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Nano titania-supported sulfonic acid catalyzed synthesis of α,α′-bis(substituted-benzylidene)cycloalkanones and of their xanthene derivatives under solvent-free conditions

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ABSTRACT

An efficient, rapid and green synthesis of α,α′-bis(substituted-benzylidene)cycloalkanones and their xanthene derivatives is reported under solvent-free conditions using nano titania-supported sulfonic acid (n-TSA) as a reusable catalyst. This method offers many advantages, such as environmental friendliness reaction conditions, simplicity, short reaction times, easy work-up, reusability of catalyst, and high yields of products. Eight new compounds are reported too.

1. Introduction

Nowadays, for considering green chemistry aspects, chemists are concerned with minimizing the environmental pollution caused by traditional solvents and try to establish methodologies based on solvent-free conditions. The drive for the development of dry media reactions are ease of purification, high reaction rates, environmentally friendly conditions, less energy requirement and considering economic and environmental demands [1].

The employment of a reusable solid supported heterogeneous catalyst for the efficient synthesis of heterocyclic compounds remains a challenge to chemists. Reactions with reagents that are immobilized on inorganic solid supports show several advantages over the conventional reactions in solution. Recently, the use of heterogeneous catalysts under solvent-free conditions has emerged as an eco-friendly alternative of great importance within organic synthesis [2–4].

As we have recently reported [5], nano titania-supported sulfonic acid (n-TSA) is a heterogeneous nano catalyst, which can be efficiently used for the promotion of the reactions that need the use of an acidic catalyst, because it acts as a Lewis and a Brønsted acid simultaneously. Simple work-up procedures, improved product yields, greater ease of purification, shorter reaction times, milder reaction conditions and recyclability of the catalyst are the main superiorities of n-TSA.

Xanthene—dibenzopyran—is a polyaromatic cyclic ether in which two benzene rings are fused to tetrahydropyran. Xanthene derivatives are very important heterocyclic compounds due to their broad spectrum of pharmacological and biological properties such as antibacterial, antidepressant, antimalarial, anti-inflammatory and antiviral activities [6]. Furthermore, they can be used

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as dyes, pH-sensitive fluorescent materials, in laser technologies and in photodynamic therapy [7–10]. Owing to their wide range of applications, their synthesis has gained a lot of attention in recent years.

The most common methodology for the synthesis of xanthene derivatives is the condensation of cyclohexan-1, 3-diones or β-naphthol with aliphatic and aromatic aldehydes in the presence of different catalysts and solvents [11–14], but there are only two reports on cyclocondensation reaction between α,α′-bis(substituted-benzylidene) cycloalkanones and 1,3-diketones in the literature that has been published in 2013 [15,16]. However, these few studies suffer from significant limitations like using toxic solvents, tedious work-up, long reaction times, poor yields, harsh conditions and difficult separation methods. Hence, a simple, rapid, efficient and green procedure is still strongly desired for this type of reaction.

In this paper, we describe a facile and efficient method for the synthesis of (*E*)-5-benzylidene-3,3-dimethyl-9-phenyl-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-1-one derivatives by using α,β-unsaturated cycloalkanones as starting materials (Scheme 1). To the best of our knowledge there are no literature reports on solvent-free conditions for this type of reaction.

2. Results and discussion

As part of our continuing efforts for the development of efficient green methodologies [17–19] and n-TSA-catalyzed organic transformations [5], herein, we report a new and simple synthesis of (*E*)-5-benzylidene-3,3-dimethyl-9-phenyl-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-1-one derivatives (**5**). As we have mentioned earlier, there are only two reports about their synthesis meaning that probably the reaction must be difficult. On the other hand, we have reported n-TSA as a very efficient new nano catalyst in our last work for a vast variety of organic syntheses. So we have decided to investigate it for this type of condensation.

As α,α′-Bis(substituted-benzylidene)cycloalkanones (**3**) are not commercially sourced, so, first of all we have reported a simple and rapid method for their synthesis. α,α′-Bis(substituted-benzylidene)cycloalkanones (**3**) are prepared by cross-Aldol condensation of aromatic aldehydes (**2**) with cyclic ketones (**1**). We have commenced our experiments by examining the model reaction of cyclohexanone and benzaldehyde in the presence of n-TSA in various amounts of catalyst, temperatures and solvents. The results are summarized in Table 1.

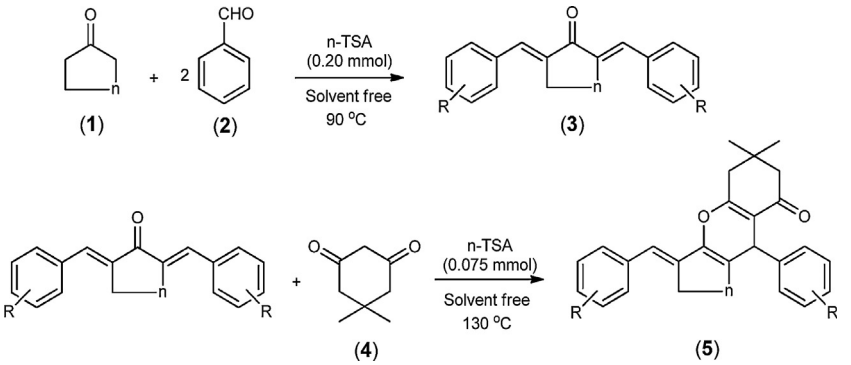
Table 1
Optimum conditions for the synthesis of α,α'-bis(Substituted-benzylidene)cycloalkanones[a].

Entry	Catalyst (mmol)	Solvent	Temperature (°C)	Yield[b] (%)
1	0	–	90	4
2	n-TSA (0.03)	–	90	42
3	n-TSA (0.05)	–	90	54
4	n-TSA (0.10)	–	90	78
5	n-TSA (0.20)	–	90	93
6	n-TSA (0.30)	–	90	92
7	n-TSA (0.20)	–	Room temperature	Trace
8	n-TSA (0.20)	–	50	63
9	n-TSA (0.20)	–	70	82
10	n-TSA (0.20)	–	110	90
11	n-TSA (0.20)	EtOH	90	41
12	n-TSA (0.20)	H_2O	90	17
13	n-TSA (0.20)	PEG	90	36
14	n-TSA (0.20)	CH_3CN	90	12
15	Nano-TiO_2 (0.20)	–	90	0
16	Bulk-TiO_2 (0.20)	–	90	0
17	Bulk-TiO_2-SO_3H (0.20)	–	90	75

[a] Reaction conditions: cyclohexanone (1 mmol), benzaldehyde (2 mmol), reaction time: 20 min.
[b] Isolated yields.

As Table 1 shows, the trial reaction gives the best yield under solvent-free conditions and proceeds smoothly at 90 °C (oil bath) with a catalytic amount of n-TSA to afford the desired product, α,α′-bisbenzylidenecyclohexanone (**3**), in 20 min (Table 1, entry 5). With other selected temperatures and solvents (Table 1, entries 7–14), the reaction gave rather lower yields within comparable reaction times. It is notable that no product formed within a reasonable time in the absence of catalyst (Table 1, entry 1) and other titanium dioxide base such as unmodified nano TiO_2 and unmodified bulk TiO_2 (Table 1, entries 15, 16). On the other hand, bulk-modified TiO_2 provides lower yield in comparison to n-TSA as we expected (Table 1, entry 17) [5].

Using the optimized reaction conditions (Table 1, entry 5), we have explored the generality of this method with different aldehydes to prepare a series of benzylidenes (Table 2).



(**1**) (**2**) (**3**) (**4**) (**5**)

Scheme 1. Synthesis of xanthene derivatives.