Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Polystyrene supported benzoylthiourea—pyrrolidine organocatalyst for the enantioselective Michael addition

Ladislav Androvič, Pavel Drabina *, Markéta Svobodová, Miloš Sedlák

Institute of Organic Chemistry and Technology, Faculty of Chemical Technology, University of Pardubice, Studentská 573, 532 10 Pardubice, Czech Republic

ARTICLE INFO

ABSTRACT

Herein the preparation of a swellable pearl-like copolymer of styrene with anchored (*S*)-1-benzoyl-3-(pyrrolidine-2-ylmethyl)thiourea (20–600 μm) and its application as a recyclable organocatalyst for the Michael addition of ketones to functionalized β-nitrostyrenes is described. The rate of the reaction taking place in the matrix of the swellable polymeric catalyst was comparable with the reaction rate in homogeneous medium. The corresponding functionalized 4-nitroketones were formed quantitatively with the enantiomeric excesses up to 98% ee. After a fivefold recycling of the catalyst, no decrease in the yield was detected, but the enantioselectivity was slightly lowered (95 → 88% ee).

1. Introduction

Asymmetric organocatalysis represents one of the most intensively developing branches of organic synthesis.[1] The present interest in this type of catalysis is predominantly derived from the fact that it enables the replacement of the enantioselective catalysts based on complexes of heavy metals, which often are very toxic.[2] Other problems associated with catalyzed reactions include the necessity of separation of the product from the catalyst, and the repeated use of homogeneous catalysts that often tends to be impossible or highly demanding economically and technologically. Thus, the used catalysts become components of potentially dangerous waste materials, which have to be further processed or disposed of.[2] From the point of view of sustainable technologies, it is advantageous to immobilize homogeneous catalysts by anchoring then onto carriers,[3] e.g., polymers.[4] A considerable advantage of polymer-supported organocatalysts lies not only in the possibility of their easy separation and recycling, but also in their possible application to continuous-flow enantioselective procedures.[5]

A method, that is very often employed for the immobilization of a catalyst, is post-modification, where the organocatalyst is anchored onto a commercially available reactive polymer.[4] Another method for immobilization is copolymerization, where the organocatalyst represents one of the monomers, which is incorporated into the polymer network during polymerization.[4b,c] A recently published paper[4c] describes the procedure, in which a functionalized thiourea simultaneously carrying an L-valine and styrene fragment, was copolymerized with styrene and the

obtained polymer was successfully tested as a highly efficient recyclable organocatalyst for enantioselective aza-Henry and Michael additions.[4c] The organocatalysis itself utilizes various types of intermolecular interactions of the organocatalyst with the reactants.[1] For organocatalysis using molecules such as thiourea-pyrrolidine **1**, a bifunctional type of catalysis takes place. This process is based on the 'enamine' activation of the donor in combination with advantageous spatial orientation and activation of the acceptor due to the hydrogen bond of the thiourea fragment[1,6] (Fig. 1). Previous publications[6] describe the successful application of benzoylthiourea-pyrrolidine catalysts for enantioselective Michael addition reactions, which provided a number of important 1,4-difunctional molecules, that could be used, e.g., as advanced intermediates in syntheses of biologically active compounds.[6] Herein the preparation of a heterogeneous recyclable variant of this catalyst, and testing its catalytic activity in asymmetric Michael addition reactions, as well as investigating the possibility of its recycling is described.
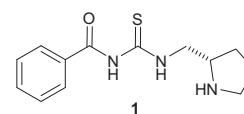
* Corresponding author. Tel.: +420 466 037 010; fax: +420 466 037 068.
E-mail address: pavel.drabina@upce.cz (P. Drabina).

Figure 1. Structure of organocatalyst thiourea-pyrrolidine **1**.[6]

2. Results and discussion

In addition to the choice of the organocatalyst itself, a key decision also lies in the selection of a suitable polymeric carrier.[3,4] The polymeric carriers that proved successful were the network

copolymers of styrene, which are distinguished by a high degree of swelling (Merrifield resin™, JandaJel resin™). However, the copolymers of styrene containing carboxylic functional groups are not commonly commercially available. Therefore, we prepared our own swelling pearl-like copolymer of styrene **2**. The synthesis of copolymer **2** made use of a suspension copolymerization of styrene with 2-chloroethyl 4-vinylbenzoate with application of tetra (ethyleneglycol)-bis(4-vinylbenzyl)ether as the crosslinker (2%)[7] (Scheme 1). The quantitative content of the carboxylic groups in the copolymer was simply determined on the basis of the determination of the chlorine content coming from incorporated 2-chloroethyl 4-vinylbenzoate. The subsequent reaction step was hydrolysis of the ester group, which gave copolymer **3**. The carboxylic group was transformed into carboxylic acid chloride group, which upon reaction with potassium thiocyanate gave acylisothiocyanate. The subsequent reaction of (*S*)-2-(aminomethyl)-1-(*t*-butoxycarbonyl)pyrrolidine with acylisothiocyanate gave copolymer **4** with a covalently anchored functionalized thiourea. The protecting *t*-butyloxycarbonyl group was removed by reaction with trifluoroacetic acid, which gave the heterogeneous organocatalyst—pearl-like copolymer **5** (Scheme 1).

The synthesized copolymers **2**–**5** were characterized by Raman spectroscopy (Fig. 2). The Raman spectrum of copolymer **2** (A) exhibits the following bands: 2962 cm^{-1} (—CH$_2$Cl symmetric vibrations), 1722 cm^{-1} (C=O ester), 1380 cm^{-1} (—CH$_2$ wagging vibrations of CH$_2$CH$_2$Cl), 1275 cm^{-1} (—C—O—C— stretching vibration or —CH$_2$Cl wagging vibrations) and 670 cm^{-1} (—C—Cl stretching vibration).[8a] The spectrum of copolymer **3** (B) contains the following signals: 1722 cm^{-1} (C=O free carboxyl groups),[8b,c] 1690 cm^{-1} (C=O hydrogen-bonded carboxyl groups),[8b,c] 1283 cm^{-1} (C—O stretching vibration), 1130 cm^{-1} (O—H in-plane bending vibration),[8d] 808 cm^{-1} and 825 cm^{-1} (ring deformation along with the O—C—OH in-plane scissoring).[8d] Furthermore, the spectrum of copolymer **4** (C) shows the following signals: 1672 cm^{-1} (C=O amide I),[8a,e] 1520 cm^{-1} (NH amide II),[8a,e] 1417 cm^{-1} (C—S asymmetric vibration,[8f] 1250 cm^{-1} (—C(CH$_3$)$_3$ skeletal vibration or/and —C—O—C— stretching vibration).[8a,e] The spectrum of copolymer **5** (D): 1672 cm^{-1} (C=O amide I), 1520 cm^{-1} (NH amide II), 1417 cm^{-1} (C—S asymmetric vibration) (Fig. 2). The hydrolysis of the ester (**2 → 3**) can be proved by the disappearance of the bands at 670 cm^{-1}, and 2962 cm^{-1} and a decrease in intensity of the band at ∼1275 cm^{-1} belonging to vibrations of C—Cl, —CH$_2$Cl and —CH$_2$CH$_2$Cl, when the intensity of band at 1722 cm^{-1} is decreased; at the same time, a weak band appears at 1690 cm^{-1} (—COOH). In copolymer **3**, new bands appear at 1130 cm^{-1} and 810 cm^{-1} and 825 cm^{-1}, which belong
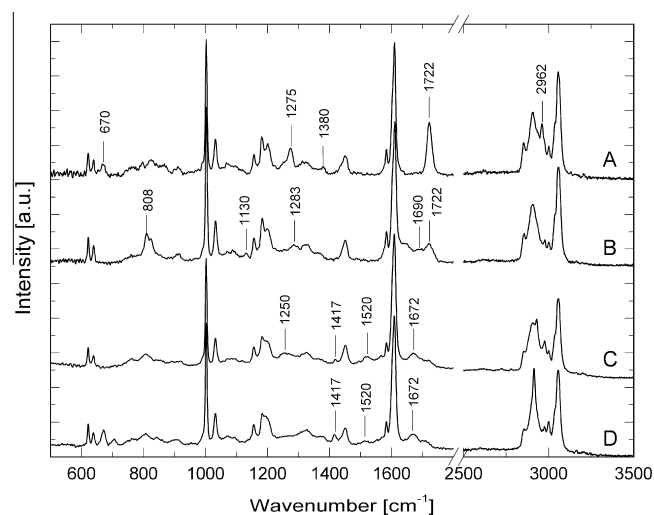
to the vibrations of the structural units of the carboxylic acid functional groups O—H and O—C—OH. After the reaction of **3 → 4**, all the above mentioned bands disappear, and the formation of bands at 1672 cm^{-1}, 1520 cm^{-1} and 1417 cm^{-1} can be detected, which confirms the incorporation of thiourea structural unit. The band at 1417 cm^{-1} belongs to C—S vibrations of a single bond rather than of a double bond. With high probability, the broad band at 1250 cm^{-1} corresponds to the vibrations of both —C (CH$_3$)$_3$ and —COC— in the protecting Boc group attached to pyrrolidine. The removal of protecting group (reaction **4 → 5**) was connected with the disappearance of the band at 1250 cm^{-1}.

The reaction sequence **2 → 5** was also monitored by means of microanalysis. The chlorine content found in copolymer **2** was ∼1 mmol g^{-1}, which corresponds to the content of carboxylic acid groups in copolymer **3**, because hydrolysis of the ester had proceeded quantitatively (<0.3% Cl). The content of nitrogen and sulfur in both copolymers **4** and **5** was ∼3 mmol g^{-1} and ∼1 mmol g^{-1}, respectively, which corresponds to the ratio of these atoms in a bonded thiourea—pyrrolidine molecule (1 mmol g^{-1}). Furthermore, the polymeric organocatalyst **5** was characterized by means of ^{13}C CP/MAS NMR (cross-polarization magic angle spinning) spectroscopy[9] (Fig. 3). The values of the signals in the spectrum (Fig. 3) can be assigned as follows: 181.2 ppm (C=S, thiourea); 169.2 ppm (C=O); 147.1 ppm (quaternary carbon of benzene ring);

Figure 2. Raman spectra of copolymers: **2** (A), **3** (B), **4** (C) and **5** (D).
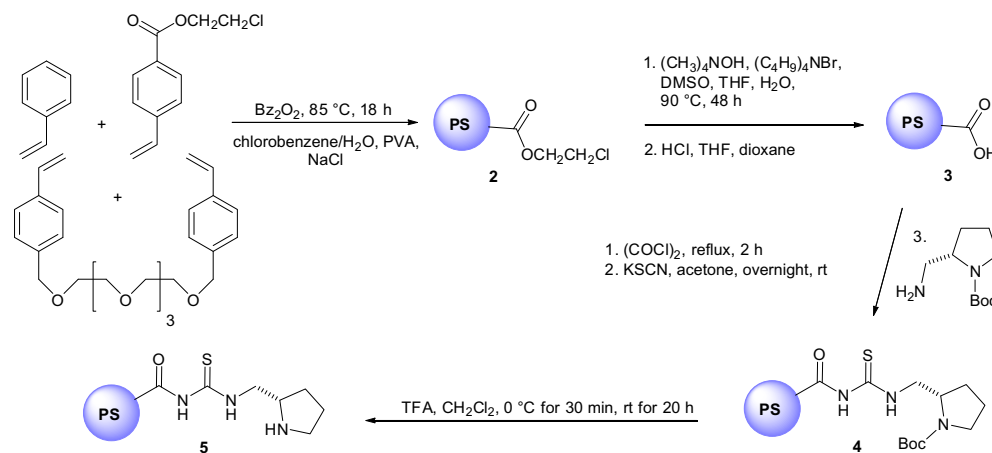
Scheme 1. Preparation of copolymer **2** by suspension polymerization with subsequent transformation giving copolymers **3**–**5**.