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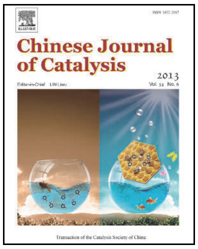

Article

Tetrabutylammonium hexatungstate $[TBA]_2[W_6O_{19}]$: Novel and reusable heterogeneous catalyst for rapid solvent-free synthesis of polyhydroquinolines via unsymmetrical Hantzsch reaction

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ABSTRACT

A novel, efficient, and environmentally friendly method for the synthesis of polyhydroquinoline derivatives by a one-pot, four-component unsymmetrical Hantzsch condensation of dimedone, aldehydes, ethyl acetoacetate, and ammonium acetate in the presence of a catalytic amount of tetrabutylammonium hexatungstate $[TBA]_2[W_6O_{19}]$ under solvent-free conditions has been developed. The results showed that this heterogeneous catalyst has high catalytic activity and the desired products were obtained in good to high yields. Moreover, the catalyst was found to be reusable and considerable catalytic activity was still achieved after the fifth run.

1. Introduction

Multicomponent reactions (MCRs) have attracted much interest and are highly regarded in modern organic synthesis and medicinal chemistry because they are one-pot processes that bring together three or more components and show high atom economy and high selectivity [1–4]. MCRs have been widely used in the convergent synthesis of complex and important organic molecules from simple and readily available starting materials, and have emerged as powerful tools for drug discovery [5,6]. The development of new MCRs and improvement of known MCRs are therefore areas of considerable current interest. One such reaction is the synthesis of polyhydroquinolines via the unsymmetrical Hantzsch reaction.

The 1,4-dihydropyridine (1,4-DHP) core is found in a range of compounds exhibiting a broad spectrum of biological activities [7–9]. Some of the representative compounds of this class possess antimicrobial [10], antitubercular [11], insecticidal [12], and neuroprotectant [13] activities. In particular, 4-aryl-1,4-DHPs are well known as calcium-channel blockers and have emerged as one of the most important classes of drugs for the treatment of cardiovascular diseases [14,15]. Recently, 1,4-DHPs have been used as organocatalysts for asymmetric reactions such as hydrogenation of quinolines in the synthesis of alkaloids [16], asymmetric reductive amination of aldehydes [17], and hydrogenation of α,β-unsaturated aldehydes and ketones [18,19].

Polyhydroquinolines are a class of fused 1,4-DHPs that have received less attention than other fused 1,4-DHPs, and comparatively few methods for their preparation have been reported. Polyhydroquinolines are generally synthesized by an unsymmetrical Hantzsch reaction, which involves the one-pot, four-component condensation of dimedone, aldehydes, ethyl acetoacetate, and ammonium acetate, using various promoting agents such as montmorillonite K-10 [20], ionic liquids [21], I_2 [22], FeF_3 [23], $Sc(OTf)_3$ (OTf = trifluoromethanesulfonate) [24], $Yb(OTf)_3$ [25], cerium(IV) ammonium nitrate [26], and trifluoroethanol [27]. Syntheses of these compounds using mi-

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crowave irradiation [28,29], solar thermal energy [30], and grinding [31] have also been reported.

However, most of these methodologies suffer from disadvantages such as unsatisfactory yields, toxic organic solvents, harsh reaction conditions, long reaction times, and the use of relatively expensive reagents. These findings prompted us to perform investigations to find new catalysts that will enable the synthesis of polyhydroquinoline derivatives using simple experimental set-ups and eco-friendly conditions.

The development of environmentally benign, efficient, and economical methods for the synthesis of biologically interesting compounds [32–35] remains a significant challenge in synthetic chemistry. Green chemistry emphasizes the need for environmentally clean synthesis, which involves improvements in selectivity, elimination of hazardous solvents, and easy work-up, using reusable catalysts. As a result, attempts to replace homogeneous catalysts by non-toxic, non-corrosive, easy to handle, and environmentally friendly heterogeneous catalysts have increased rapidly in recent years [36–39]. Reactions under solvent-free conditions have also continued to attract the attention of researchers both from academia and industry [40,41]. This is because solvent-free reactions usually need shorter reaction times and have simpler work-up procedures.

As a result of our interest in the synthesis of heterocyclic compounds [42–45], and as part of our research on the development of environmentally friendly methods for the synthesis of organic compounds using reusable catalysts [46–50], we recently investigated the use of tetrabutylammonium hexatungstate, $[TBA]_2[W_6O_{19}]$, as a catalyst in the Knoevenagel condensation [51], the Biginelli reaction [52], and in the syntheses of biscoumarins [53] and 1,8-dioxodecahydroacridines [54]. This new reusable heterogeneous catalyst performed well and showed high catalytic activity in these transformations. These facts encouraged us to explore the use of this catalyst in the synthesis of polyhydroquinoline derivatives under solvent-free conditions.

2. Experimental

2.1. Synthesis of $[TBA]_2[W_6O_{19}]$

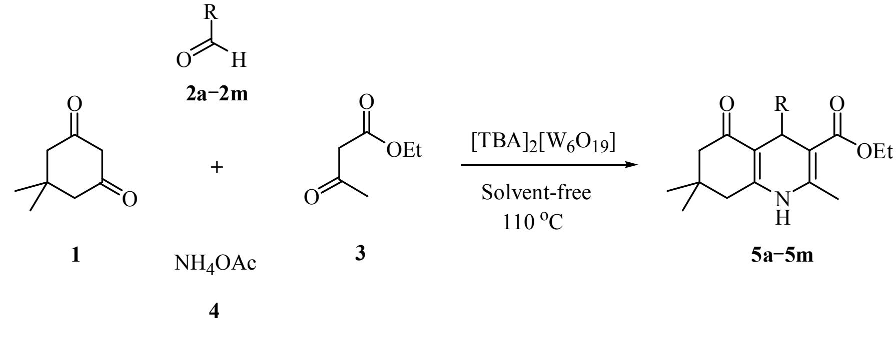
A mixture of sodium tungstate dihydrate ($Na_2WO_4\cdot 2H_2O$, 99%, 33 g, 0.1 mol), acetic anhydride (40 ml), and *N,N*-dimethylformamide (DMF, 30 ml) was heated at 100 °C for 3 h to obtain a white cream. A solution of acetic anhydride (20 ml) and 12 mol/L HCl (18 ml) in DMF (50 ml) was then added drop-wise 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. The resulting suspension was stirred for 5 min and the product was then collected by filtration. Recrystallization from a minimum amount of hot dimethyl sulfoxide gave the product as colorless diamond-shaped crystals [55].

2.2. General procedure for synthesis of polyhydroquinolines **5a–5m**

A mixture of dimedone **1** (1 mmol), an aldehyde **2a–2m** (1 mmol), ethyl acetoacetate **3** (1 mmol), ammonium acetate **4** (1 mmol), and $[TBA]_2[W_6O_{19}]$ (0.07 mmol, 7 mol%) was heated in an oil bath at 110 °C for 20–30 min. The reaction was monitored using thin-layer chromatography. On completion of the transformation, the reaction mixture was cooled to room temperature and hot ethanol was added. This resulted in precipitation of the catalyst, which was collected by filtration. The product was collected from the filtrate after cooling to room temperature and recrystallized from ethanol to give compounds **5a–5m** in high yields (Scheme 1). The melting points were recorded using a Stuart SMP3 melting-point apparatus. The IR spectra of the products were obtained with KBr disks, using a Tensor 27 Bruker spectrophotometer. The ^1H NMR (400 and 500 MHz) spectra were recorded using Bruker 400 and 500 spectrometers.

Ethyl 2,7,7-trimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (**5a**). ^1H NMR (500 MHz, $CDCl_3$): δ 0.97 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 1.23 (t, 3H, J = 7.1 Hz, CH_3), 2.15–2.39 (m, 4H, $2CH_2$), 2.41 (s, 3H, CH_3), 4.09 (q, 2H, J = 7.1 Hz, OCH_2), 5.01 (s, 1H, CH), 6.18 (s br., 1H, NH), 7.12 (t, 1H, J = 7.3 Hz, arom-H), 7.22 (t, 2H, J = 7.5 Hz, arom-H), 7.33 (d, 2H, J = 7.7 Hz, arom-H); IR (KBr, cm^{-1}): ν 3289, 3219, 3082, 2963, 1699, 1644, 1611, 1485, 1381, 1213, 1072, 761, 698, 530.

Ethyl 4-(4-bromophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (**5b**). ^1H NMR (400 MHz, $CDCl_3$): δ 0.95 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.22 (t, 3H, J = 7.2 Hz, CH_3), 2.14–2.37 (m, 4H, $2CH_2$), 2.39 (s, 3H, CH_3), 4.08 (q, 2H, J = 7.2 Hz, OCH_2), 5.04 (s, 1H, CH), 6.21 (s br., 1H, NH), 7.21 (d, J = 8.4 Hz, 2H, arom-H), 7.34 (d, J = 8.4 Hz, 2H, arom-H); IR (KBr, cm^{-1}): ν 3275, 3206, 3076, 2958, 1703, 1649, 1604, 1487, 1381,



Scheme 1. $[TBA]_2[W_6O_{19}]$-catalyzed synthesis of polyhydroquinoline derivatives.