroxycoumarin derivatives **IVa–IVk**

Aldehyde no.	Amine	Product no.	Yield, %	Time, min	Melting point, °C	
					observed	reported
IIa	Piperidine	**IVa**	97	15	180–182	182 [17]
IIb	Piperidine	**IVb**	93	15	142–144	143 [17]
IIc	Piperidine	**IVc**	94	20	170–172	170 [17]
IId	Piperidine	**IVd**	96	15	186–188	190 [17]
IIe	Piperidine	**IVe**	97	15	180–182	182 [17]
IIf	Piperidine	**IVf**	95	20	190–192	188–190 [16]
IIa	Morpholine	**IVg**	96	20	164–166	168 [17]
IIb	Morpholine	**IVh**	97	15	148–150	146 [17]
IIc	Morpholine	**IVi**	95	20	174–176	176 [17]
IId	Morpholine	**IVj**	96	20	198–200	202 [17]
IIe	Morpholine	**IVk**	94	15	158–160	156 [17]

or morpholine (1.0 mmol), and nanocrystalline TiO_2 (15 mol %) in ethanol (15 mL) was stirred for 15–20 min at room temperature (25°C). When the reaction was complete (TLC), the mixture was filtered to separate the catalyst which can be used in further runs. The filtrate was concentrated, and the crude product was finally purified by recrystallization from ethanol (Table 4).

4-Hydroxy-3-[phenyl(piperidin-1-yl)methyl]-2*H*-chromen-2-one (IVa). IR spectrum, ν, cm^{-1}: 3058, 1676, 1610, 1485, 1388, 1239, 1180, 747. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.48–1.59 m (6H), 2.45 m (4H), 4.50 s (1H), 6.17 s (1H), 7.23–7.26 m (5H), 7.42–7.84 m (4H). Mass spectrum: *m*/*z* 336.15 $[M + H]^+$.

4-Hydroxy-3-[(4-methylphenyl)(piperidin-1-yl)-methyl]-2*H*-chromen-2-one (IVd). IR spectrum, ν, cm^{-1}: 3429, 2988, 1671, 1449, 1390, 1118, 749. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.52–1.58 m (6H), 2.34 s (3H), 2.46 m (4H), 4.59 s (1H), 6.72 s (1H), 7.11–7.26 m (4H), 7.45–7.88 m (4H). Mass spectrum: *m*/*z* 350.17 $[M + H]^+$.

4-Hydroxy-3-[(morpholin-4-yl)(phenyl)methyl]-2*H*-chromen-2-one (IVg). IR spectrum, ν, cm^{-1}: 3102, 1669, 1618, 1548, 1448, 1389, 1178, 1121, 755. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.67 m (4H), 3.59 m (4H), 4.54 s (1H), 6.18 s (1H), 7.23–7.33 m (5H), 7.42–7.84 m (4H). Mass spectrum: *m*/*z* 338.13 $[M + H]^+$.

4-Hydroxy-3-[(4-methylphenyl)(morpholin-4-yl)methyl]-2*H*-chromen-2-one (IVj). IR spectrum, ν, cm^{-1}: 3033, 2987, 2469, 1675, 1612, 1384, 753. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.62 m (4H), 2.42 s (3H), 3.48 m (4H), 5.05 s (1H), 6.48 s (1H), 7.23–7.39 m (4H), 7.47–7.68 m (4H). Mass spectrum: *m*/*z* 352.15 $[M + H]^+$.

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