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An efficient synthesis of α,α'-benzylidene bis(4-hydroxycoumarin) derivatives catalyzed by Tl_2O_3 nanoparticles

Mohammad Reza Nazarifar*

Young Researchers and Elites Club, Shiraz Branch, Islamic Azad University, Shiraz, Iran.

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ABSTRACT

In this work, we attempted to synthesize thallium (III) oxide nanostructures by direct thermal decomposition using thallium I phenylsuccinic acid coordination polymer $[Tl(PsucH)]_n$ as a precursor. Also, Tl_2O_3 nanoparticles have been characterized by scanning electron microscopy (SEM), X-Ray powder diffraction (XRD) and IR spectroscopy and then we report a simple and efficient method for the synthesis of α,ά-benzylidene bis(4-hydroxycoumarin) derivatives by aromatic aldehyde and 4-hydroxycoumarin by using Tl_2O_3 nanoparticles in H_2O/EtOH at room temperature. A wide spectrum of functional groups, were tolerated in the developed protocol. The target molecules were obtained in good to excellent yield applying the current method. The catalyst can be recover for the subsequent reactions and reused without loss of activity.

***Keywords**: Thallium (III) oxide nanostructures; 4-Hydroxycoumarin; α,ά-Benzylidene bis(4-hydroxycoumarin); Aromatic aldehyde.*

1. Introduction

The increasing attention during recent decades for environmental protection has led modern academic and industrial groups to develop chemical processes with maximum yield and minimum cost whilst using nontoxic reagents and solvents. One of the tools used to combine economic aspects with the environmental ones is the multicomponent reaction (MCR) strategy, this process consists of two or more synthetic steps which are carried out without the isolation of any intermediate, thus reducing time and saving money, energy and raw materials [1-5]. We performed the synthesis of α,ά-benzylidene bis(4-hydroxycoumarin) derivatives through a multicomponent reaction employing nano Tl_2O_3 as an efficient catalyst in H_2O/EtOH as a green solvent at room temperature.

Biscoumarin derivatives show a wide range of biological activities such as anti-cancer, antioxidant, antimicrobial, anticoagulant, antibacterial and are also utilized as urease inhibitors [6-11].

These compounds are synthesized by the condensation of 4-hydroxycoumarin and aromatic aldehydes using catalysts such as molecular iodine [12], sodium dodecyl sulfate (SDS) [13], tetrabutylammonium bromide (TBAB) [14], 3-methyl-1-(4-sulfonic acid) butylimidazolium hydrogen sulfate ($[MIM(CH_2)_4SO_3H][HSO_4]$) [15], tetrabutylammonium hexatungstate ($[TBA]_2[W_6O_{19}]$) [16], sulfated titania (TiO_2/SO_4^{2-}) [17], ruthenium(III) chloride hydrate ($RuCl_3{\cdot}nH_2O$) [18], *n*-dodecylbenzene sulfonic acid (DBSA) [19], and silica chloride nanoparticles (nano SiO_2Cl) [20]. However, these methods show varying degrees of success as well as limitations such as prolonged reaction times, unsatisfactory yield, use of toxic solvents and catalysts, requirement of large amounts of expensive reagents and catalysts, laborious work-up procedures and harsh reaction conditions. Thus, the development of an alternate milder and clean procedure is highly demanding for the synthesis of α,ά-benzylidene bis(4-hydroxycoumarin) derivatives, which surpasses those limitations. In view of our ongoing efforts to explore newer reactions for synthesis of heterocyclic compounds [21-23], we examined Tl_2O_3 nanoparticles as reusable heterogeneous catalyst for synthesis of α,ά-benzylidene bis(4-hydroxycoumarin) derivatives.

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*Corresponding author email: mohammadreza.nazarifar@gmail.com

Tel.: +98 917 703 3810, Fax: +98 71 3633 4523

2. Experimental

2.1. General

All reagents were purchased from Merck, Fluka and Aldrich with high-grade quality, and used without any purification. The reactions were monitored by TLC. Visualization of the developed chromatogram was performed by UV light (254 nm). All yields refer to isolated products after purification. Products were characterized by comparison with authentic samples and by spectroscopy data (IR, ^{1}HNMR spectra). The NMR spectra were recorded on a Bruker Avance 400 MHz instruments. The spectra were measured in DMSO-d_6 relative to TMS (0.00 ppm). IR spectra were recorded from KBr disk on the FT–IR Bruker Tensor 27. Melting points were measured by using the capillary tube method with IA 9000 series thermal analyzer. X-Ray powder diffraction (XRD) measurements were performed using an X'pert diffractometer of Phillips Company with monochromatized CuKa radiation. The nano-oxide with gold coating was characterized with a scanning electron microscope (SEM) (Philips XL 30).

2.2. Preparation of Tl_2O_3 nanostructure

The compound [Tl(PsucH)]$_n$ was prepared as follows: 1 mmol of phenylsuccinic acid was dissolved in 10 ml methanol and was mixed and stirred with a solution of 1 mmol KOH in 5 ml H_2O. Then a solution of 1 mmol $TlNO_3$ in 5 ml H_2O was added to the mixture and was refluxed for 3 h. After filtering, it was allowed to evaporate for several days and then suitable white crystals were obtained. The [Tl(PsucH)]$_n$ was calcined at 600 °C under air atmosphere. The whole organic component was combusted and the thallium (III) oxide nanostructure was produced [24].

2.3. Preparation of α,ά-benzylidene bis (4-hydroxycoumarin) derivatives

A mixture of the aromatic aldehyde (1 mmol), 4-hydroxycoumarin (2 mmol) and Tl_2O_3 nanoparticles (0.005 g), in H_2O/EtOH (5 mL) was stirred at room temperature for the appropriate time. The progress of the reaction was followed by TLC. After the completion of the reaction, the reaction mixture was filtered off and washed with *n*-hexane (2 × 5 mL), to obtain pure products. The solid was dissolved in acetone and the catalyst was separated by filtration. The recycled catalyst was washed with acetone, dried and reused. Products were characterized through m.p., IR, and ^{1}HNMR.

Selected spectral data

3,3′-(3-Nitrobenzylidene)-bis-(4-hydroxycoumarin) ***(3h)****:*

White crystalline solid. m.p.= 234-236ºC, IR (KBr): $\bar{\nu}$ = 3424, 2925, 1655, 1616, 1564, 1494, 1450, 1347, 762 cm^{-1}. ^{1}HNMR (400 MHz, DMSO-d$_6$): δ= 6.39 (s, 1H, CH), 7.28-8.04 (m, 12H, ArH), 8.04-9.52 (m, 2H, OH) ppm.

3,3′-(4-Cholorobenzylidene)-bis-(4-hydroxycoumarin) ***(3f)****:*

Yellow crystalline solid. m.p.= 256-258ºC, IR (KBr): $\bar{\nu}$ = 3420, 2923, 1668, 1606, 1563, 1490, 1451, 1351, 765 cm^{-1}. ^{1}HNMR (400 MHz, DMSO-d$_6$): δ= 6.63 (s, 1H, CH), 7.16-7.90 (m, 12H, ArH), 7.90-9.00 (m, 2H, OH) ppm.

3,3′-(4-Methoxybenzylidene)-bis-(4-hydroxycoumarin) ***(3m)****:*

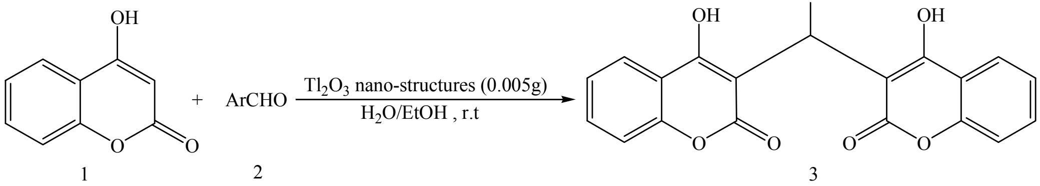
White crystalline solid. m.p.= 246-248ºC, IR (KBr): $\bar{\nu}$ = 3443, 2926, 1668, 1606, 1563, 1510, 1452, 1352, 767 cm^{-1}. ^{1}HNMR (400 MHz, DMSO-d$_6$): δ 3.71 (s, 3H, CH_3O), 6.31 (s, 1H, CH), 6.80-7.93 (m, 12H, ArH), 8.16-8.78 (m, 2H, OH) ppm.

3,3′-(4-Choloro-3-nitrobenzylidene)-bis-(4-hydroxy-coumarin) ***(3k)****:*

Light yellow crystalline solid. m.p.= 269-270ºC, IR (KBr): $\bar{\nu}$ = 3423, 2920, 1665, 1613, 1558, 1536, 1450, 1348, 765 cm^{-1}. ^{1}HNMR (400 MHz, DMSO-d$_6$): δ= 6.28 (s, 1H, CH), 7.26-7.85 (m, 11H, ArH), 8.15-8.56 (m, 2H, OH) ppm.

3. Results and Discussion

We herein present efficient and eco-friendly procedure for the synthesis of α,ά-benzylidene bis (4-hydroxycoumarin) derivatives **3** by condensation of 4-hydroxycoumarin **1** and aromatic aldehyde **2** catalyzed by Tl_2O_3 nanostructures in water–ethanol solvent system at room temperature (Scheme 1).



Scheme 1. The synthesis of α,ά-benzylidene bis(4-hydroxycoumarin) derivatives from 4-hydroxycoumarin, and aromatic aldehydes using Tl_2O_3 nanostructures as a catalyst.

For this study, a reaction between 4-hydroxycoumarin (2 mmol) and 3-nitrobenzaldehyde (1 mmol) were examined as the model reaction. Initial studies showed that better results could be obtained in the presence of (0.005 g) Tl_2O_3 nanostructures in aqueous ethanol (1:1, H_2O–EtOH) at room temperature.

To optimize the amount of catalyst, the above reaction was performed with different amount of Tl_2O_3 nanostructures such as 0.001, 0.003, 0.004, 0.005, 0.006, 0.007 and 0.009 g. The results are summarized in (Table 1) which shows that the reaction catalyzed by about 0.005 g Tl_2O_3 nanostructures results in the highest yield (Table 1, entry 4). In the presence of less than this amount, the yield decreased. When the amount of Tl_2O_3 nanostructures was increased over 0.005 g; neither the yield nor the reaction time was improved.

To study the effect of temperature on this synthesis, we also performed four experiments in aqueous ethanol at room temperature, 50, 70 °C and under reflux condition (Table 2). It was observed that the yield of the product is maximum at room temperature (Table 2, entry 1).

During the optimization of the reaction condition, various solvents were also screened to test their efficiency and the results are summarized in (Table 3).

Table 1. Optimization of the catalyzed model reaction for synthesis of 3,3'-(3-Nitrobenzylidene)-bis-(4-hydroxycoumarin)[a].

Entry	Catalyst	Amount of catalyst (g)	Time (s)	Yield (%)[b]
1	Tl_2O_3 nanostructures	0.001	300	50
2	Tl_2O_3 nanostructures	0.003	180	85
3	Tl_2O_3 nanostructures	0.004	60	95
4	Tl_2O_3 nanostructures	0.005	40s	99
5	Tl_2O_3 nanostructures	0.006	40s	99
6	Tl_2O_3 nanostructures	0.007	35s	95
7	Tl_2O_3 nanostructures	0.009	35s	88

[a] All reactions were carried out in aqueous ethanol at room temperature.

[b] Isolated yields.

Table 2. Optimization of temperature for synthesis of 3,3'-(3-Nitrobenzylidene)-bis-(4-hydroxycoumarin) using Tl_2O_3 nanostructures (0.005g) as catalyst in aqueous ethanol.

Entry	Catalyst	Temperature ˚C	Time (s)	Yields (%)[a]
1	Tl_2O_3 nanostructures	Room temperature	40	99
2	Tl_2O_3 nanostructures	Reflux	30	90
3	Tl_2O_3 nanostructures	70	30	90
4	Tl_2O_3 nanostructures	50	40	95

[a] Isolated yield of the pure compound.

Table 3. Effect of solvents in reaction of 3-nitrobenzaldehyde and 4-hydroxycoumarin catalyzed by Tl_2O_3 nanostructures[a].

Entry	Catalyst	Solvent	Time (s)	Yields (%)[b]
1	Tl_2O_3 nanostructures	EtOH	120	85
2	Tl_2O_3 nanostructures	H_2O	90	94
3	Tl_2O_3 nanostructures	H_2O–EtOH (1:2)	180	89
4	Tl_2O_3 nanostructures	H_2O–EtOH (2:1)	65	95
5	Tl_2O_3 nanostructures	H_2O–EtOH (1:1)	40	99
6	Tl_2O_3 nanostructures	Solvent free	1 h	Trace

[a] All reactions were catalyzed by Tl_2O_3 nanostructures at room temperature.

[a] Isolated yields.

The highest reaction activity was achieved in the system using aqueous ethanol (1:1, H_2O–EtOH) as a solvent in comparison to other solvents under similar reaction conditions (Table 3, entry 5).

With these encouraging results in hand, the generality of this reaction was examined using various aromatic aldehydes containing electron-donating as well as electron-withdrawing groups. In all cases, the reactions gave the corresponding products in good yields and short reaction times (Table 4). Substituent on the aromatic ring had no obvious effect on yield or reaction time under the above optimal conditions.

In order to assess the efficiency of this methodology, the obtained result from the reaction of 3-nitrobenzaldehyde with 4-hydroxycoumarin by this method has been compared with those of the previously reported methods. As demonstrated in Table 5, the use of Tl_2O_3 nanostructures leads to an improved protocol in terms of reaction time, yield of the product and amount of the catalyst when compared with other catalyst.

In order to investigate the possibility of recycling Tl_2O_3 nanostructures, a recycling experiment was conducted using the above mentioned model reaction. After the separation of the products, the Tl_2O_3 nanostructures containing filtrate was reused in the next run without further purification. The catalyst could be reused at least five times without the apparent loss of catalytic activity (yield: 99%, 99%, 98%, 97%, 97%) (Table 6).

Table 4. Tl_2O_3 nanostructures catalyzed synthesis of α,ά-benzylidene bis(4-hydroxycoumarin) derivatives[a].

Entry	Ar	Product	Time (s)	Yield (%)[b]	m.p. (°C) Found	m.p. (°C) Reported	Ref.
1	C_6H_5	**3a**	60	90	230-232	229-231	[15]
2	$3\text{-}ClC_6H_4$	**3b**	90	97	221-223	221-223	[15]
3	$4\text{-}FC_6H_4$	**3c**	60	98	211-212	212-214	[20]
4	$4\text{-}BrC_6H_4$	**3d**	80	98	264-266	266-268	[20]
5	$4\text{-}CNC_6H_4$	**3e**	50	96	240-242	240-242	[18]
6	$4\text{-}ClC_6H_4$	**3f**	50	97	256-258	261-263	[15]
7	$2\text{-}O_2NC_6H_4$	**3g**	70	96	195-197	198-200	[15]
8	$3\text{-}O_2NC_6H_4$	**3h**	40	99	234-236	235	[25]
9	$4\text{-}O_2NC_6H_4$	**3i**	50	98	238-239	232-234	[27]
10	$2\text{-}ClC_6H_4$	**3j**	50	95	201-203	201-203	[15]
11	$4\text{-}Cl,3O_2NC_6H_3$	**3k**	50	96	269-270	269-270	[21]
12	$4\text{-}CH_3C_6H_4$	**3l**	120	92	266-268	271-273	[16]
13	$4\text{-}CH_3OC_6H_4$	**3m**	90	94	246-248	251-253	[16]

[a] Reaction conditions: aromatic aldehyde (1 mmol), 4-hydroxycoumarin (2 mmol), Tl_2O_3 nanostructures (0.005 g), aqueous ethanol (5 mL), at room temperature.

[b] Yields refer to isolated products.

Table 5. Comparison of Tl_2O_3 nanostructures with other catalysts for the synthesis of α,ά-benzylidene bis(4-hydroxycoumarin) derivatives.

Entry	Catalyst	Conditions	Time	Yield (%)	Ref.
1	SDS, 20 mol%	H_2O, 60°C	2.15 (h)	95	[13]
2	Nano-SiO_2Cl, 75 mg	CH_2Cl_2, 40°C	3.5 (h)	90	[20]
3	$NaHSO_4\cdot SiO_2$ or Indion 190 resin, 150 mg	Toluene, 100°C	30 (min)	90	[25]
4	$[P_4VPy\text{-}BuSO_3H]Cl\text{-}X(AlCl_3)$, 0.07 mmol	Toluene, 90°C	30 (min)	96	[26]
5	SBPPSP, 0.06 g	EtOH/H_2O, reflux	15 (min)	94	[27]
6	$[TBA]_2[W_6O_{19}]$, 0.08 mmol	EtOH, reflux	7 (min)	85	[16]
7	PTTH, 0.03 mol%	H_2O, 80°C	8 (min)	95	[28]
8	$[P(4\text{-}VPH)ClO_4]$, 30 mg	H_2O, 80°C	15 (min)	87	[29]
9	Tl_2O_3 nanostructures, 0.005 g	EtOH/H_2O, RT	40 (s)	99	This work

Table 6. Recycling and reuse of the catalyst[a].

Entry	Number of recycle	Yield (%)[b]
1	First	99
2	1	99
3	2	99
4	3	98
5	4	97
6	5	97
7	6	93

[a]Reaction conditions: 3-nitrobenzaldehyde (5 mmol) and 4-hydroxycoumarin (10 mmol), Tl_2O_3 nanostructures (0.025 g), aqueous ethanol (25 mL), at room temperature.

[b]Isolated yields.

4. Conclusions

In conclusion this paper describes a highly efficient and environmentally green process for the synthesis of α,ά-benzylidene bis(4-hydroxycoumarin) derivatives by condensation of 4-hydroxycoumarin and aromatic aldehyde catalyzed in the presence of catalytic amount of Tl_2O_3 nanoparticles at room temperature in aqueous media. Simple reaction procedure, reusable catalyst, high yields of the products, short reaction time, easy product separation, generality and cost efficiency make our methodology a valid contribution to the existing processes in the field of α,ά-benzylidene bis(4-hydroxycoumarin) derivatives synthesis.

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