

A Rapid and Green Method for Solvent-Free Synthesis of 1,8-Dioxodecahydroacridines Using Tetrabutylammonium Hexatungstate as a Reusable Heterogeneous Catalyst

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Abstract: Tetrabutylammonium hexatungstate, $[TBA]_2[W_6O_{19}]$, has been used as an efficient, inexpensive, and recyclable green catalyst for the one-pot three-component synthesis of 1,8-dioxodecahydroacridines by the reaction of dimedone with aromatic or aliphatic aldehydes in the presence of a nitrogen source (ammonium acetate or aromatic amines) under neat conditions. There are several advantages to the current process over the standard procedures available in the literature, including shorter reaction times (7–14 min), higher yields, facile work-up, and minimal environmental impact. Furthermore, the catalyst can be conveniently recovered and reused.

Key words: 1,8-dioxodecahydroacridine; solvent-free condition; tetrabutylammonium hexatungstate

CLC number: O643 **Document code:** A

Received 12 July 2012. Accepted 21 August 2012.

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This work was supported by Islamic Azad University, Mashhad Branch.

English edition available online at Elsevier ScienceDirect (<http://www.sciencedirect.com/science/journal/18722067>).

1,4-Dihydropyridines (1,4-DHPs) have been the subject of considerable attention because of their wide range of pharmaceutical and biological properties, including antitubercular, antibacterial, antihypertensive, anticancer, and anti-inflammatory effects [1–5]. 1,4-DHPs are also commercially used as calcium channel blockers for the treatment of cardiovascular diseases, including hypertension [6,7]. Furthermore, dimeric 4-aryl-1,4-DHPs have been shown to act as HIV-1 protease inhibitors [8,9]. 1,8-Dioxodecahydroacridines and their derivatives are polyfunctionalized 1,4-DHP derivatives and have received less attention than other 1,4-DHP derivatives. The most straightforward synthesis of these compounds involves the three-component cyclocondensation of 1,3-cyclohexanedione or 5,5-dimethyl-1,3-cyclohexanedione (dimedone) with aromatic aldehydes and ammonium acetate or amines in the presence of a catalyst such as $[Hmim]TFA$ [10], $B(C_6F_5)_3$ [11], a Brønsted acidic imidazolium salt [12], $Zn(OAc)_2$ [13], proline [14], Amberlyst-15 [15], $CeCl_3 \cdot 7H_2O$ [16], silica-bonded S-sulfonic acid (SBSSA) [17], and silica-bonded *N*-propyl sulfamic acid (SBNPSA) [18]. These compounds have also been synthesized using the classical Hantzsch procedure [19] and by the reaction of aldoximes with dimedone under microwave irradiation and conventional heating conditions [20]. Although each of these individual methods has their own merits, with the exception of the microwave irradiation procedure they all require relatively long reaction times (1–7 h). Furthermore,

some of these procedures suffer other disadvantages, including the requirement for an expensive catalyst or the use of an excess of catalyst. To avoid these limitations and to improve the reaction conditions available for the synthesis of 1,8-dioxodecahydroacridines, the discovery of new methodologies using new heterogeneous and reusable catalysts is still in demand.

The development of heterogeneous catalysts and how they affect specific transformations in chemical synthesis has become a major area of research. The potential advantages of these materials over homogeneous systems, in terms of their simplified recovery and reusability, could potentially allow for the development of environmentally benign chemical procedures in both academic and industrial settings. Catalysts of this type have the potential to make the processes in which they are applied cleaner, safer, higher-yielding, and relatively inexpensive [21–25]. During the course of our recent studies directed towards the development of practical and environmentally friendly procedures for the synthesis of organic compounds using reusable catalysts [26–34], we investigated the application of the isopolytungstate, tetrabutylammonium hexatungstate $[TBA]_2[W_6O_{19}]$, as a catalyst for a series of organic transformations. This new reusable heterogeneous catalyst performed well and showed a high level of catalytic activity in the Knoevenagel condensation [35] and Biginelli [36] reactions, as well as in the synthesis of bis-coumarins [37]. This fact prompted us to investigate the catalytic activity of this material in the syn-

thesis of 1,8-dioxodecahydroacridines.

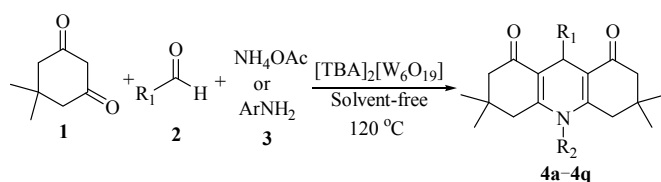
1 Experimental

1.1 Synthesis of tetrabutylammonium hexatungstate [TBA]₂[W₆O₁₉]

A mixture of sodium tungstate dihydrate, Na₂WO₄·2H₂O (99%, 33 g, 0.1 mol), acetic anhydride (40 ml), and *N,N*-dimethylformamide (DMF, 30 ml) was heated at 100 °C for 3 h to obtain a white cream. A solution of acetic anhydride (20 ml) and 12 mol/L HCl (18 ml) in DMF (50 ml) was then added in a drop-wise manner over a period of time with stirring, and the resulting mixture was filtered to remove the undissolved white solids. A solution of tetrabutylammonium bromide (15.1 g, 0.047 mol) in methanol (50 ml) was then added to the filtrate with rapid stirring to give a white precipitate, and the resulting suspension was stirred for 5 min and the product subsequently collected by filtration. Recrystallization from a minimum amount of hot dimethyl sulfoxide (DMSO) gave the product as colorless diamond-shaped crystals [38].

1.2 General procedure for the synthesis of 1,8-dioxodecahydroacridines catalyzed by [TBA]₂[W₆O₁₉]

A mixture of dimedone **1** (2 mmol), aromatic or aliphatic aldehyde **2** (1 mmol), ammonium acetate or aromatic amine **3** (1 mmol), and [TBA]₂[W₆O₁₉] (0.04 g, 2 mol% based on the aldehyde) was heated in an oil bath at 120 °C for 7–14 min. The reaction process was monitored by TLC. Upon completion of the transformation, the reaction mixture was cooled to room temperature and hot chloroform was added. This resulted in the precipitation of the catalyst, which was collected by filtration. The filtrate was then collected and distilled to dryness to give the crude product, which was recrystallized from a mixture of EtOH and H₂O to give compounds **4a–4q** in high yields (Scheme 1). Melting points of the compounds were recorded on a Stuart SMP3 melting point apparatus. The IR spectra were obtained using a Tensor 27 Bruker spectrophotometer from KBr disks. The ¹H NMR (400 and 500 MHz) spectra were recorded with Bruker 400 and 500 spectrometers.



Scheme 1. Synthesis of 1,8-dioxodecahydroacridines catalyzed by [TBA]₂[W₆O₁₉].

2 Results and discussion

The [TBA]₂[W₆O₁₉] catalyst was prepared according to the method reported by Fournier [38]. Our efforts to develop an efficient and environmentally benign methodology for the synthesis of 1,8-dioxodecahydroacridines focused initially on the three-component cyclocondensation of dimedone with 4-chlorobenzaldehyde and ammonium acetate as a model reaction. Thus, a catalytic amount of [TBA]₂[W₆O₁₉] was added to a mixture of dimedone, 4-chlorobenzaldehyde, and ammonium acetate in different solvents and under solvent-free conditions (Table 1). Pleasingly, we discovered that the reaction was efficiently catalyzed by [TBA]₂[W₆O₁₉] under solvent-free conditions at an elevated temperature, providing a high yield of product **4d**. The reaction conditions were then optimized by conducting the reac-

Table 1 Synthesis of compound **4d** in the presence of the [TBA]₂[W₆O₁₉] catalyst under different reaction conditions

Entry	Catalyst (g)	Solvent	Temperature (°C)	Time (min)	Yield ^a (%)
1	—	—	120	60	35
2	0.015	—	80	25	54
3	0.015	—	100	20	60
4	0.015	—	120	15	75
5	0.015	—	130	15	75
6	0.030	—	80	20	65
7	0.030	—	100	15	70
8	0.030	—	120	10	85
9	0.030	—	130	10	84
10	0.040	—	80	15	68
11	0.040	—	100	12	80
12	0.040	—	120	7	93
13	0.040	—	130	7	93
14	0.050	—	80	15	65
15	0.050	—	100	12	74
16	0.050	—	120	10	85
17	0.050	—	130	10	85
18	0.040	H ₂ O	reflux	120	50
19	0.040	EtOH	reflux	120	87
20	0.040	MeOH	reflux	120	80
21	0.040	CHCl ₃	reflux	120	65
22	0.040	CH ₃ CN	reflux	120	70

Reaction conditions: dimedone 2 mmol, 4-chlorobenzaldehyde 1 mmol, ammonium acetate 1 mmol. ^aIsolated yields.

4a: R₁ = C₆H₅, R₂ = H

4b: R₁ = 4-BrC₆H₄, R₂ = H

4c: R₁ = 2-ClC₆H₄, R₂ = H

4d: R₁ = 4-ClC₆H₄, R₂ = H

4e: R₁ = 4-MeC₆H₄, R₂ = H

4f: R₁ = 3,4-(MeO)₂C₆H₃, R₂ = H

4g: R₁ = 4-Me₂NC₆H₄, R₂ = H

4h: R₁ = 3-O₂NC₆H₄, R₂ = H

4i: R₁ = 4-O₂NC₆H₄, R₂ = H

4j: R₁ = C₆H₅, R₂ = C₆H₅

4k: R₁ = 4-ClC₆H₄, R₂ = 4-MeC₆H₄

4l: R₁ = 4-MeC₆H₄, R₂ = 4-MeC₆H₄

4m: R₁ = 3-O₂NC₆H₄, R₂ = 4-MeC₆H₄

4n: R₁ = 4-ClC₆H₄, R₂ = 4-MeOC₆H₄

4o: R₁ = 4-MeC₆H₄, R₂ = 4-MeOC₆H₄

4p: R₁ = Et, R₂ = H

4q: R₁ = *n*-Pr, R₂ = H

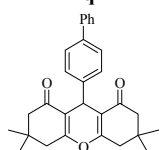
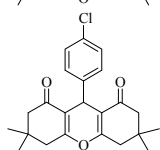
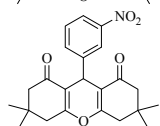
tion at different temperatures and employing different loadings of the catalyst. The results are summarized in Table 1. A low yield of the product was only obtained in the absence of the catalyst at 120 °C following a 60 min reaction time (Table 1, entry 1), indicating that the catalyst was necessary to the reaction. The best result was obtained when the reaction was conducted at 120 °C in the presence of 0.040 g (2 mol%) of the $[TBA]_2[W_6O_{19}]$ catalyst (Table 1, entry 12).

To evaluate the scope of this catalytic transformation, the optimized reaction conditions were subsequently applied to the reaction of dimedone **1** with a variety of different aromatic and aliphatic aldehydes **2** in the presence of one of two nitrogen sources, including ammonium acetate or an aromatic amine **3** (Table 2). A wide range of aromatic and aliphatic aldehydes bearing either electron-donating or elec-

tron-withdrawing substituents reacted successfully with dimedone and ammonium acetate or aromatic amines to give the corresponding 1,8-dioxodecahydroacridines products in high yields over short reaction times. When an aromatic amine substituted with an electron-withdrawing group was used, however, 1,8-dioxooctahydroxanthenes [39] were formed as the products (Table 2, entries 18–20). According to Shen's report [12], aromatic amines substituted with an electron-withdrawing group are not nucleophilic enough to produce 1,8-dioxodecahydroacridines.

To further evaluate the overall utility of the current methodology, we compared our results with those of the other methods reported for the synthesis of 1,8-dioxodecahydroacridines. This comparison is shown in Table 3. It is clear from the data that our method reduces the

Table 2 Synthesis of the 1,8-dioxodecahydroacridines **4a–4q** using the $[TBA]_2[W_6O_{19}]$ catalyst

Entry	Product ^a	Time (min)	Yield ^b (%)	Melting point (°C)	
				Found	Reported
1	4a	7	90	288–290	258–260 [16]
2	4b	7	90	314–316	312–315 [16]
3	4c	10	88	225–227	221–223 [20]
4	4d	7	93	298–299	298–300 [16]
5	4e	8	90	322–324	318–320 [16]
6	4f	14	84	260–263	258–260 [20]
7	4g	14	84	265–267	264–266 [20]
8	4h	10	87	302–304	294–296 [16]
9	4i	10	94	284–286	288–289 [16]
10	4j	12	85	257–259	254–256 [15]
11	4k	10	89	275–278	269–271 [12]
12	4l	14	85	297–300	292–294 [12]
13	4m	13	88	280–282	283–284 [12]
14	4n	10	89	250–253	251–252 [12]
15	4o	10	87	236–238	238–241 [12]
16	4p	13	86	258–260	282–283 [20]
17	4q	13	85	257–258	286–287 [20]
18		10	88	204–207	204–205 [39]
19		10	85	228–230	230–233 [39]
20		10	87	172–174	170–173 [39]

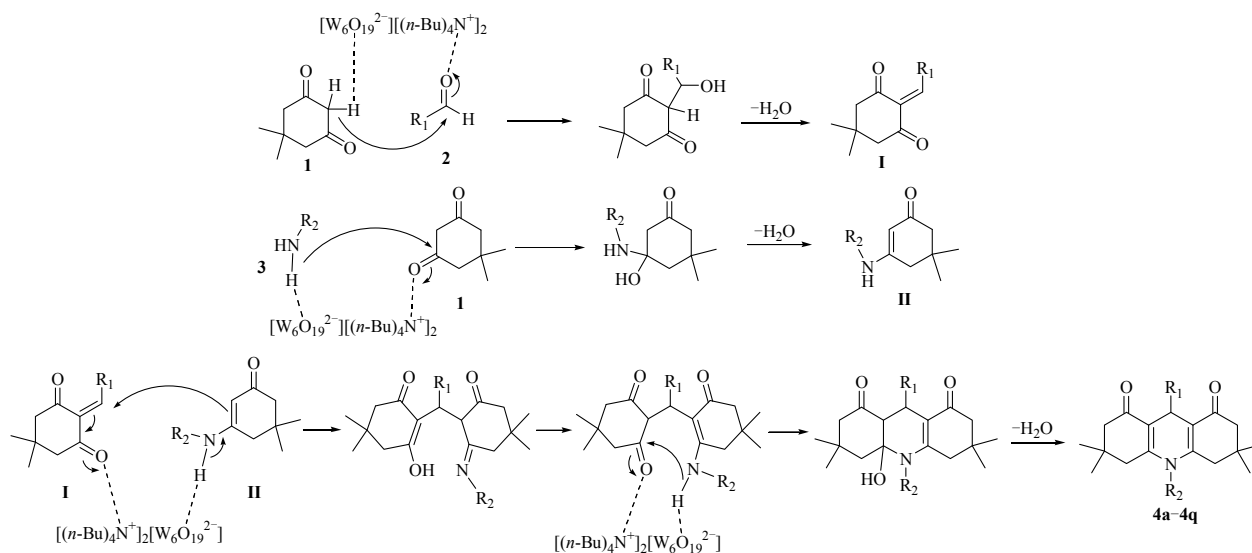
Reaction conditions: dimedone 2 mmol, aldehyde 1 mmol, ammonium acetate or aromatic amine 1 mmol, $[TBA]_2[W_6O_{19}]$ 0.04 g (2 mol%), 120 °C, solvent-free.

^aAll the products were characterized according to their IR spectral data and a comparison of their melting points with those of authentic samples. The structures of some products were also confirmed by ¹H NMR analysis.

^bIsolated yields.

Table 3 Comparison of the efficiencies of different catalysts for the synthesis of 1,8-dioxodecahydroacridines

Catalyst	Solvent	Temperature (°C)	Time (min)	Yield (%)	Ref.
[Hmim]TFA	—	80	240–420	78–89	[10]
[B(C ₆ F ₅) ₃]	—	r.t.	90–180	75–90	[11]
Bronsted acidic imidazolium salts	H ₂ O	reflux	240	79–91	[12]
Zn(OAc) ₂	H ₂ O	reflux	120–180	84–94	[13]
Proline	H ₂ O/EtOH	65	300–360	73–88	[14]
Amberlyst-15	CH ₃ CN	reflux	270–390	81–95	[15]
CeCl ₃ ·7H ₂ O	[bmim][BF ₄]	100	180	82–94	[16]
SBSSA	EtOH	reflux	60–270	84–96	[17]
SBNPSA	EtOH	reflux	120–300	86–93	[18]
[TBA] ₂ [W ₆ O ₁₉]	—	120	7–14	84–94	this work

**Scheme 2.** Plausible mechanism for the formation of 1,8-dioxodecahydroacridines in the presence of the [TBA]₂[W₆O₁₉] catalyst.

reaction times significantly and provides higher yields of the products.

In the interests of green chemistry and developing an environmentally benign process, the reusability of the catalyst was explored using the model reaction system under the optimized conditions. The catalyst itself could be readily recovered from the reaction mixture according to the procedure outlined in the experimental section. The separated catalyst was washed with cold ethanol and subsequently dried at 60 °C under vacuum for 1 h before being reused in a similar reaction. The catalyst could be used at least three times without significant reduction in its activity (93% yield for first use, 93% for second use, and 92% for third use).

A plausible mechanism for the formation of the 1,8-dioxodecahydroacridine products using [TBA]₂[W₆O₁₉] as a catalyst has been depicted in Scheme 2. Based on our previous reports [35,37], we were aware that [TBA]₂[W₆O₁₉] can play a dual role. Thus, we propose that the tetrabutylammonium ion [(*n*-Bu)₄N⁺] induces the polarization of the carbonyl groups, whereas the terminal oxygen atoms or the bridging oxygen atom in the poly-

oxometalate anion, W₆O₁₉²⁻, are slightly basic and can promote the necessary reactions. The [TBA]₂[W₆O₁₉] can therefore activate the reactants and the intermediates in this reaction. As shown in Scheme 2, we propose that [TBA]₂[W₆O₁₉] facilitates the formation of the intermediates **I** and **II** that subsequently react together to give the final products **4a–4q**.

3 Conclusions

The isopolytungstate, [TBA]₂[W₆O₁₉], showed high catalytic activity in the synthesis of 1,8-dioxodecahydroacridines via the one-pot three-component reaction of dimedone with aromatic or aliphatic aldehydes and ammonium acetate or aromatic amines under solvent-free conditions. This procedure offers several advantages over the other techniques available in the literature, including much shorter reaction times, higher yields, facile workup, and the absence of any hazardous organic solvents, which makes it a useful and attractive protocol for the synthesis of these compounds. Furthermore, the catalyst could be recycled after a simple

work-up, and used at least three more times without significant reduction in its catalytic activity. The procedure is also advantageous in the sense that it is a solvent-free reaction and therefore operates under environmentally friendly conditions.

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