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Synthesis and characterization of novel polystyrene-supported TBD catalysts and their use in the Michael addition for the synthesis of Warfarin and its analogues

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ABSTRACT

In the search for efficient and polymeric supports for organic bases to be used in environmentally friendly media and conditions, novel polystyrene-bound 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) has been prepared and characterized. Their catalytic properties have been tested in the Michael additions of 4-hydroxycoumarin to α,β-unsaturated ketones as a representative useful process for the syntheses of 4-hydroxy-3-(3-oxo-1-phenylbutyl)-2H-chromen-2-one (Warfarin™), 4-hydroxy-3-(1-(4-nitrophenyl)-3-oxobutyl)-2H-chromen-2-one (Acenocumarol™), 4-hydroxy-3-(1-(4-chlorophenyl)-3-oxobutyl)-2H-chromen-2-one (Coumachlor™), and 4-hydroxy-3-(1-(4-methoxyphenyl)-3-oxobutyl)-2H-chromen-2-one. Products were obtained in high to quantitative conversion yields. The novel catalytic systems showed promising catalytic properties, and they could be all easily recovered by filtration and have been reused for three representative consecutive runs without any significant lowering of their activity.

1. Introduction

Polymer-supported catalysts have greatly attracted the interest of the chemical community in recent decades [1]. Immobilization of catalyst over an inert solid support demonstrated to be an efficient strategy to simplify the isolation of products and catalyst recycling, leading to economic and environmental advantages [1]. Among the wide range of supports, chloromethylated polystyrene cross-linked with divinylbenzene (PS/DVB) is one of the most used [1] (Scheme 1). However, when employed as gel-type resin, PS/DVB suffers from a limited accessibility of the reactants to catalytic sites when the reaction medium selected is a poor swelling solvent, and a consequent sensitive reduction in efficiency of the supported catalyst is generally observed [2]. On the other hand, macroporous PS/DVB resins do not generally suffer from such limitations, because of their permanent porous structure that is almost independent from the solvent nature and persists in the dry state [3].

According to our research, which is devoted to the development of an environmentally sustainable chemistry [4,5], the support is truly important for the definition of efficient synthetic procedures especially when safer reaction media are used (e.g. water [4], solvent-free conditions (SolFC) [5] or greener alternative to organic solvents [6]).

Among organic bases, highly basic guanidines, and in particular the bicyclic member 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) (**2**) (Scheme 2) are widely useful in chemical synthesis [7].

The equivalent PS-TBD is a polymer-supported organocatalyst consisting of a covalently linked guanidinic TBD moiety to polystyrene which has been successfully used in a wide range of reactions [8–12] as epoxide ring opening [9], aldol-type condensation [9], Knoevenagel condensation [9], Michael additions to α,β-unsaturated ketones [9], cyanosilylation of aldehydes, ketones and imines [10], ring opening of aziridines [11] and addition of dialkylphosphites to unsaturated systems [12]. Generally, commercially available PS/DVB has been used as polymeric supports, while as an example, it has been proved that to reach highest efficiency and compatibility with sustainable reaction conditions, support played a dramatic role [5c–d,9,13]. Excellent results have been obtained using Janda polymers [1d,14], but limitations can be encountered if used under solvent-free conditions (SolFC) due to the very low loading of the commercially available materials [13].

In this work, three different chloromethylated macroporous polystyrene–divinylbenzene supports (**1a–c**) were successfully prepared by suspension polymerization and used to immobilize TBD (**2**). The supports as well as the resulting catalysts (**3a–c**) were

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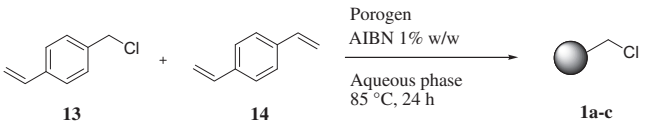
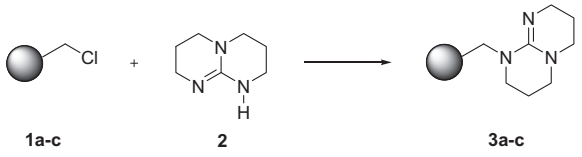


Scheme 1. Synthesis of chloromethylated resins **1a–c**.



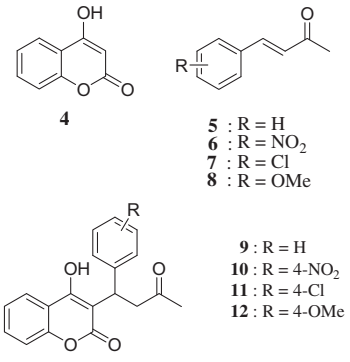
Scheme 2. Synthesis of catalysts **3a–c**.

characterized in terms of composition, structure, thermal stability, and morphology. The commercially available macroporous PS-TBD (**c-PS-TBD**) was also characterized for comparison purposes. The efficiencies of the newly synthesized as well as commercial polymeric-TBD catalysts were evaluated in the Michael reactions between 4-hydroxycumarine (**4**) and α,β-unsaturated ketones (**5**–**8**) to access Warfarin (**9**) and its analogues (**10**–**12**) (Scheme 3). Attention has been directed to a Michael addition process which is of very general interest and use in the chemical synthesis of target molecules and considering our goal to investigate the use of polymeric–organic bases in environmentally friendly reaction media, we directly pointed our attention toward the preparation of Warfarins. This process is based on the reactions of 4-hydroxycumarines that are generally poorly reactive and insoluble making the use of heterogeneous catalysts very challenging. Note that Warfarin is one of the most used anticoagulant worldwide [15]. Sold as racemate (Coumadin™), this coumarin-based anticoagulant is one of the most employed for the prevention of thrombosis and thromboembolism. The nitro derivative of Warfarin (**10**) is also a powerful anticoagulant and it is known as Acenocoumarol (Sintrom™). Despite the fact that several methods for the preparation of Warfarin using organocatalysis have been reported in recent years [15,16], the development of catalysts and sustainable efficient catalytic procedures for the synthesis of Warfarin and its analogues is still therefore of great importance. This molecule is thus of great pharmacological and economical relevance, and we found worthy to plan our academic study on this case study.

2. Materials and methods

2.1. General remarks

All the commercially available chemicals were purchased at Sigma–Aldrich and used without any further purification, unless otherwise noted. Commercial polystyrene-bound TBD (**c-PS-TBD**) was purchased at Polymer Laboratories, Varian Inc. (1.81 mmol TBD/g, 100/200 mesh; Elemental Analysis: N: 7.14%; C: 76.71%; H: 7.54%). 4-Vinylbenzylchloride (**13**) and divinylbenzene (**14**) (80% grade) were extracted three times with a 5% w/w NaOH solution to remove the polymerization inhibitor (tert-butyl catechol). AIBN was recrystallized from methanol. (3E)-4-(4-nitrophenyl)-but-3-en-2-one (**6**) and (3E)-4-(4-methoxyphenyl)-but-3-en-2-one (**8**) were prepared according to previously reported procedures [17]. Suspension polymerizations were run using a three-neck cylinder-shaped glass vessel (Fig. 1), equipped with a mechanical stirrer, condenser, and nitrogen inlet. A silicon oil bath was used as heating source. ^{1}H NMR and ^{13}C NMR spectra were recorded using a Bruker DRX-ADVANCE 400 MHz spectrometer. Deuterated solvents were used with the residual peak as internal standard. Elemental microanalyses were performed using a Fison's EA1106 CHN analyzer using atropine, 2,5-bis-2-(5-tert-butylbenzoxazolyl)-thiophene (BBOT) and phenanthrene as reference standard, with an accuracy of ca. 2 μmol/g. Commercial polystyrene-bound TBD (**c-PS-TBD**) was purchased at Polymer Laboratories, Varian Inc. and the porogen used for its preparation is not known (1.81 mmol TBD/g, 100/200 mesh; Elemental Analysis: N: 7.14%; C: 76.71%; H: 7.54%). Modulated differential scanning calorimetry analyses (MDSC) were performed with a TA instruments 2920 calorimeter with modulated cell cooled by nitrogen flow. Samples were analyzed in opened capsules with heating rate of 10 °C/min, ±0.5 °C modulation and 60 s period. Scanning electron microscopy (SEM) analyses were performed using an Auriga Zeiss HR FESEM instrument. SEM imaging of the surfaces of resin samples was performed with accelerating voltages between 5 keV and 30 keV, achieving magnifications ranging from 100× to 200k×. FTIR spectra were recorded on a VERTEX 70 Bruker Optics instrument, spectral range 4000–400 cm^{-1}, resolution 4 cm^{-1}, equipped with single reflection diamond ATR cell. Brunauer–Emmett–Teller (BET) analyses were performed by using an Autosorb iQ-MP/MP-XR instrument (Quantachrome).



Scheme 3. Warfarins and their precursors.

Fig. 1. Suspension polymerization reactor used in this study.